What interventions are the most effective for improving women's psychological and/or emotional health following pain, bleeding or pregnancy loss, in the first trimester of pregnancy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Nikcevic,A.V., Kuczmierczyk,A.R., Nicolaides,K.H., The influence of medical and psychological interventions on women's distress after miscarriage, Journal of Psychosomatic Research, 63, 283-290, 2007 **Ref Id** 65400 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To establish the impact of the provision of medical and psychological counselling following	**Sample size** N = 149 Medical + psychological counselling n = 39 Medical counselling n = 41 Control n = 69 **Characteristics** <u>Age of women - mean (years) ± SD</u> Medical + psychological counselling = 36.2 ± 3.7 Medical counselling = 34.3 ± 4.6 Control = 34.3 ± 4.1 <u>Duration of pregnancy at loss</u> Not reported <u>Women with children - n/N (%)</u> Medical + psychological counselling = 22/33 (67%) Medical counselling = 23/33 (70%) Control = 34/61 (56%) <u>Women with history of miscarriage* - n/N (%)</u>	**Interventions** <u>Medical + psychological counselling</u> A 20-minute follow-up appointment with an obstetrician 5-weeks post-miscarriage. Obstetrician discussed the results and implications of medical investigations performed at time of diagnosis as well as aspects of general health and planning of future pregnancies. Women were then invited to stay for the 50-minute psychological counselling session with a psychologist, which was based broadly on cognitive therapy framework. Main aims were encouragement of expression of feelings regarding loss, normalisation of such expressed emotions, exposure to memories, cognitive restructuring (where evidence of self-blame was apparent), and reframing and reorganising of the experience in context of available information as to causes of miscarriage. Worries concerning future attempts at	**Details** Women were recruited for the medical + psychological counselling group and the medical counselling group from the Harris Birthright Research Centre, where women with missed miscarriage were offered the option of further investigations, including fetal karyotyping and blood testing for lupus anticoagulant. At the time of diagnosis women were invited to attend the miscarriage 5-week follow-up clinic. At the miscarriage follow-up appointment women received the medical counselling intervention. On the basis of computer generated random number tables women were allocated to psychological counselling. At the end of the medical consultation the doctor opened a sealed envelope and, accordingly, invited the women allocated to medical + psychological counselling group to stay for the psychological	**Results** <u>Emotional and psychological outcomes of women</u> <u>7 weeks post-miscarriage</u> Hospital Anxiety and Depression Scale - Anxiety score (mean ± SD, N) Medical + psychological counselling = 7.2 ± 5.2, 33 Medical counselling = 6.7 ± 4.1, 33 Control = 6.9 ± 4.4, 61 Hospital Anxiety and Depression Scale - Depression score (mean ± SD, N) Medical + psychological counselling = 4.1 ± 4.2, 33 Medical counselling = 3.4 ± 2.9, 33 Control = 3.3 ± 3.2, 61 Texas Grief Inventory - summary score (mean ± SD, N) Medical + psychological counselling = 46.2 ± 12.5, 33 Medical counselling = 40.9 ± 11.0, 33	**Limitations** 80/98 (82%) women eligible for the intervention arms of the study returned the first questionnaire and were randomised to either the medical + psychological counselling group or the medical counselling group. 66/80 (83%) women returned the second and third questionnaires. 69/111 (62%) women eligible for the control arm of the study returned the first questionnaire. 61/69 (88%) returned the second and third questionnaires. Allocation concealment unclear. **Other information** Hospital Anxiety and Depression Scale: 14-items, seven items assessing anxiety and seven items assessing depression. Each item scores 0 to 3, so total subscale scores from 0 to 21. Score of 11 is threshold

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miscarriage on women's distress. **Study dates** Not reported **Source of funding** Supported by a grant from the Fetal Medicine Foundation (Charity No. 1037116)	Medical + psychological counselling = 14/33 (42%) Medical counselling = 10/33 (30%) Control = 13/61 (21%) * unclear whether any of these women experienced recurrent miscarriage <u>Anxiety, depression and grief scores at baseline (4-weeks post-miscarriage)</u> Hospital Anxiety and Depression Scale - Anxiety score (mean ± SD, N) Medical + psychological counselling = 7.7 ± 4.4, 33 Medical counselling = 8.4 ± 3.8, 33 Control = 8.5 ± 5.0, 61 Hospital Anxiety and Depression Scale - Depression score (mean ± SD, N) Medical + psychological counselling = 5.4 ± 4.5, 33 Medical counselling = 5.8 ± 5.2, 33 Control = 4.7 ± 4.1, 61 Texas Grief Inventory - summary score (mean ± SD, N) Medical + psychological counselling = 52.8 ± 13.1, 33 Medical counselling = 48.4 ± 13.3, 33 Control = 46.7 ± 14.5, 61	reproduction were discussed. <u>Medical counselling</u> A 20-minute follow-up appointment with an obstetrician 5-weeks post-miscarriage. Obstetrician discussed the results and implications of medical investigations performed at time of miscarriage (including fetal karyotyping and blood testing for lupus anticoagulant) as well as aspects of general health and planning of future pregnancies. <u>Control</u> No specific postmiscarriage counselling.	counselling session. The control group was derived from the consecutive series of women diagnosed with missed miscarriages at the antenatal clinics of three London hospitals where the 10-14 week scan is offered routinely but there is no dedicated miscarriage follow-up care. Psychological assessment by postal questionnaire [Hospital Anxiety and Depression Scale (HADS), modified Texas Grief Inventory and Likert-type scales for questions about self-blame, feelings of responsibility, worry concerning future pregnancies and aspect of post-miscarriage care] was carried out at 4, 7 and 16 weeks post-miscarriage.	Control = 43.0 ± 13.8, 61 <u>4 months post-miscarriage</u> Hospital Anxiety and Depression Scale - Anxiety score (mean ± SD, N) Medical + psychological counselling = 5.6 ± 4.5, 33 Medical counselling = 7 ± 4.4, 33 Control = 6.4 ± 4.4, 61 Hospital Anxiety and Depression Scale - Depression score (mean ± SD, N) Medical + psychological counselling = 2.8 ± 4.1, 33 Medical counselling = 3.7 ± 3.7, 33 Control = 2.8 ± 3.6, 61 Texas Grief Inventory - summary score (mean ± SD, N) Medical + psychological counselling = 39.9 ± 12.4, 33 Medical counselling = 42 ± 13.4, 33 Control = 40.9 ± 13.4, 61 <u>Women's views/experiences of care</u> 100% of women endorsed moderate to strong agreement regarding helpfulness of doctor's	for probable psychiatric 'caseness'. Higher scores indicate higher levels of anxiety and depression. Texas Grief Inventory Scale: modified version, 17 items with summary score ranging between 17 and 85. Higher scores indicate higher grief levels. [Data for medical + psychological counselling and medical counselling groups used in GRADE profile]

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	All women who took part in the study had a surgical evacuation of the retained products of conception within 4 days from diagnosis of miscarriage. **Inclusion criteria** Women attending for a routine scan at 10-14 weeks of gestation and found to have a missed miscarriage. **Exclusion criteria** Women with a history of perinatal death, elective termination for fetal abnormality and recurrent miscarriage, inability to speak and read English fluently, and those under current psychological or psychiatric care.			consultation; 94% of women agreed at least moderately that consultation with psychologist was helpful. 14/61 women in the control group attended a follow-up with their GP/obstetrician. 30/47 (64%) women in the control group who received no follow-up of any kind expressed that some follow-up would have been helpful.	
Full citation Nikcevic,A.V., Tunkel,S.A., Nicolaides,K.H., Psychological outcomes following missed abortions and provision of follow-up care, Ultrasound in Obstetrics and Gynecology, 11, 123-128, 1998	**Sample size** N = 263 Attended a follow-up appointment n = 52 Not offered a follow-up appointment n = 143 **Characteristics** Median age of women = 36 years (range = 24 – 45 years) Median time since miscarriage = 187 days (range = 19 – 400	**Interventions** Follow-up appointment with local hospital or general practitioner	**Details** The study was conducted at the Harris Birthright Research Centre for Fetal Medicine, London. Pregnant women living in London and the surrounding areas were invited to participate in an ultrasound screening study for chromosomal abnormalities at 10–14 weeks of gestation. Following the diagnosis of	**Results** <u>Women's views/experiences of care</u> Desire for follow-up, offer of and attendance at follow-up: 187/204 (92%) women thought a follow-up appointment was desirable. Such an appointment, with a local hospital or general practitioner, was offered to 61/204 (30%) women. 52/61	**Limitations** Questionnaires were returned by 211/268 (79%); 204/211 questionnaires were fully completed and included in authors' analysis. Timing of follow-up appointments post-miscarriage for those women who attended an appointment was not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 69533 **Country/ies where the study was carried out** UK **Study type** Cross-sectional survey **Aim of the study** To determine the availability and desirability of routine follow-up care, and whethe rsuch care is associated with reduced psychological morbidity following the pregnancy loss **Study dates** January 1995 – March 1996 **Source of funding** The study was supported by a grant from the Fetal Medicine Foundation (Charity no. 1037116)	days) <u>Women with children - n/N (%)</u> Full study population = 122/204 (60%) Attended follow-up appointment = 26/52 (50%) Not offered follow-up appointment = 91/143 (64%) <u>Women with history of miscarriage* - n/N (%)</u> Full study population = 67/204 (33%) Attended follow-up appointment = 17/52 (33%) Not offered follow-up appointment = 46/143 (32%) * unclear whether any of these women experienced recurrent miscarriage **Inclusion criteria** Diagnosis of a missed abortion or anembryonic pregnancy at 10–14 weeks of gestation during the study period **Exclusion criteria** History of elective termination for fetal abnormality, stillbirth or neonatal death		a missed miscarriage, women were referred to their local hospitals for the evacuation of retained products of conception. A search was made of the study database and, on the basis of the stated inclusion and exclusion criteria, women were invited to complete a study questionnaire. The outcomes of interest were anxiety and depression assessed with Hospital Anxiery and Depression Scale, grief assessed with a modfifed version of the Expanded Texas Grief Inventory of Grief and women's experience of follow-up care, assessed with a specifically designed questionniare examining: (1) Whether a follow-up after miscarriage would be helpful (2) Whether a follow-up either by their hospital or by general practitioner was offered to them (3) Whether they attended the follow-up or not (4) Whether they had an opportunity to discuss their	(85%) women attended the follow-up appointment Content of follow-up: 22/52 (42%) reported not being given the opportunity to discuss feelings during the follow-up Anxiety and depression in women not given opportunity to discuss feelings at follow-up: those who felt they were not given the opportunity to discuss their feelings had significantly higher mean anxiety and depression scores than the women who did not have any follow-up care and women who attended follow-up and felt they had the opportunity to discuss their feelings. Expectations from a follow-up clinic: 72% of women suggested clinic should be conducted by a doctor, 28% would have preferred to see a midwife or counsellor. 177/204 (87%) women reported it was 'very' or 'extremely' important to them to have an explanation as to why the	reported. **Other information** Only data extracted for women's experiences/views of care. Of the 61 women who were offered a follow-up appointment, 52 attended, 4 did not attend and 5 were waiting to attend at the time of questionnaire completion.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			feelings about the miscarriage during the follow-up (5) How long after the miscarriage such a follow-up should be organised (6) Who they think is the most appropriate medical professional to conduct the follow-up (7) Which issues should be discussed during such follow-up (8) Whether they had contacted the Miscarriage Association (9) Whether they would find it useful to have some help/guidance from a counsellor concerning the emotional aspects of their loss	miscarriage happened. Contact with the Miscarriage Association: prior to discharge from the Harris Birthright Research Centre all women were given an information leaflet that included the telephone number of the Miscarriage Association. 18/204 (9%) women had made contact, significantly moreso in the gorup that attended a follow-up clinic. Emotional counselling: 73/204 (36%) women reported that they would find emotional counselling helpful. The comparison between women who expressed a wish for emotional counselling and those who did not revealed that those who did not want counselling had significantly lower levels of anxiety (t test = −2.44, d.f. = 200, $p < 0.05$), depression (t test = −2.51, d.f. = 200, $p < 0.05$) and grief (t test = −4.30, d.f. = 199, $p < 0.001$). Women's opinions about ways to improve support from medical professionals: many	

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				women wanted more information concerning the reasons for their miscarriage and its implications, outlined the importance of a sensitive and sympathetic attitude on the part of medical professionals and emphasised the fact that the evacuation of the retained products of conception after miscarriage is a trauma that is too often dismissed as a routine surgical procedure by the medical staff involved.	
Full citation Sejourne,N., Callahan,S., Chabrol,H., The utility of a psychological intervention for coping with spontaneous abortion, Journal of Reproductive and Infant Psychology, 28, 287-296, 2010 **Ref Id** 81226 **Country/ies where the study was carried out** France	**Sample size** N = 134 Intervention n = 66 Control n = 68 **Characteristics** <u>Age of women - mean (years) ± SD</u> Intervention = 31.01 ± 4.45 Control = 31.87 ± 5.32 <u>Duration of pregnancy at time of loss - mean (weeks) ± SD</u> Intervention = 9.05 ±2.46 Control = 9.31 ± 2.13 <u>Women with children - n/N (%)</u> Intervention = 24/56 (42.8%)	**Interventions** <u>Intervention</u> A support intervention consisting of one psychological session on the day of surgical intervention (dilation and curettage or vacuum aspiration). Support was composed of three elements. (1) Empathic listening was used to encourage therapeutic alliance and emotional expression. (2) A psychoeducational approach aimed at helping women understand the context of miscarriage, their incidence and understanding normal psychological reactions and their repercussions e.g. asking	**Details** Women were met on the day of their surgical intervention (dilation and curettage or vacuum aspiration) and were assigned, based on the date, to either immediate intervention on odd-numbered days or delayed intervention on even-numbered days. All women received the Hospital Anxiety Depression Scale (HADS) and Impact of Events Scale-Revised (IES-R) questionnaires at 3 weeks, 10 weeks and 6 months	**Results** <u>Emotional and psychological outcomes of women</u> <u>3 weeks post-miscarriage</u> Hospital Anxiety Depression Scale - Anxiety score (mean ± SD, N) Intervention = 7.21 ± 3.02, 50 Control = 9.06 ± 3.95, 52 Hospital Anxiety Depression Scale - Depression score (mean ± SD, N) intervention = 3.93 ± 3.38, 50	**Limitations** Alternate randomisation was used. In the intervention group 50/66 (75%) women responded at 3 weeks, 45/66 (68%) at 10 weeks and 33/66 (50%) at 6 months. However, the authors report an n of 56 (not 50) for the intervention group in 'general characteristics' table (assumed measured at 3 weeks). In the control group 52/68 (78%) women responded at 3 weeks, 37/68 (54%) at 10 weeks and 34/68 (50%) at

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Quasi-randomised controlled trial **Aim of the study** To develop and evaluate a cognitive behaviour therapy based intervention for women dealing with miscarriage. **Study dates** October 2005 – March 2007 **Source of funding** Not reported	Control = 31/52 (59.6%) <u>Women with history of miscarriage - n/N (%)</u> Intervention = 11/56 (19.6%) Control = 14/52 (26.9%) **Inclusion criteria** Adult French-speaking women who had undergone dilation and curettage or vacuum aspiration for the uncomplicated and unanticipated loss of pregnancy **Exclusion criteria** Poor mastery of French language, no stable postal address	women if they were aware of the actual frequency of miscarriage and providing correct information where necessary. (3) Cognitive reframing was used to help women deal with feelings of guilt or responsibility. Problem resolution was used to help women find concrete solutions to problems anticipated and encountered and facilitate adapative coping strategies. Interviews lasted on average 37 minutes (SD = 14.38 min, range 20 – 90 min). Two weeks after the interview, women received a telephone follow-up (content of telephone follow-up not described). <u>Control</u> Women were informed that they were participating in a study on the psychological experience of miscarriage.	post-miscarriage. When 10-week questionnaires were sent, women in the control group were offered the support intervention (at 3 months post-miscarriage).	Control = 5.08 ± 3.60, 52 Impact of Events Scale-Revised - Total score (mean ± SD, N) Intervention = 26.15 ± 16.87, 50 Control = 33.77 ± 17.65, 52 <u>10 weeks post-miscarriage</u> Hospital Anxiety Depression Scale - Anxiety score (mean ± SD, N) Intervention = 6.22 ± 3.52, 45 Control = 7.16 ± 4.25, 37 Hospital Anxiety Depression Scale - Depression score (mean ± SD, N) intervention = 3 ± 2.46, 45 Control = 3.48 ± 3.20, 37 Impact of Events Scale-Revised - Total score (mean ± SD, N) Intervention = 20.37 ± 17.23, 45 Control = 23.67 ± 15.62, 37 <u>6 months post-miscarriage</u> Hospital Anxiety Depression Scale - Anxiety score (mean ± SD, N) Intervention = 5.33 ± 3.42,	6 months. Women who did not respond at 6 months had significantly higher anxiety scores (t(40) = 2.05, p = 0.04) and IES-R (t(40) = 2.53, p = 0.01) at 3 weeks than those who responded. **Other information** Not all women in the control group responded when contacted at 10 weeks post-miscarriage. 48/68 women in the control group were offered the support intervention: 24 refused, 10 accepted and 14 did not follow up on the offer.

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				33 Control = 6.50 ± 3.49, 34 Hospital Anxiety Depression Scale - Depression score (mean ± SD, N) intervention = 2.24 ± 2.79, 33 Control = 2.44 ± 2.50, 34 Impact of Events Scale-Revised - Total score (mean ± SD, N) Intervention = 16.68 ± 15.43, 33 Control = 16.02 ± 14.65, 34 <u>Women's views/experiences of care</u> 43/50 (86%) felt the support intervention was helpful (3 weeks post-miscarriage) 9/45 (20%) felt it was insufficient, some women felt the need for more support (10 weeks post-miscarriage)	
Full citation Adolfsson,A., Bertero,C., Larsson,P.G., Effect of a structured follow-up visit to a midwife on women with early	**Sample size** N = 116 Intervention n = 56 Control n = 60 **Characteristics**	**Interventions** <u>Intervention</u> Structured follow-up visit - 60-minute structured cnversation with one midwife. Focused on woman's own experience of her miscarriage, what she had	**Details** All women attending a gynecologic clinic in southwest Sweden who had experienced an early miscarriage were invited to participate in the study.	**Results** <u>Emotional and psychological outcomes of women (4 months postmiscarriage)</u> Perinatal Grief Scale, Swedish short version -	**Limitations** 116/146 (79%) women invited to participate attended the follow-up visit with a midwife. 43/56 (77%) women in

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miscarriage: a randomized study, Acta Obstetricia et Gynecologica Scandinavica, 85, 330-335, 2006 **Ref Id** 165136 **Country/ies where the study was carried out** Sweden **Study type** Randomised controlled trial **Aim of the study** To identify women's need of a follow-up visit to the midwife after miscarriage and, in such cases, what the visit should include. **Study dates** July 2002 – May 2003 **Source of funding** Supported by grants from the research and	Mean age of women = 31.3 years (SD not reported) Mean gestation at time of miscarriage = 9.7 weeks (SD not reported) Of the women completing the study, 11/88 (12%) had complete miscarriage, 6/88 (7%) had incomplete miscarriage with heavy haemorrhage, 28/88 (32%) had incomplete miscarriage with little haemorrhage and 43/88 (49%) had missed miscarriage <u>Women with history of miscarriage* - n/N (%)</u> Intervention = 9/43 (21%) Control = 13/45 (29%) *unclear whether any of these women experienced recurrent miscarriage <u>Emotional and psychological outcomes of women (baseline)</u> Perinatal Grief Scale, Swedish short version - Active grief score [mean (95% CI), N] Intervention = 45.8 (38.5 to 53.3), 43 Control = 42.6 (35.4 to 49.7), 45 Perinatal Grief Scale, Swedish short version - Difficulty in coping score [mean (95% CI), N] Intervention = 27.3 (22.1 to	lost and gained, who she could share her losses with. Women were asked about their feelings 'just now', how to go public, the risk of being reminded of their loss when they meet pregnant women etc. Women had to work through their emotions and physical loss before they could be themselves again. <u>Control</u> Regular follow-up visit - 30-minute visit with one of five midwives. Midwives asked women about general health and any complications after their miscarriages. Midwife did not ask about woman's feelings and emotions and only if woman took initiative of asking questions did the conversation continue.	Women were informed of the study and offered a follow-up visit to a midwife 21 – 28 days after their initial visit. Included women were randomised to a structured or standard follow-up visit. A pregnancy test was performed to confirm that miscarriage was complete and tests for Chlamydia trachomatis and bacterial vaginosis were also taken. The woman's need for contraception was investigated. Women in both groups answered the perinatal grief scale Swedish short version (PGS) at the follow-up visit to the midwife. Three months after the follow-up visit (4 months after miscarriage) women were sent the PGS by post.	Active grief score [mean (95% CI), N] Intervention = 31.0 (25.1 to 36.9), 43 Control = 32.7 (26.7 to 38.7), 45 Perinatal Grief Scale, Swedish short version - Difficulty in coping score [mean (95% CI), N] Intervention = 21.7 (17.7 to 25.8), 43 Control = 22.9 (18.1 to 27.6), 45 Perinatal Grief Scale, Swedish short version - Despair score [mean (95% CI), N] Intervention = 20.7 (16.5 to 24.8), 43 Control = 20.6 (16.4 to 24.7), 45 Perinatal Grief Scale, Swedish short version - Total PGS score [mean (95% CI), N] Intervention = 73.4 (60 to 86.8), 43 Control = 76.2 (62.2 to 90.1), 45 <u>Women's views/experiences of care (4 months postmiscarriage)</u>	intervention group and 45/60 (75%) in control group returned 3-month follow-up questionnaires. Study was designed to detect a 50% difference between groups and required 50 women in each group. Unclear if women knew that they had been randomised to structured or standard follow-up before attending the follow-up visit. **Other information** In cases of incomplete miscarriage with heavy haemorrhage women were treated with emergency curettage. Women with incomplete miscarriage with little haemorrhage were scheduled for a new visit to the gynaecologist 5 – 7 days after initial visit. If endometrial thickness was > 15 mm, curettage was performed. Missed miscarriage was treated with curettage within a few days. In all cases the midwife follow-up visit was scheduled 21 – 28 days

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development unit, Skaraborgs Hospital, Skövde and the Skaraborgs Institute for Research and Development	32.6), 43 Control = 26 (20.4 to 31.6), 45 Perinatal Grief Scale, Swedish short version - Despair score [mean (95% CI), N] Intervention = 23.8 (19.2 to 28.3), 43 Control = 25.1 (19.2 to 30.9), 45 Perinatal Grief Scale, Swedish short version - Total PGS score [mean (95% CI), N] Intervention = 97 (80.7 to 113.3), 43 Control = 93.7 (75.7 to 111.6), 45 **Inclusion criteria** Visit to the gynaecologic outpatient clinic for a miscarriage before 13 weeks' gestation, over 18 years of age, Swedish speaking **Exclusion criteria** Pregnancy kept secret from next of kin, e.g. husband, extrauterine pregnancy, suspicion of extrauterine pregnancy			Women's estimation of the importance of follow-up visit - Visual analog scale 1 to 10 Intervention = 8.6* Control = 7.0* *assume author report mean, measure of variance not reported	after initial visit. Women with missed abortion had siginifcantly higher total PGS scores than women with other diagnoses (85.2 vs. 65.0, p < 0.05), independent of which kind of follow-up visit women attended. Perinatal Grief Scale has three subscales: active grief, difficulty coping and despair. Each subscale gives a sum of 11 – 110 points. Total minimum score of Perinatal Grief Scale is 33, maximum score is 330. Minimal important difference not reported.
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Lee,C., Slade,P.,	N = 39	Intervention	At recruitment women	Emotional and	Methods of randomisation

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Lygo,V., The influence of psychological debriefing on emotional adaptation in women following early miscarriage: a preliminary study, British Journal of Medical Psychology, 69, 47-58, 1996 **Ref Id** 165775 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** A preliminary investigation of the effects of psychological follow-up on emotional adaptation in women who miscarry during early pregnancy. The intervention aims to take into account the whole experience of miscarriage.	Intervention group n = 21 Control group n = 18 **Characteristics** Mean age of women = 29.3 years (SD ± 6.1; range 19 to 42) Mean gestation at time of miscarriage = 10.8 weeks (SD ± 3.0; range 6 to 17) 56% of women had children, with the majority having no or one child (range 1 to 4). 85% of women had an evacuation of the uterus, while 15% had complete miscarriage and were followed up with blood tests to exclude retention of any placental tissue. 80% of women had planned their pregnancies, but all wanted their pregnancies to continue at the time of their miscarriage. <u>Anxiety, depression and impact of events scores at baseline (1-week postmiscarriage)</u> Hospital Anxiety and Depression Scale - Anxiety score (mean ± SD, N) Intervention = 8.8 ± 5.3, 21 Control = 9.7 ± 5.3, 18 Hospital Anxiety and	1-hour long psychological debriefing, by a female psychologist, in woman's own home, at approximately 2 weeks postmiscarriage. Debriefing process consisted of six phases: (1) Introductory phase = brief explanation of study, structure of the session and confidentiality issues (2) Fact phase = women asked to describe incidents in detail, beginning at pregnancy and ending at current time (3) Feeling phase = women asked to describe their feelings around particular incidents from beginning to end (4) Symptom phase = asking women to desribe any unusual sensations and any changes in their lives since miscarriage (5) Teaching phase = validation of symptoms and coping methods, information on stress symptoms and anticipatory guidance (6) Re-entry phase = answering outstanding questions, agreeing plan of action for immediate and longer-term future, and disengagement <u>Control</u> Women received a letter thanking them for the completed questionnaires and reminding them that they would	were randomised to intervention or control groups. Two days post-miscarriage, all women recruited were sent the Hospital Anxiety and Depression Scale (HADS), Impact of Events Scales (IES) and Reaction to Miscarriage Questionnaire (RMQ) by post, together with a form concerning demographic and obstetric details, whether the woman had been offered a follow-up appointment and whther she would want one should there be an opportunity. Following return of completed questionnaires, women in intervention group were offered 1-h psychological debriefing session. Approximately 4 months after miscarriage all participants received HADS, IES, RMQ and Perceptions of Care (POC) through the post.	<u>psychological outcomes of women (4-months postmiscarriage - endpoint measurement)</u> Hospital Anxiety and Depression Scale - Anxiety score (mean ± SD, N) Intervention = 7.4 ± 5.9 (21) Control = 8.1 ± 6.2 (18) Hospital Anxiety and Depression Scale - Depression score (mean ± SD, N) Intervention = 3.2 ± 4.2 (21) Control = 4.8 ± 7.0 (18) Impact of Events Scale - Intrusion score (mean ± SD, N) Intervention = 13.2 ± 11.3 (21) Control = 18.1 ± 11.5 (18) Impact of Events Scale - Avoidance score (mean ± SD, N) Intervention = 13.5 ± 12.0 (21) Control = 11.4 ± 11.3 (18) <u>Women's views/experiences of care</u> Women receiving psychological follow-up asked to rate its	and allocation concealment not reported. 60 women were recruited but 21 excluded from study: 7 women did not return questionnaires, 14 women indicated they did not wish to have a follow-up appointment. Unclear to which groups these women were randomised. **Other information** HAD anxiety score of 11 or more is threshold for 'caseness'. 'Caseness' threshold for depression score on HAD not reported. Women in the study had not had a previous miscarriage Significantly more women in the control group had tried to obtain information (from hospital staff and friends) than those in the intervention group (79% vs 29%, r = 9.39, d.f. = 1, p < 0.01)

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Study dates Not reported **Source of funding** Not reported	Depression Scale - Depression score (mean ± SD, N) Intervention = 5.5 ± 5.4, 21 Control = 7.7 ± 5.5, 18 Impact of Events Scale - Intrusion score (mean ± SD, N) Intervention = 20.3 ± 11.1, 21 Control = 24.4 ± 10.8, 18 Impact of Events Scale - Avoidance score (mean ± SD, N) Intervention = 20.5 ± 11.1, 21 Control = 17.4 ± 13.1, 18 **Inclusion criteria** Pregnancy of 6 to 19 weeks at the time of miscarriage; no previous miscarriage; aged 18 years or over; able to speak and read English fluently; had wanted the pregnancy to continue; and were not under psychological or psychiatric care, or taking psychoactive drugs at the time of miscarriage **Exclusion criteria** Women who had been intending to terminate the pregnancy because of the potential complexity of the emotional responses	receive a second set.		helpfulness on 100mm scale 'extremely unhelpful' (0) to 'extremely helpful' (100) (mean ± SD, N) Intervention = 74 ± 21.1, 21 Positive comments on care: having opportuinty to express feelings and thoughts, having someone to talk to, who listened to them. Negative comments on care: having to relive experience, limited medical knowledge of debriefer. Women commented that they would have liked more of a medical explanation for their miscarriage, as well as emotional support.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Neugebauer,R., Kline,J., Markowitz,J.C., Bleiberg,K.L., Baxi,L., Rosing,M.A., Levin,B., Keith,J., Pilot randomized controlled trial of interpersonal counseling for subsyndromal depression following miscarriage, Journal of Clinical Psychiatry, 67, 1299-1304, 2006 **Ref Id** 165952 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To test whether telephone-administered interpersonal counselling was superior to treatment as usual in reducing	**Sample size** N = 19 Intervention n = 10 Control n = 9 **Characteristics** Mean age of women = 29.7 years (SD ± 7.6) Mean gestation at time of miscarriage = 12 weeks (SD ± 5.8) 7/19 (37%) women had prior pregnancy losses <u>Depression and role functioning scores at baseline</u> HAM-D-17 (mean ± SD, N) Intervention = 18.0 ± 8.4, 10 Control = 14.8 ± 6.6, 9 Role Functioning (mean ± SD, N) Intervention = 40.1 ± 25.8, 10 Control = 48.1 ± 26.4, 9 **Inclusion criteria** 18 years or older, English- or Spanish-speaking, reachable by telephone, had a medically documented pregnancy loss within 18 weeks prior to the baseline interview and reported at least mildly elevated depressive symptoms	**Interventions** <u>Interpersonal counselling</u> The first counselling session lasted approximately 1 hour, the remaining sessions 30 minutes each. Women concluded treatment whenever they wished, without counsellor interference. Two women received 6 sessions; no others had more than 3 sessions. Three female therapists provided counselling; one an experienced psychiatric social worker and two psychotherapists. Each session included a brief review of depressive symptoms, exploration of the established interpersonal problem area(s), psychoeducation about depression and its interpersonal context, and techniques for solving interpersonal difficulties. Women were also free to seek other mental health care during the trial. <u>Treatment as usual</u> Consisted of whatever lay counselling or professional care women sought on own initiative.	**Details** Participants were women seeking medical care for miscarriage at two New York hospitals. Potential trial participants were identified by the treating clinician or through a record review by study staff. After consent was given for telephone contact, a clinically trained rater phoned patients and administered the HAM-D-17 and the Structured Clinical Interview for DSM-IV-Clinical Version to assess exclusion criteria. Enrolled women were randomly assigned, after being stratified by hospital payment status (public, private insurance) and by weeks between miscarriage and baseline interview (≤ 4, 5–7, 8–12, 13–18), to intervention or control group. Post-intervention assessment (blind to treatment assignment) with HAM-D-17 and Role Functioning scale was scheduled 9 weeks after randomisation.	**Results** <u>Emotional and psychological outcomes of women (9 weeks after randomisation)</u> HAM-D-17 (mean ± SD, N) Intervention = 11.6 ± 8.2, 10 Control = 12.9 ± 8.3, 9 Role Functioning (mean ± SD, N) Intervention = 52.2 ± 29.2, 10 Control = 62.3 ± 21.4, 9	**Limitations** Of the 151 women seeking care for miscarriage, 72 were interviewed for eligibility. 42 were ineligible because HAM-D-17 scores < 8. 19 out of the 20 eligible women gave consent to participate. 15/19 (79%) women completed post-intervention assessment; intervention = 8/10, control = 7/9. Groups were not comparable at baseline: 8/10 (80%) women in intervention group vs 4/9 (44%) in control group were Hispanic. Authors report post-intervention HAM-D-17 mean score for Hispanic women (15.3 ± 7.2; both arms combined) was significantly higher than for non-Hispanic women (7.0 ± 7.0, $p < 0.03$). Baseline HAM-D-17 scores not reported by ethnicity, however authors state that the two trial arms at baseline did not differ significantly on mean HAM-D-17 scores.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
subsyndromal depression among miscarrying women. **Study dates** October 2001 – April 2002 **Source of funding** Independent Investigator Award 001395 from the National Alliance for Research on Schizophrenia and Depression, Great Neck, N.Y., and grant NIH 1 RO3 MH59179-01A1 from the National Institutes of Health, Bethesda, Md.	(Hamilton Rating Scale for Depression - 17-item (HAM-D-17) score > 7 **Exclusion criteria** Suicidality, current major depressive disorder, substance use disorder, history of psychosis, life threatening physical illness, mental retardation, and refusal to have sessions audio-taped.				**Other information** Women completing the trial received $20 It was unclear whether the study included women who had undergone a previous miscarriage. Authors report intention to treat analysis for mean score change on HAM-D-17 and Role Functioning scales, using baseline scores for women missing post-intervention assessment. Between baseline and post-intervention assessment one woman in the treatment group and no women in the control group sought mental health care.
Full citation Swanson,K.M., Effects of caring, measurement, and time on miscarriage impact and women's well-being, Nursing Research, 48, 288-298, 1999 **Ref Id**	**Sample size** N = 242 Intervention n = 116 (early assessment n = 56, delayed assessment n = 60) Control n = 126 (early assessment n = 64, delayed assessment n = 62) **Characteristics**	**Interventions** <u>Intervention</u> Three 1-hour counselling sessions were conducted at 1, 5 and 11 weeks after enrollment in the study. When partners accompanied women to counselling, sessions began with a reminder that the purpose was to focus on the woman's experience. Sessions were	**Details** Care providers throughout the area shared recruitment pamphlets at the time of loss and during follow-up appointments. When women called the study site they were reminded there was as 50% chance of receiving counselling. A Solomon four-group	**Results** <u>Emotional and psychological outcomes of women</u> <u>6 weeks after study enrolment</u> Profile of Mood States - Emotional disturbance score (mean ± SD, N) Intervention (early assessment) = 39 ± 27.2, 43	**Limitations** All surveys were returned by 185/242 (76%) women: intervention = 90/116 (78%), control = 96/126 (76%). Loss to follow up was similar between early and delayed assessment in the intervention group but in the control group loss to follow up was 33% in the early assessment group

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
166255 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To test the effects of caring-based counselling, measurement (early versus delayed) and the passage of time on the integration of loss (miscarriage impact) and women's emotional well-being (self-esteem and moods) in the first year subsequent to miscarrying. **Study dates** Not reported **Source of funding** Funding was provided by NIH, National Institute of Nursing Research (R29	Mean age of women = 32.5 years ± 5.5 Mean gestational age at loss = 10.41 weeks ± 3.3 (79% less than 12 weeks) Mean time from miscarriage to study enrollment = 7.86 days ± 7.5 72% of women had prior pregnancies and 54.2% currently had children. 30.3% had previous miscarriages and 4.5% had late gestation losses. <u>Anxiety, depression and emotional disturbance scores at baseline (1 week after study enrolment)</u> Profile of Mood States - Emotional disturbance score (mean ± SD, N) Intervention (early assessment) = 74.9 ± 27, 43 Control (early assessment) = 68.9 ± 33.5, 40 Profile of Mood States - Anxiety score (mean ± SD, N) Intervention (early assessment) = 17.3 ± 6.7, 43 Control (early assessment) = 16.2 ± 8.1, 40 Profile of Mood States - Depression score (mean ± SD, N) Intervention (early assessment)	conducted by the principal investigator or a research associate. Session 1: women detailed coming to know and considered what was lost and possibly gained. Session 2: explored women's experiences of going public and sharing the loss. Session 3: women chronicled their own experience of getting through it and openly discussed trying again. <u>Control</u> No treatment.	randomised experimental design with delayed measurement for some was chosen to address the possibility that early survey completion (outcome measurement) could, in itself, serve as a form of treatment. Women were randomised to intervention or control, and then again to early assessment or delayed assessment. Early assessment was performed at enrollment but prior to intervention, and then at 6 weeks (1 week after counselling session 2), 4 months (5 weeks after counselling session 3) and 1 year after enrollment. Delayed assessment was performed at enrollment, and then at 4 months and 1 year after enrollment. Self-reported obstetric history and demographics was gathered at enrollment for early assessment women and at 4 months after enrollment for delayed assessment women. The same outcome data	Control (early assessment) = 46.7 ± 32.9, 40 Profile of Mood States - Anxiety score (mean ± SD, N) Intervention (early assessment) = 10 ± 5.4, 43 Control (early assessment) = 11.5 ± 7.3, 40 Profile of Mood States - Depression score (mean ± SD, N) Intervention (early assessment) = 12.1 ± 11.0, 43 Control (early assessment) = 14.8 ± 12.7, 40 <u>4 months after study enrolment</u> Profile of Mood States - Emotional disturbance score (mean ± SD, N) Intervention (early assessment) = 36.7 ± 23.5, 43 Control (early assessment) = 43 ± 35.3, 40 Profile of Mood States - Anxiety score (mean ± SD, N) Intervention (early assessment) = 10.9 ± 6.8, 43 Control (early assessment)	and 15% in the delayed assessment group. Study met sample size required for 60% chance of detecting treatment effect of 1/2 standard deviation and 90% chance of detecting treatment effect of 3/4 standard deviation. Minimial important difference and 'caseness' for the utilised scales not reported. More than two-thirds of the interventions were conducted by the principal investigator, who was also responsible for developing the counselling protocol and the caring theory tested via the investigation. The Impact of Miscarriage Scale was also developed by the principal investigator [IMS results not extracted as this is not a validated measure - as specified in review protocol] **Other information** Groups were equivalent in terms of baseline characteristics at 1 year. Authors report dropping

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
NR01899) and the University of Washington Center for Women's Health Research (1P30 NR04001)	= 27.1 ± 12.2, 43 Control (early assessment) = 24.1 ± 13.9, 40 **Inclusion criteria** At least 18 years of age, miscarried at 20 weeks or less, within 5 weeks of loss, and could speak and write English. **Exclusion criteria** Not reported		was gathered at each measurement point. Self-esteem measured by Rosenberg scale, mood states measured by Profile of Mood States (POMS), impact of miscarriage measured by Impact of Miscarriage Scale (IMS) - a scale developed and tested throughout the study by the prinicipal investigator.	= 11 ± 7.3, 40 Profile of Mood States - Depression score (mean ± SD) Intervention (early assessment) = 9.8 ± 8.7, 43 Control (early assessment) = 12.6 ± 13.7, 40 <u>12 months after study enrolment</u> Profile of Mood States - Emotional disturbance score (mean ± SD, N) Intervention (early assessment) = 30.2 ± 22.4, 43 Control (early assessment) = 35.2 ± 34.8, 40 Profile of Mood States - Anxiety score (mean ± SD) Intervention (early assessment) = 8.7 ± 5.6, 43 Control (early assessment) = 9.3 ± 7.3, 40 Profile of Mood States - Depression score (mean ± SD) Intervention (early assessment) = 8.4 ± 9.3, 43 Control (early assessment)	vigor and fatigue subscales of Profile of Mood States (POMS) scale as these would be confounded by physical pregnancy-related changes experienced by many women in first year after miscarriage. Authors report data at 1 and 6 weeks only for those women in the early assessment group (intervention and control) who completed assessment at all four timepoints. Authors report only 4 and 12 month data for women in both early and delayed assessment groups (intervention and control) who completed assessement at those time points. No baseline data reported for comparison with 4 and 12 month data. Only data for three subscales of the validated Profile of Mood States scale were extracted (data was also reported for anger and confusion subscales). Assume higher score = worse outcome. Data was not extracted for the Impact of Miscarriage scale as this was not a validated

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				= 11.4 ± 14.5, 40 [In a second table (Table 3) the authors report the following data for early and delayed assessment groups] <u>4 months after study enrolment</u> Profile of Mood States - Emotional disturbance score (mean ± SD, N) Intervention (early assessment) = 63.5 ± 32.1, 47 Intervention (delayed assessment) = 75.2 ± 36.5, 43 Control (early assessment) = 68.8 ± 44.6, 42 Control (delayed assessment) = 79.2 ± 38.0, 53 Profile of Mood States - Anxiety score (mean ± SD, N) Intervention (early assessment) = 10.4 ± 6.7, 47 Intervention (delayed assessment) =12.3 ± 6.9, 43 Control (early assessment) = 10.9 ± 7.1, 42 Control (delayed assessment) = 11.6 ± 6.6,	measure. [Data for early assessment groups used in GRADE profile]

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				53 Profile of Mood States - Depression score (mean ± SD) Intervention (early assessment) = 9.2 ± 8.5, 47 Intervention (delayed assessment) = 12.8 ± 11.7, 43 Control (early assessment) = 12.4 ± 13.4, 42 Control (delayed assessment) = 14.3 ± 12.3, 53 <u>12 months after study enrolment</u> Profile of Mood States - Emotional disturbance score (mean ± SD, N) Intervention (early assessment) = 57.3 ± 28.9, 47 Intervention (delayed assessment) = 61.5 ± 31.9, 43 Control (early assessment) = 60.7 ± 40.9, 42 Control (delayed assessment) = 66.1 ± 34.4, 53 Profile of Mood States - Anxiety score (mean ± SD) Intervention (early assessment) = 8.8 ± 5.6, 47	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Intervention (delayed assessment) = 9.9 ± 6.6, 43 Control (early assessment) = 9 ± 7.3, 42 Control (delayed assessment) = 11 ± 7.5, 53 Profile of Mood States - Depression score (mean ± SD) Intervention (early assessment) = 8 ± 9.1, 47 Intervention (delayed assessment) = 8.7 ± 7.6, 43 Control (early assessment) = 11.1 ± 14.3, 42 Control (delayed assessment) = 10.2 ± 9.6, 53	
Full citation Swanson,K.M., Chen,H.T., Graham,J.C., Wojnar,D.M., Petras,A., Resolution of depression and grief during the first year after miscarriage: a randomized controlled clinical trial of couples-focused interventions, Journal of Women's Health, 18, 1245-1257, 2009	**Sample size** N = 682 (341 couples) Nurse caring n = 168 (84/168 women) Self-caring n = 172 (86/172 women) Combined caring n = 170 (85/170 women) Control n = 172 (86/172 women) **Characteristics** Age of women - mean (years) ± SD Nurse caring = 32.7 ± 6.4	**Interventions** Nurse caring Three 1-hour counselling sessions with a nurse counsellor trained by the prinicipal investigator (Swanson), using Swanson's Caring Theory and Meaning of Miscarriage Model. Counselling took place in the couples' homes or an alternate private location. Self-caring Three videos of approximately 18 minutes each featured	**Details** Volunteer couples called the research project in response to recruitment posters, print and media ads, or pamphlets found in health care facilities. Upon receipt of consent and baseline data couples were randomised in blocks of 12, using a card-pulling procedure, to one of the three intervention groups or control group.	**Results** Emotional and psychological outcomes of women Women in all three treatment groups exhibited a faster rate of recovery from depression, measured with Center for Epidemiological Studies-Depression scale (CES-D) compared with women receiving no treatment, but only the nurse caring group had a Bayseian odds ratio > 3.2, suggesting 'substantial'	**Limitations** 46/682 (7%: 17/341 couples, plus an additional 3 women and 9 men) returned no data after baseline. The proportion of dropouts was not equal across groups: the self-caring group had the highest proportion of individuals (25/172, 14.5%) who never returned data after baseline, nurse caring group had the lowest proportion (1/168, 0.6%).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 166259 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To examine the effects of three theory-based couples-focused interventions (nurse, self, and combined caring) and a control condition (no treatment) on the rates at which women and men resolve depression and grief during the first year after miscarriage. **Study dates** January 2003 – June 2006 **Source of funding** Funding was provided	Self-caring = 32.0 ± 5.3 Combined caring = 32.5 ± 5.8 Control = 32.5 ± 6.5 <u>Days since pregnancy loss at baseline - mean ± SD</u> Nurse caring = 29.1 ± 22.7 Self-caring = 30.7 ± 24.2 Combined caring = 28.3 ± 19.5 <u>Depression at baseline for those completing study - Center for Epidemiological Studies-Depression scale - mean ± SD</u> Nurse caring = 21.4 ± 10.8 Self-caring = 16.5 ± 5.1 Combined caring = 22 ± 13.2 Control = 21.7 ± 12.5 Couples had been together for a mean of 6.9 years (SD = 4.5, range 3 months to 24 years). They had up to 6 children, with 181 couples (53.1%) having none and 107 (31.4%) having one. Women had from 1 to 6 miscarriages, with the current loss being the first for 232 (68%) women. The men in the study were statistically significantly older than the women, and were significantly less likely to have ever been treated for	Swanson coaching couples on ways to practice self and partner caring. Videos also included clips of eight ethnically diverse actors scripted as four couples sharing stories of what it eas like to go through Meaning of Miscarriage Model experiences and care for each other. Videos were accompanied by two workbooks (his and hers). Workbooks included seven daily questions that elicited reflective writing about Meaning of Miscarriage Model topics. Workbooks were not collected by the investigators. Couples returned a self-report checklist on their use of self-care modules. <u>Combined caring</u> Couples received only one 1-hour counselling session (as above). At the end of the session nurses gave the couples the first self-caring module (as above) and encouraged its use. The next two self-caring modules were mailed. <u>Control</u> No treatment.	Interventions were offered 1, 5 and 11 weeks after enrollment and took place in couples' homes. All the interventions offered at week 1 focused on 'coming to know' (balancing evidence of impending loss against hopes for a healthy pregnancy outcome) and losing and gaining. Content at 5 weeks dealt with sharing the loss and going public. Content at 11 weeks focused on getting through it and trying again. Data were gathered via mailed surveys at 1, 3, 5 and 13 months after miscarriage. Depression was assessed with the Center for Epidemiological Studies-Depression scale (CES-D). Grief was measured using two subscales (PG: focuses on thinking about the miscarriage and crying inwardly and outwardly about the lost baby; and GRE: focuses on feelings that indicate distance and distress) from the Miscarriage Grief Inventory, which was adapted from the Texas Grief Inventory.	evidence. Change in CES-D score at 3 months Nurse caring ≈ −2.9 Self-caring ≈ −2.3 Combined caring ≈ −2.3 No treatment ≈ −2.2 Change in CES-D score at 5 months Nurse caring ≈ −5.7 Self-caring ≈ −4.9 Combined caring ≈ −4.7 No treatment ≈ −4.3 Change in CES-D score at 13 months Nurse caring ≈ −8.2 Self-caring ≈ −7.1 Combined caring ≈ −6.9 No treatment ≈ −6.2 [data extracted from small Fig.2 graphs, numbers not accurate] <u>Emotional and psychological outcomes of men</u> Change in CES-D score at 3 months Nurse caring ≈ −1.8 Self-caring ≈ −0.5 Combined caring ≈ −0.4 No treatment ≈ −1.7 Change in CES-D score at	Those who dropped out had siginificantly higher than average baseline scores on the GRE subscale of the Miscarriage Grief Inventory. Authors assumed dropout status was equivalent across groups at baseline. **Other information** Couples were compensated up to $260. Scores of 16 on CES-D are associated with higher risk for clinical depression and suggest the need for further assessment. Authors report Bayesian odds ratios and use Jeffreys (1961) guidelines for interpretion: Bayesian odds ratio > 3.2 is 'substantial' evidence favouring one treatment over another, Bayesian odds ratio > 10 is 'strong' evidence.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
by the NIH, National Institute of Nursing Research, 5 R01 NR005343.	depression, anxiety, or grief. **Inclusion criteria** Couples were eligible if both agreed to participate, they reported an unplanned, unexpected loss of pregnancy prior to 20 weeks gestation, they could speak and write in English, they were in a self-proclaimed committed relationship, geographically accessible and within 3 months of loss. **Exclusion criteria** Unmarried people aged < 18 were not eligible. Couples were excluded if only one member returned the baseline survey.			5 months Nurse caring ≈ −1.7 Self-caring ≈ −1.0 bined caring ≈ −0.8 No treatment ≈ −1.6 Change in CES-D score at 13 months Nurse caring ≈ −2.7 Self-caring ≈ −1.5 Combined caring ≈ −1.3 No treatment ≈ −2.6 [data extracted from small Fig.2 graphs, numbers not accurate]	

What is the clinical and cost effectiveness of early pregnancy assessment units (EPAUs) compared with other models of service provision in improving women's clinical and psychological outcomes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Tunde-Byass,M., Cheung,V.Y., The value of the early pregnancy assessment clinic in the management of early pregnancy complications, Journal of Obstetrics and Gynaecology Canada: JOGC, 31, 841-844, 2009 **Ref Id** 69659 **Country/ies where the study was carried out** Canada **Study type** Retrospective observational study **Aim of the study** To determine whether or not an early pregnancy assessment clinic (EPAC) can reduce the number of women attending the ER for early pregnancy	**Sample size** Total assessment: Year 0 (1 year prior to the opening EPAC) n = 64113 Year 1 (January to December 2006) n = 67932 Year 2 (January to December 2007) n = 70 509 **Characteristics** Not reported **Inclusion criteria** Women who had complications of pregnancy before 20 weeks gestation **Exclusion criteria** Not reported	**Interventions** Early pregnancy assessment clinic (EPAC)	**Details** The EPAC was established at North York General Hospital in August 2005. Women with complications of pregnancy before 20 weeks' gestation were offered prompt diagnosis, options for management, bereavement counselling, and follow-up. **Opening time:** Three mornings per week from 0900 to 1200. **Staffing:** A team of dedicated gynaecologists and experienced obstetrical nurses, with on-site ultrasound (transabdominal and transvaginal) services performed by the gynaecologists. **Referral:** n = 1448 referral made between January 2006 to December 2007; 38% from ER (emergency room), 31% from family physicians, 24% from by obstetricians and gynaecologists, 2% from midwives and 5% from other sources. Women identified having miscarriages or ectopic pregnancies were counselled and were offered	**Results** **Patients requiring ER reassessment for miscarriage, ectopic pregnancy, and hemorrhage** Miscarriage Year 0 n (%) = 95/487 (19.5) Year 1 n (%) = 55/438 (12.6) Year 2 n (%) = 78/462 (16.9) Ectopic pregnancy Year 0 n (%) = 24/65 (37.0) Year 1 n (%) =14/58 (24.0) Year 2 n (%) = 9/62 (14.5) p < 0.005 (when comparing yr 0 with year 2) Haemorrhage Year 0 n (%) = 312/962 (32.4) Year 1 n (%) = 285/963 (29.6) Year 2 n (%) = 297/1079 (27.5)	**Limitations** Unclear how data were analysed and no clear report of inclusion and exclusion criteria **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
complications **Study dates** January 2006 to December 2007 **Source of funding** Not reported			appropriate interventions. Methotrexate and anti D immunoglobulin were administered in the clinic as required. Psychological support and follow-up visits were also provided when necessary. Nurses communicated by telephone with patients regarding their test results. **Data collection:** The data were reviewed from the EPAC database . The number of patients being assessed, the sources of referral, the reasons for referral, and the treatments provided in the clinic between January 2006 and December 2007 were analysed. The data for the number of patients who attended the ER for first consultation and repeat assessment were obtained from the medical record office. The records of women who presented to the ER with diagnoses of abortion, early pregnancy haemorrhage, and ectopic pregnancy during the year prior to the opening of the EPAC (July 2004 to June 2005, year 0), during the first subsequent year (January to December 2006, year 1), and during the second subsequent year (January to December 2007, year 2) were analysed. **Data analysis:** Not reported		
Full citation Brownlea,S., Holdgate,A.,	**Sample size** Total n = 346 A power calculation	**Interventions** EPPS = Early	**Details** EPPS was established in June 1996 in	**Results** Length of stay of women	**Limitations** Small study with low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Thou,S.T., Davis,G.K., Impact of an early pregnancy problem service on patient care and Emergency Department presentations, Australian and New Zealand Journal of Obstetrics and Gynaecology, 45, 108-111, 2005 **Ref Id** 104311 **Country/ies where the study was carried out** Australia **Study type** Retrospective study **Aim of the study** To examine the hypothesis that the introduction of the EPPS (early pregnancy problem service) reduced the length of stay in ED (emergency department) for women with early pregnancy problems who did not required hospital admission	based on the mean length of stay for all discharged women of 180 min in 1996 estimated that 45 women in each group would be required to detect a 50% reduction in length of stay with a power of 80% at the 5% significance level. **Characteristics** <u>1996</u> Women with early pregnancy problem n = 88 Admitted n = 37 (42%)* Discharged n = 51 (58%) US in ED n = 15 (17%) Re-presentations n = (16%)** Total women presenting to ED n = 5835 <u>1997</u> Women with early pregnancy problem n = 95 Admitted n = 41 (43%)* Discharged n = 54 (57%) US in ED n = 16 (17%) Re-presentations n = 12 (13%)** Total women presenting to ED n = 6018 <u>2000</u> Women with early pregnancy problem n = 82 Admitted n = 28 (34%)* Discharged n = 54 (66%) US in ED n = 11 (13%) Re-presentations n = 12 (15%)**	pregnancy problem service	order to streamline care of women with complications in the first trimester of pregnancy. Data were collected from January and February (prior to establishment of EPPS) and 1997 (6 months after the establishment of EPPS), 2000 and 2003. EPPS was also intended to provide an alternative site of referral (other than ED) for women seen in the community with early pregnancy problems. Women referred to EPPS were reviewed on the following weekday morning by an obstetrics and gynaecology registrar who was able to perform a transvaginal US. The clinic received referral from ED and general practice for stable women with pain and bleeding in the first 12 weeks of pregnancy. Women presenting to the ED with EPP were identified by an initial screen of potentially relevant diagnostic codes in the ED Information System (EDIS), followed by a review of the full medical records by the single blinded abstractor. <u>Data collection:</u> From the EDIS database 364 women met the inclusion criteria. Data were collected from EDIS database and medical records then compared over a one month period for the years 1996, 1997, 2000 and 2003. Data on EPPS were collected from the month of January and February in 1997, 2000 and 2003.	<u>discharged from the ED</u> <u>1996 n = 51</u> Mean (minutes): 183 Median (minutes): 136* % departed within 3 h: 60%** <u>1997 n = 54</u> Mean (minutes): 165 Median (minutes): 107* % departed within 3 h: 64%** <u>2000 n = 54</u> Mean (minutes): 89 Median (minutes): 76* % departed within 3 h: 90%** <u>2003 n = 52</u> Mean (minutes): 126 Median (minutes): 107* % departed within 3 h: 86% * All year p < 0.001 Kruskal test ** All year p < 0.0001 chi-square <u>Proportion of women with EPP who represented to the ED with further pain and/or bleeding</u> 1996: 16% 2003: 7 %	statistical power, it was estimated that 229 women per group would have been required to determine whether the observed difference in re-presentation rates was significant at the 5% level (power 80%) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates January and February in 1996 (prior to establishment of EPPS), 1997 (6 months after establishment of EPPS), 2000 and 2003 (current EPPD activity) **Source of funding** Not reported	Total women presenting to ED n = 6376 <u>2003</u> Women with early pregnancy problem n = 81 Admitted n = 29 (36%)* Discharged n = 52 (64%) US in ED n = 7 (9%) Re-presentations n = 6 (7%)** Total women presenting to ED n = 7013 * p = 0.6 for proportion of women admitted to hospital ** p = 0.15 for proportion representing in ED **Inclusion criteria** Women with pain and/or bleeding in the 12 weeks of pregnancy, with pregnancy confirmed by β-hCG and/or ultrasound. **Exclusion criteria** Not reported		<u>Analysis:</u> Data were analysed using the Chi squared test and Mantel Haenszel test for trend, continuous outcomes were compared using Mann-Whitney U and Kruskal-Wallis test in SPSS. <u>Referral:</u> Made by GP and emergency department (ED) <u>Staffing:</u> Women were reviewed in EPPS by an obstetrics and gynaecology registrar who were able to perform a transvaginal US. <u>Opening time</u> Not clearly reported	p = 0.15 <u>Proportion of women with EPP who requiring hospital admission</u> 1996: 42% 2003: 36% p = 0.6 <u>Proportion of ED presentations women with early pregnancy unit</u> 1996: 1.5% 2003: 1.1 % p = 0.09	
Full citation Bigrigg,M.A., Read,M.D., Management of women referred to early pregnancy assessment unit: care and cost effectiveness, BMJ, 302, 577-579, 1991	**Sample size** Total n = 1141 **Characteristics** Pregnant women with pain and bleeding in early pregnancy. No	**Interventions** Early pregnancy assessment unit (EPAU)	**Details** <u>Management procedure before July 1989 (before EPAU):</u> After admission most women who did not require emergency treatment had to wait, often for some time, until the appropriate investigations could be arranged to confirm the diagnosis.	**Results** The number of women referred or admitted, the length of stay in hospital, and the cost of treatment were compared for the two periods.	**Limitations** Inconsistent with the study's claim and objective, the efficacy of EPAU in the care of women with pain and bleeding was not thoroughly assessed. Length of stay and the related cost

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 104329 **Country/ies where the study was carried out** UK **Study type** Retrospective observational cohort study **Aim of the study** To assess the efficiency of an early pregnancy assessment unit (EPAU) in the care of women with bleeding and/or pain in early pregnancy **Study dates** January 1989 to July 1990 **Source of funding** Not reported	other characteristics reported **Inclusion criteria** All women admitted to the hospital with pain or bleeding in early pregnancy in the 6 months before the EPAU was set up (1st January to 30 June 1989) and all those referred to the unit in its first year (17 July 1989 to 16 July 1990). **Exclusion criteria** Not reported		Most of these women had a viable pregnancy and were subsequently allowed home. Those who required either an evacuation of retained products of conception or laparoscopy often had to wait again until a space was found on the "urgent" operating list; in many cases space was found only late at night. MANAGEMENT PROCEDURE OF UNIT BETWEEN JULY 1989 TO JULY 1990 (after EPAU): When a woman required a referral for bleeding or pain in early pregnancy, or both, her GP contacted the on duty SHO and made an appointment for her at 8.15 am on the next day, provided that the woman was not shocked or bleeding heavily, in which case she was admitted to hospital immediately. Women who had had a previous ectopic pregnancy were also seen in the day assessment unit to confirm the presence of an intrauterine pregnancy. The SHO took a brief history including parity, gravidity, and length of amenorrhoea. Venepuncture was performed and a full blood count and blood group analysis was done. While waiting for the results the woman had ultrasonography. Referral Made by GP Opening time seven days a week (time not reported)	**Results of assessment in women admitted to hospital or referred to early assessment unit with pain or bleeding in early pregnancy** Six months before unit opened (n=370): Viable pregnancy n = 118 (32%) Possible viable pregnancy (repeat ultrasonography required) n = 20 (5%) Evacuation of uterus required n = 196 (53%) Not pregnant or complete abortion n = 18 (5%) Laparoscopy required n = 18 (5%) First year of unit's operation (n=771) Viable pregnancy n = 292 (38%) Possible viable pregnancy (repeat ultrasonography required) n = 88 (11%) Evacuation of uterus required n = 233 (30%) Not pregnant or complete abortion n = 125 (16%) Laparoscopy required n = 33 (4%) Hospital stay for women who required no treatment	effectiveness was assessed in the study. Data analysis method not reported **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Staffing in EPAU The woman was then seen again by the SHO, who looked at the results and decided on the appropriate management . Assessment of the woman were completed by 10.00 am. The duty registrar and consultants were available on site at this time if necessary. Women not requiring admission will have spent an average of less than two hours in the hospital.	Before EPAU: 1.5 days (range 0.5 to 3 days) After EPAU: 2 hours Hospital stay for women requiring evacuation of the uterus Before EPAU: 3 days (1.5 to 5 days) After EPAU: 1 day (Maximum 1.5 days) Between n = 318 and 505 women were estimated to have been saved from unnecessary admission during the study period, and n = 233 had their stay reduced; the associated saving was between £95,000 and £120,000 Cost of management and savings produced by assessment unit women requiring admission: Cost of dilatation and curettage as day case £80 Cost of dilatation and curettage as overnight stay £130 Saving per case £50 Total saving= 233 x £50 = £11 650 Women admitted unnecessarily:	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Cost of overnight stay without treatment £90 Total saving based on extrapolated data= 934 x £90 = £84060 Total saving based on first year's data= 1216 x £90 = £109440	
Full citation Bignardi,T., Burnet,S., Alhamdan,D., Lu,C., Pardey,J., Benzie,R., Condous,G., Management of women referred to an acute gynecology unit: impact of an ultrasound-based model of care, Ultrasound in Obstetrics and Gynecology, 35, 344-348, 2010 **Ref Id** 134899 **Country/ies where the study was carried out** Australia **Study type** Before and after retrospective observational study	**Sample size** Total: n = 290 Before establishment of the AGU: n = 133 After establishment of the AGU: n = 157 **Characteristics** No statistically significant differences observed between the two groups in age, reason for presentation (pelvic pain, follow up after expectant management). The frequency of vaginal bleeding was significantly higher in traditional model of care (Before AGU) p = 0.007 and more women in After AGU group were presented for pregnancy viability check (p = 0.02) No statistically significant differences observed between the two groups in intrauterine pregnancy, failing pregnancy, and ectopic pregnancy. n = 96/133 (72%) women in	**Interventions** Acute Gynaecology Unit (AGU)	**Details** Data were prospectively collected from women presented with acute gyaenecological symptoms to Nepean Hospital prior to the establishment of the AGU, and after the unit had been established for 4 months. <u>Before AGU:</u> In the traditional model of care, before the of the AGU establishment, women with gynaecological problems were assessed initially in the emergency department (ED), and then referred to the gynaecology team for further assessment. An initial assessment consisted of history taking and clinical examination. Then a decision was made whether an ultrasound examination was required. If ultrasound was required, it was arranged through the radiology or perinatal ultrasound department. Following the scan, the woman was re-reviewed by the gynaecology team to make a care plan. This information was recorded prospectively on the data sheet <u>After AGU:</u>	**Results** Before AGU: n = 133 After AGU: n = 157 <u>Mean time to see trainee gynaecologist (min)</u> Before AGU: 205 min After AGU: 172 P = 0.00089 <u>Mean time to ultrasound examination (min)</u> Before AGU: 533 After AGU: 199 P = < 0.0001 <u>Admission rate (%)</u> Before AGU: n = 48/133 (36.1) Before AGU: n = 11/157 (7) P =< 0.0001 <u>Admitted for purpose of ultrasound examination (%)</u>	**Limitations** More advanced model of ultrasound was used in after AGU group. Ultrasounds were carried out by more senior person in the after AGU group. Only two third of women in the study were pregnant. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate the impact of an ultrasound-based model of care, the AGU, in the management of women with acute gynaecological problems. **Study dates** Between July and September 2006, prior to the establishment of the AGU, and between March and May 2007, i.e. after the unit had been established for 4 months. **Source of funding** Not reported	Before AUG group and n = 103/157 (65%) women in After AUG group were pregnant **Inclusion criteria** All clinically stable women with a positive pregnancy test and all clinically stable women with any gynaecological problem **Exclusion criteria** Women were excluded from study: With incomplete records Women already inpatient at the time of referral for acute gynaecological symptoms		After the AGU establishment, all clinically stable women with a positive pregnancy test and all clinically stable women with any gynaecological complaint underwent history taking, clinical examination and systematic TVs (transvaginal scan) of the pelvis by G.C (a named consultant in charge of the unit on a daily basis). The same data sheet as was used before the AGU was filled out prospectively. Women were followed-up until a final diagnosis was made. Final diagnoses were made on the basis of swab results, biochemical data, ultrasound follow-up or histological confirmation. The AGU was not a walk-in centre and women had to be referred by another practitioner. the majority of women were referred directly from ED or by their GP. <u>Staffing:</u> A named consultant was in charge of the unit on a daily basis who performed history taking and ultrasound. <u>Opening time:</u> Monday to Friday between 9.00 am to 13.00 pm. <u>Statistical analysis</u> Data were analysed using R. Two-sample Welch t-tests were used to compare continuous variables. In order to normalise data with skewed distributions, log transformation was applied before the tests. Categorical variables were analysed using chi-	Before AGU: n = 20/133 (15) After AGU: n = 4/157 (2.5) P = 0.00028 <u>Mean length of stay as outpatient</u> Before AGU: 248 (min) After AGU: 45 (min) P < 0.0001 <u>Mean length of stay as inpatient</u> Before AGU: 833 (min) After AGU: 274 (min) P = 0.0111 <u>Total occupied bed days</u> Before AGU: 85 After AGU: 30 P < 0.0001 <u>Surgery (n%)</u> Before AGU n = 39/133 (29.3) After AGU n = 21/157 (13.4) P = 0.00025 <u>Expectant management (n%)</u> Before AGU n = 11/133 (8.3) After AGU n = 40/157	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			square tests or Fisher's exact tests.	(25.5) P = 0.00023 <u>Medical management (n%)</u> Before AGU n = 5/133 (3.8) After AGU n = 7/157 (4.5) P = 0.9984 **Costs of bed occupancy and saving by an AUG** <u>Total bed occupancy (days)</u> Before AGU: 85 After AGU: 30 <u>Total cost of the period ($)</u> Before AGU: 47600 After AGU: 16800 <u>Daily cost ($)</u> Before AGU: 1034.8 After AGU: 329.4 **<u>Annual saving: $257617</u>**	

What is the appropriate model for service organisation and delivery of EPAUs?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Akhter,P., Padmanabhan,A., Babiker,W., Sayed,A., Molelekwa,V., Geary,M., Introduction of an early pregnancy assessment unit: audit on the first 6 months of service, Irish Journal of Medical Science, 176, 23-26, 2007 **Ref Id** 69234 **Country/ies where the study was carried out** Ireland **Study type** Retrospective audit **Aim of the study** To monitor the first 6 months of the EPAU service to identify short comings and ensure effective future EPAU care **Study dates**	**Sample size** Women: N = 650 attended the clinic (However only 605 (92%) had charts available to review and 2 were excluded for not being pregnant) Clinics: N = 1 **Characteristics** 310 (51.2%) of women presented with pain, 405 (66.9%) presented with light bleeding, and 80 (13.2%) presented with heavy bleeding **Inclusion criteria** Women attending the EPAU during the study period **Exclusion criteria** Not reported	**Interventions** EPAU (based in Rotunda Hospital)	**Details** A retrospective case note review was carried out during the study period. Patients' charts were reviewed for a variety of information, although the majority of outcomes are not relevant for this review question.	**Results** **Staff that run the clinic:** Senior sonographer Junior doctor Dedicated counselling midwife (Note: consultant input is required in complicated cases) **Number of patients attending** 650 women attended during the study period (approximately 6 months) **Source of referral (n (%))** Self-referred: 502 (83.4%) The remainder were referred by their GP or the A&E department of other hospitals. **Waiting time/hours (range):** 1 - 3 **Women who required a repeat scan (n%):** 121 (20%) **Further details reported** The clinic is based in a hospital in a dedicated clinic area. It is open Monday to Friday from 7.30 am to 10 am. The setting is separate from the antenatal clinic and has a dedicated area for counselling.	**Limitations** Single unit's experience **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
July to December 2002 **Source of funding** None stated				There is easy access to lab facilities, and TVU is available when needed.	
Full citation Tunde-Byass,M., Cheung,V.Y., The value of the early pregnancy assessment clinic in the management of early pregnancy complications, Journal of Obstetrics and Gynaecology Canada: JOGC, 31, 841-844, 2009 **Ref Id** 69659 **Country/ies where the study was carried out** Canada **Study type** Retrospective observational study **Aim of the study** To determine the value of the early pregnancy assessment clinic (EPAC) in the management of early	**Sample size** Women: N = 1448 Clinics: N = 1 **Characteristics** **Reasons for referral (n (%))** Missed miscarriage: 450 (31%) Threatened miscarriage: 471 (32.5%) Complete miscarriage: 182 (12.6%) Ectopic: 111 (7.7%) Incomplete miscarriage: 59 (4.1%) Hyperemesis gravidarum: 23 (1.6%) Other: 152 (10.5%) **Inclusion criteria** Not reported **Exclusion criteria** Not reported	**Interventions** Early pregnancy assessment clinic	**Details** The database for the EPAC was reviewed, to establish the sources of referral, reasons for referral and treatments provided. Data was collected from year 0 (1 year prior to opening of EPAC), year 1 and year 2 following the opening of the EPAC.	**Results** **Source of referrals (n/total (%))** ER: 557/1448 (38.5%) Family physicians: 445/1448 (30.7%) Obstetrician-gynaecologists: 349/1448 (24.1%) Midwives: 30/1448 (2.1%) Other sources: 67/1448 (4.6%) **Staff** The clinic is run by a team of dedicated gynaecologists and experienced obstetrical nurses. On-site ultrasound (TVA and TVU) is performed by gynaecologists, and there is easy access to laboratory services and readily available operating room services. The clinic nurse is responsible for taking blood and sending lab samples. **Further details reported** The clinic is open three mornings per week from 9 – 12. New referrals are booked to be seen within 24 hours. **Number of women presenting to the ER for miscarriage, ectopic pregnancy or haemorrhage, out of**	**Limitations** Indirectness: the clinic admits women with complications of pregnancy up to 20 weeks gestation. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pregnancy complications and its effect on the number of emergency room (ER) visits **Study dates** Year 0: July 2004 to June 2005 Year 1: January to December 2006 Year 2: January to December 2007 **Source of funding** None stated				**<u>total ER presentations (n/total (%))</u>** Year 0: 1514/64113 (2.4%) Year 1: 1459/67932 (2.1%) Year 2: 1603/70509 (2.3%) (NS) **<u>Number of women requiring repeat ER assessment for miscarriage, ectopic pregnancy or haemorrhage (n/total (%))</u>** Year 0: 431/1514 (28.5%) Year 1: 354/1459 (24.3%) Year 2: 384/1603 (24.0%)	
Full citation Hill,K., Improving services provided in an early pregnancy assessment clinic, Nursing Times, 105, 18-19, 2009 **Ref Id** 71236 **Country/ies where the study was carried out** UK **Study type** Patient satisfaction survey	**Sample size** Women: N = 82 Clinics: N = 1 **Characteristics** The clinic assesses women who are 6-18 weeks pregnancy and experiencing complications, such as pain and bleeding, have had prior tubal surgery, or experienced an ectopic **Inclusion criteria**	**Interventions** Early pregnancy assessment clinic (EPAC)	**Details** The clinical audit was carried out over three months to monitor patient throughput and timekeeping, and to improve these if needed. The survey was conducted at the clinical over a 2 month period, and had a 100% response rate. Answers were anonymous, with patients posting completed questionnaires into a sealed box.	**Results** **<u>Number of patients seen</u>** 82 over a two-month period **<u>Results of audit</u>** **<u>Patients seen on time (n/total (%))</u>** Yes: 217/237 (92%) No: 1/237 (0.4%) Not stated: 12/237 (5%) N/A: 2/237 (0.8%) DNA: 5/237 (2%) **<u>Source of referral (n/total (%))</u>** A&E: 24/230 (10%)	**Limitations** Unclear how audit was done. Reporting one clinic's experience only (non-comparative) Indirectness: women up to 18 weeks pregnant are eligible to attend the clinic **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and clinical audit **Aim of the study** To improve the service's quality and promote high standards of care **Study dates** Not reported **Source of funding** None stated	Not reported **Exclusion criteria** Not reported			Reg: 3/230 (1%) Antenatal: 8/230 (3%) Consultant: 27/230 (12%) EPAC: 44/230 (19%) GP: 96/230 (42%) Jas: 2/230 (0.9%) Midwife: 14/230 (6%) Rescan: 3/230 (1%) SHO: 9/230 (4%) **Acceptable wait for EPAC appointment referral (n (%))** Yes: 161 (68%) No: 1 (0%) Probable rescans or further treatment: 75 (32%) **Results of patient survey** **Patients seen on time (n (%))** Yes: 79 (96%) No: 3 (4%) **Patient felt wait for appointment was acceptable (n (%))** Yes: 76 (94%) No: 5 (6%) **Patient felt care in scanning department was given in a sensitive manner (n (%))** Yes: 80 (99%) No: 1 (1%) **Sonographer explained results in**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				a way that patients could understand (n (%)) Yes: 81 (99%) No: 1 (1%) **Patient given information leaflet(s) (n (%))** Yes: 50 (61%) No: 32 (39%) **Patients found leaflets useful (n (%))** Yes: 46 (94%) No: 3 (6%) **Patients felt they were given a thorough explanation (n (%))** Yes: 81 (99%) No: 1 (1%) **Patients felt questions were answered in a way they could understand (n (%))** Yes: 80 (98%) No: 2 (2%) **Patient satisfaction with interaction with different staff (n/total (%))** **a. Receptionist** Excellent: 27/63 (43%) Good: 30/63 (48%) Fair: 5/63 (8%) Poor: 1/63 (2%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				b. EPAC Nurse Specialist Excellent: 76/82 (93%) Good: 6/82 (7%) Fair: 0/82 Poor: 0/82 **c. Sonographers** Excellent: 66/81 (81%) Good: 14/81 (17%) Fair: 1/81 (1%) Poor: 0/81 **d. Doctors** Excellent: 13/22 (59%) Good: 9/22 (41%) Fair: 0/22 Poor: 0/22 **Patient satisfaction with privacy, dignity and care (n/total (%))** **a. Privacy** Excellent: 65/80 (81%) Good: 14/80 (18%) Fair: 1/80 (1%) Poor: 0/80 (0%) **b. Dignity** Excellent: 69/80 (86%) Good: 11/80 (14%) Fair: 0/80 (0%) Poor: 0/80 (0%) **c. Care** Excellent: 69/80 (86%) Good: 11/80 (14%) Fair: 0/80 (0%) Poor: 0/80 (0%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Staff The clinic is staffed by a nurse, two ultrasonographers, and, when required, an on-call registrar **Further details reported** The clinic is open weekday mornings. **Number of patients seen** 82 patients were seen over a 2 month period, according to the 100% response rate of the survey.	
Full citation Shillito,J., Walker,J.J., Early pregnancy assessment units, British Journal of Hospital Medicine, 58, 505-509, 1997 **Ref Id** 71962 **Country/ies where the study was carried out** UK **Study type** Descriptive, non-comparative study **Aim of the study**	**Sample size** Women: N = 100 Clinics: N = 1 **Characteristics** No relevant characteristics reported **Inclusion criteria** Women attending the clinic **Exclusion criteria** Not reported	**Interventions** EPAU	**Details** This is simply a descriptive paper, describing one hospital's experience in opening and running an EPAU	**Results** **Prior to the EPAU (1994)** Admissions to ward with early pregnancy bleeding: 506 Proportion staying at least 1 night: 457/506 (90%) Maximum stay/days: 5 **Post EPAU survey** Out of 100 women, over half wanted to see a specialist nurse and < 10% expected to see a doctor during their visit. Workload/week (average): 30 Time of discharge (%) Same day: 89 - Immediately: 80 - After same-day evacuation: 9	**Limitations** Non-comparative study - simply reports one clinic's experience. Methodology of data collection is not reported. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not stated **Study dates** Unclear **Source of funding** Not stated				**Referrals** Most come from GPs or through A&E. **Other details reported** The clinic is open Monday to Friday from 8 am to 12.30 pm; however staff deal with telephone enquiries until 8 pm. The unit is in a specific area on the outpatient floor with a dedicated scan room and day room.	
Full citation Harper,J., Midwives and miscarriage: the development of an early pregnancy unit, MIDIRS Midwifery Digest, 13, 183-185, 2003 **Ref Id** 78157 **Country/ies where the study was carried out** UK **Study type** Descriptive study, non-comparative **Aim of the study** To explore the relationship that midwives have with	**Sample size** Not applicable **Characteristics** No characteristics relevant to this review question are reported **Inclusion criteria** Not applicable **Exclusion criteria** Not applicable	**Interventions** Early pregnancy unit (EPU)	**Details** This is a descriptive study, documenting the experience of running an EPU in a hospital in Bolton.	**Results** **Referrals** Referrals are taken from: - miscarriage assessment clinic based in the women's health care department (Monday to Friday 9 - 12) - antenatal clinic - GPs - A&E - Self referrals - Team-based midwives **Staffing** Care is provided by a midwife, with later referral to medical personnel if needed. **Out of hours care** Women are provided with a 24-hour telephone advice number following miscarriage management	**Limitations** Women up to 24 weeks gestation are eligible to visit the clinic Non-comparative study, simply reporting one clinic's experience. Methodology of data collection is not reported. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
women who are experiencing miscarriage and pregnancy loss under 24 weeks, and the subsequent patterns of care and management provided **Study dates** Not reported **Source of funding** None stated					
Full citation Edey,K., Draycott,T., Akande,V., Early pregnancy assessment units, Clinical Obstetrics and Gynecology, 50, 146-153, 2007 **Ref Id** 91225 **Country/ies where the study was carried out** UK **Study type** Descriptive, non-comparative study **Aim of the study**	**Sample size** Clinics: N = 1 **Characteristics** Not reported **Inclusion criteria** Not applicable **Exclusion criteria** Not applicable	**Interventions** Early pregnancy assessment unit (EPAU)	**Details** This is simply a description of the authors' experiences at an EPAU in Bristol.	**Results** **<u>Staffing</u>** An audit of the unit found that only 29% of the women needed to be seen by the junior doctor in the clinic, with the rest being managed by the sonographer and nurse practitioner. **<u>Source of referrals (%)</u>** GPs: 40 A&E: 2 (No further details given) **<u>Availability of out of hours care</u>** The clinic is open daily, but no further details are given. It is unclear whether this includes weekends or not. **<u>Further details reported</u>**	**Limitations** Non-comparative study, simply reporting one clinic's experiences **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To discuss the clinic structure, referral process, and ongoing challenges **Study dates** Not reported **Source of funding** None stated				The clinic is held adjacent to the gynecology clinic, to avoid contact with women with a more advanced pregnancy.	
Full citation Sellappan,K., Mcgeown,A., Archer,A., A survey to assess the efficiency of an early pregnancy unit, International Journal of Gynecology and Obstetrics, #19th FIGO World Congress of Gynecology and Obstetrics Cape Town South Africa. Conference Start, S542-, 2009 **Ref Id** 101346 **Country/ies where the study was carried out** UK (Northern Ireland) **Study type** Prospective questionnaire	**Sample size** Women: N = 188 Clinics: N = 1 **Characteristics** 51% presented at 7 – 9 weeks gestation **<u>Reason for presentation (n (%))</u>** Bleeding/staining per vagina: 81 (43%) Abdominal pain: 45 (23.9%) The remainder presented for anxiety, recurrent miscarriage, repeat US, and post road traffic	**Interventions** Early pregnancy unit	**Details** This was a prospective questionnaire audit of patients attending the EPU during the study period. Questionnaires were designed and distributed to patients, and the data was analysed manually.	**Results** **<u>Source of referral (n/total (%))</u>** GP: 90/188 (47.8%) Self-referral: 31/188 (16.5) Emergency department: 17/188 (9%) (Note: this does not total 100% - no further details reported) **<u>Proportion of women managed by each type of practitioner (n/total (%))</u>** Midwives only: 125/188 (66.5%) Medical staff: 45/188 (23.9%) (Note: the women seen by 'midwives only' were seen, scanned and managed by midwives, and did not have input from medical staff) **<u>Waiting time/minutes (n)</u>** Up to 30 minutes: 95	**Limitations** Missing data: 50/188 women have missing data for how they were referred to the EPAU. 18/188 women have missing data for who they were managed by. An estimated 20/188 women have missing data for waiting time. Poster presentation with few details given **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
audit **Aim of the study** To monitor service provision, waiting time, staffing and to identify shortcomings so as to ensure effective care of patients presenting at the early pregnancy unit (EPU) To identify sources of referrals, reason behind referrals and waiting time in clinic **Study dates** May – June 2008 **Source of funding** None stated	accidents **Inclusion criteria** Women attending an EPU **Exclusion criteria** Not reported			Up to 60 minutes: 55 More than 60 minutes: 18 (Note: these are estimates measured from a graph) Average waiting time: 11 minutes **Need for a repeat scan:** 25/188 (13.3%) **Further details reported** The clinic also reported that it was adequately staffed on all days except for 5 during the study period, but does not give any further details to do with how many study days there were, and what constitutes adequate staffing	
Full citation Davies,M., Geoghegan,J., Developing an early pregnancy assessment unit, Nursing Times, 90, 36-37, 1994 **Ref Id** 104273 **Country/ies where the**	**Sample size** Not applicable **Characteristics** Not applicable **Inclusion criteria** Not applicable	**Interventions** Early pregnancy assessment unit	**Details** This is a descriptive study, detailing the model of care in a single EPAU.	**Results** **Staffing** The unit is nurse-led; however there is also a team consisting of ward clerks, doctors, scan stenographers and phlebotomists. Stenographers perform the scans in the morning, and then the registrar compares the patient's history with the scan results and makes a diagnosis. **Referrals**	**Limitations** Non-comparative study, just detailing the experience of one clinic. Methodology of data collection is not reported. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out UK **Study type** Descriptive study **Aim of the study** To describe the work of a nurse-rin early pregnnacy assessment service in Sheffield **Study dates** Not reported **Source of funding** None stated	**Exclusion criteria** Not applicable			Referrals are taken from GPs. **<u>Number of women seen</u>** The unit can accomodate 6 scans per day.	
Full citation Fox,R., Savage,R., Evans,T., Moore,L., Early pregnancy assessment; a role for the gynaecology nurse-practitioner, Journal of Obstetrics and Gynaecology, 19, 615-616, 1999 **Ref Id** 104283 **Country/ies where the**	**Sample size** Women: N = 198 **Characteristics** No characteristics relevant to this question were reported. **Inclusion criteria**	**Interventions** Early pregnancy assessment clinic (EPAC)	**Details** The case notes of 200 consecutive new referrals were reviewed to determine what proportion were cared for by the nurse-practitioner alone. 2 of the records were missing. The case notes were evaluated to assess whether the initial categorisation of the nurse was correct, according to the written guidelines, and to establish whether anti-D was given correctly.	**Results** **<u>Staff providing care (n/total (%))</u>** Nurse only: 120/198 (61%) Requiring medical assessment: 78/198 (39%) **<u>Referrals</u>** Women are referred by midwives or GPs. **<u>Further details reported</u>** The EPAC is open 5 days a week.	**Limitations** Retrospective case series **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out UK **Study type** Retrospective case review, non-comparative **Aim of the study** To determine whether an early pregnancy clinic could be run safely by a nurse practitioner **Study dates** Unclear **Source of funding** None stated	Not reported **Exclusion criteria** Not reported		All admissions for ectopic pregnancy over a 6 month period were retrieved from the computerised record to establish whether the care given in the EPAC was sufficient.	The nurse practitioner had prior experience of working in an EPAC, and then gained additional expertise by attending consultant gynaecology and obstetrics ultrasound clinics. The nurse also took a diploma course for obstetric ultrasonography. In all 198 cases, the nurse had made the correct classification. No ectopics were missed during the first 6 months of the clinic.	
Full citation Twigg,J., Moshy,R., Walker,J.J., Evans,J., Early pregnancy assessment units in the United Kingdom: An audit of current clinical practice, Journal of Clinical Excellence, 4, 391-402, 2003 **Ref Id** 104284	**Sample size** Clinics: N = 103 **Characteristics** No relevant details reported **Inclusion criteria** Units that provide an early	**Interventions** EPAU	**Details** At the time of the study, there was no official way of establishing which hospitals in the UK had an EPAU. Therefore, the authors had to devise a way of identifying them. The authors identified a list of District Tutors of the RCOG (accurate at March 2000) and contracted them with an audit form and covering letter which they were asked to forward to the individual managing their	**Results** **<u>Characteristics of scanning practitioners (%)</u>** **<u>a. Status</u>** Ultrasonographer: 52.0 Radiologist: 2.0 Gynaecologist: 11.8 Gynaecology nurse: 4.9 Other: 2.9 Midwife: 2.9 Combination: 23.5	**Limitations** The authors state that there is missing data, therefore the results are just reported as %. 153/256 (60%) of questionnaires were not returned. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out UK **Study type** Postal, questionnaire-based audit **Aim of the study** To determine existing standards of clinical practice, facilities and support services available to EPAUs within the UK **Study dates** March 2000 **Source of funding** None stated	pregnancy assesment service **Exclusion criteria** None reported		local EPAU. The questionnaire addressed the following areas of service provision: - ultrasound scanning - information technology and audit - EPAU facilities - clinical access - gynaecological support services - patient and staff support A total of 256 tutors were contacted, of whom 103 questionnaires were returned. The authors then did a random telephone survey of 85 units in six regions from the District Tutor list. Of those, 11.7% did not have an EPAU service. Therefore, the authors calculated that the estimated numbers of EPAUs returning completed questionnaires was 45.6%.	**b. Qualifications** DMU: 55.9 PgC: 5.9 FRCR: 2.0 RCR: 18.6 RCOG Dip: 1.0 None: 2.0 Non-respondents: 14.7 **c. Proficiency** Regular audit of clinical competence: 54.9 Formal training in breaking bad news: 54.9 **Location of ultrasound equipment (%)** EPAU: 33 Antenatal clinic: 25 Gynaecology department: 10.3 Radiology: 14.4 **Referral systems (%)** Other clinicians and GPS: 100 Direct from patient: 51 Other (e.g. midwives, A&E, gynaecology): 21 **Availability of service (%)** Weekday only: 77.4 Seven-day: 13.7 Once per week: 1 24-hour: 7	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Further details reported 51.5% of units said that all patients were seen by a gynaecologist. 95.8% of EPAUs said that they received adequate gynaecology back-up.	
Full citation Brownlea,S., Holdgate,A., Thou,S.T., Davis,G.K., Impact of an early pregnancy problem service on patient care and Emergency Department presentations, Australian and New Zealand Journal of Obstetrics and Gynaecology, 45, 108-111, 2005 **Ref Id** 104311 **Country/ies where the study was carried out** Australia **Study type** Retrospective study comparing before and after the opening of an Early Pregnancy Problem Service (EPPS) **Aim of the study**	**Sample size** Women: N = 364 Clinic: N = 1 **Characteristics** **Inclusion criteria** Pain and/or bleeding in the first 12 weeks of pregnancy Pregnancy confirmed using hCG or ultrasound **Exclusion criteria** Pregnancy related problems beyond 12 weeks Non-pregnancy related bleeding	**Interventions** EPPS (early pregnancy problem service)	**Details** This study was a retrospective chart review of women with pain and bleeding in the first 12 weeks of pregnancy. Data from 1996 (prior to establishment of EPPS) were compared to 1997 (6 months after establishment of EPPS), 2000 and 2003.	**Results** **Number of patients seen (n)** Jan – Feb 1997: 15 Jan – Feb 2003: 61 **Referrals** Referrals are received from both the emergency department (ED) and the GP. No appointment is needed. Referrals from the emergency department only occur after they have undergone clinical assessment and had blood sent for quantitative hCG and blood group analysis. - % of referrals from a non-ED source 1997: 26% 2003: 48% **Proportion of ED patients with pain and/or bleeding in first 12 weeks (n/total (%))** 1996: 88/5835 (1.5%) 1997: 95/6018 (1.6%) 2000: 82/6376 (1.3%) 2003: 81/7013 (1.2%) (p = 0.09)	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To examine the hypothesis that the introduction of the early pregnancy problem service (EPPS) reduced the length of stay in the emergency department for women with early pregnancy issues who did not require admission **Study dates** January – February 1996 (pre-EPPS), 1997, 2000, 2003 (post-EPPS) **Source of funding** None reported				**Proportion of patients discharged from the ED who were followed up in the EPPS (n/total (%))** 1997: 11/54 (20%) 2003: 36/52 (69%) **Proportion of EPP patients re-presenting to ED with further pain and/or bleeding (n/total (%))** 1996: 14/88 (16%) 1997: 12/95 (13%) 2000: 12/82 (15%) 2003: 6/81 (7%) **Length of stay of EPP patients discharged from ED / minutes (mean / median)** 1996: 183 / 136 (n = 51) 1997: 165 / 107 (n = 54) 2000: 89 / 76 (n = 54) 2003: 126 / 107 (n = 52) (Median: p<0.001) **Proportion of patients departing within 3 hours from ED (%)** 1996: 60% (n = 51) 1997: 64% (n = 54) 2000: 90% (n = 54) 2003: 86% (n = 52) (Chi-square: P < 0.001) **Proportion of EPP patients requiring hospital admission (n/total (%))**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1996: 37/88 (42%) 1997: 41/95 (43%) 2000: 28/82 (34%) 2003: 29/81 (36%) (p = 0.6 for trend) **Staff** The referred patients are reviewed by an obstetrics and gynecology registrar who performs TVU. **Proportion of women discharged within 3 hours of seeing a doctor (%)** Pre-EPPS: 60% Post-EPPS: 86% **Further details reported** This clinic is based at a hospital, and patients referred to the clinic are reviewed the following weekday morning.	
Full citation Bigrigg,M.A., Read,M.D., Management of women referred to early pregnancy assessment unit: care and cost effectiveness, BMJ, 302, 577-579, 1991 **Ref Id** 104329 **Country/ies where the**	**Sample size** N = 1141 (This is the total study sample size; however the population of interest for this review is only women seen once the EPAU was set up, which is 771) **Characteristics**	**Interventions** Early pregnancy assessment unit	**Details** This was a chart review of the women referred to the EPAU in the first year following its establishment. (Data comparing before and after is reported in another review and is not relevant for this review question). For women with pain and bleeding in early pregnancy, her GP contacts the duty SHO and	**Results** **Staffing** Women are seen by a senior house officer; however a registrar and consultant are available on site if needed. **Referral** Referrals are made through GPs	**Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out UK **Study type** Retrospective observational study **Aim of the study** To assess the efficiency of an early pregnancy assessment unit in the care of women with pain or bleeding in early pregnancy **Study dates** 1st January to 30 June 1989 (prior to EPAU) 17th July 1989 to 16th July 1990 (first year of EPAU) **Source of funding** None stated	No characteristics relevant to this review question were reported **Inclusion criteria** Women admitted with pain and bleeding **Exclusion criteria** Not reported		makes an appointment for the next day. The woman is asked to bring a sample of urine. The duty SHO then takes a brief history, and venepuncture, FBC and blood group analysis is done. While waiting for the results, the woman had an ultrasound. She is then seen again by the SHO, who decides on appropriate management. A duty registrar and consultant are available on site if needed.	**Length of stay / days** a. maximum: 1.5 b. for women with a viable IUP or not pregnant: 0.08 [reported as 2 hours] c. for women needing evacuation of the uterus: 1 **Need for repeat ultrasound (%):** 11 **Number of women seen** In the first year of operation, 771 women were referred to the unit. **Further details reported** The unit is open seven days a week. There is a limited on-call system, and out-of-hours operating is avoided.	
Full citation Bignardi,T., Burnet,S., Alhamdan,D., Lu,C., Pardey,J., Benzie,R., Condous,G., Management of women referred to an acute gynecology unit: impact of an ultrasound-based model of	**Sample size** Women: N = 290 (however, only 157 were seen following the establishment of the AGU and therefore constitute the population of interest for this review)	**Interventions** Acute gynaecological unit (AGU)	**Details** This study assessed women presenting with acute gynaecological symptoms before and after the establishment of the AGU; however, the comparison data is covered in another review in this guideline; therefore only	**Results** **Waiting time / minutes (mean) (n = 157)** a. to see trainee gynaecologist: 172 b. for ultrasound examination: 199 **Admission rate (n (%))**	**Limitations** 47/157 (30%) of the women seen were not pregnant and therefore do not match the population of interest for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
care, Ultrasound in Obstetrics and Gynecology, 35, 344-348, 2010 **Ref Id** 134899 **Country/ies where the study was carried out** Australia **Study type** Prospective comparative observational study **Aim of the study** To assess the impact of the introduction of an ultrasound based model of care for women with acute gynaecological complications **Study dates** Prior to AGU: July – September 2006 Post AGU: March – May 2007 **Source of funding** None stated	Clinics: N = 1 **Characteristics** 67 (42.7%) of women presented with vaginal bleeding, 37 (23.6%) presented with pelvic pain, 15 (9.6%) presented for a pregnancy viability check, and 10 (6.4%) presented for a follow-up of expectant management. **Inclusion criteria** Women with first trimester vaginal bleeding with or without lower abdominal pain are eligible to be seen at the AGU. In addition, women who are not pregnant, with lower abdominal pain or abnormal bleeding can be seen there. **Exclusion criteria**		data from post-AGU will be reported here. The AGU is an ultrasound based unit, aiming to provide rapid diagnostic and management services for women with acute gynaecological and early pregnancy complications. It also aims to provide training for obstetric and gynaecological trainees. In the AGU, all clinically stable women with a gynaecological complaint underwent history-taking, examination, and transvaginal ultrasound by a consultant. Women were followed up until a diagnosis was made. Final diagnosis was made on the basis of swab results, biochemical data, ultrasound or histological confirmation.	a. Total: 11 (7) b. For ultrasound: 4 (2.5) **Length of stay/minutes (mean)** a. as an outpatient: 45 b. as an inpatient: 274 **Staffing** A consultant is in charge of the unit on a day to day basis **Referrals** Women must be referred by another medical practitioner (walk-ins are not permitted). The majority are referred by the Emergency Department or by their GP. **Further details reported** The clinic is open from 9 am until 1 pm Monday to Friday.	this review. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Poddar,A., Tyagi,J., Hawkins,E., Opemuyi,I., Standards of care provided by Early Pregnancy Assessment Units (EPAU): A UK-wide survey, Journal of Obstetrics & Gynaecology,J Obstet Gynaecol, 31, 640-644, 2011 **Ref Id** 152044 **Country/ies where the study was carried out** UK **Study type** Cross-sectional survey **Aim of the study** To assess the standard of services provided by the EPAUs across the UK against the benchmark set by the RCOG **Study dates** April to June 2010	**Sample size** Clinics: N = 140 **Characteristics** **<u>Location of the unit (n (%))</u>** Southeast and London: 30 (21%) Southwest: 11 (8%) East England: 10 (7%) West Midlands: 16 (11%) Wales: 9 (6%) East Midlands: 10 (7%) Northwest: 12 (9%) Yorkshire: 11 (8%) Northeast: 4 (3%) Scotland: 19 (14%) Northern Ireland: 2 (1%) Not disclosed: 6 (4%) **Inclusion criteria** Early pregnancy assessment unit, attached to an NHS hospital, and registered on the Association of Early Pregnancy Units (AEPU) website **Exclusion criteria** None reported	**Interventions** EPAU	**Details** A questionnaire was designed, with the questions presented in a nominal response format. The authors identified 181 EPAUs that were attached to an NHS hospital and listed as members on the Association of Early Pregnancy Units website. The questionnaire was piloted by telephone 19 of the units at random from the list of 181. A total of 162 letters were posted to the remaining EPAUs, containing a questionnaire, a covering letter to the clinical lead, and an envelope. Out of the letters sent out, 121 (75%) postal questionnaires were returned. The 19 telephone results were added to that, giving a total of 140 responses.	**Results** **<u>Practitioner performing ultrasound scans (n/total (%))</u>** Sonographers: 67/140 (47.9%) EPAU nurse specialist: 12/140 (8.6%) Trained midwife: 7/140 (5%) Medical staff: 2/140 (1.4%) Combination: 52/140 (37.1%) **<u>Direct referral system for women (n/total (%))</u>** a. With previous EP: 125/140 (89%) b. With recurrent miscarriage: 113/140 (81%) **<u>Availability of service in clinics (n/total (%))</u>** **Weekday:** 3-5 hours each weekday: 47/135 (34.8%) 6-11 hours each weekday: 74/135 (54.8%) 3 days a week: 1/135 (0.7%) 2 hours a day: 1/135 (0.7%) Mean opening time/hours: 7.3±3.6 Median (range) opening time/hours: 8 (2 - 24) **Weekend:** Full or partial weekend service: 42/140 (30%) - Open Saturday and Sunday: 21/140 (15%) - Open Saturday: 11/140 (7.9%)	**Limitations** Out of 250 known EPAUs in the UK, only 181 were registered on the association website **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding None reported				- Open Sunday: 8/140 (5.7%) Inconsistent weekend service: 2/140 (1.4%) **Availability of 24 hour contact telephone number** For women receiving conservative/medical miscarriage management: 103/140 (74%) For women receiving MTX for ectopic pregnancy: 99/125 (79%) **Location of EPAU (n/total (%))** Gynaecology ward: 46/140 (32.9%) Dedicated area: 44/140 (31.4%) Outpatient department: 29/140 (20.7%) Antenatal clinic: 18/140 (12.9%) Ultrasound department: 2/140 (1.4%) Not reported: 1/140 (0.7%)	

What are the signs and symptoms associated with ectopic pregnancy?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Barnhart,K.T., Rinaudo,P., Hummel,A., Pena,J., Sammel,M.D., Chittams,J., Acute and chronic presentation of ectopic pregnancy may be two clinical entities, Fertility and Sterility, 80, 1345-1351, 2003 **Ref Id** 68010 **Country/ies where the study was carried out** USA **Study type** Case-series **Aim of the study** To compare women with "early" or acute presentation with those with "late" or chronic presentations of ectopic pregnancy	**Sample size** N=452 **Characteristics** **Age/years (mean):** 28.6 **Gravida (mean):** 3.6 **Parity (mean):** 1.2 **Duration of amenorrhea/days (mean):** 45.0 **Duration of bleeding/days (mean):** 8.5 **Race (% African American):** 377/452 (83.4) **Inclusion Criteria** Diagnosed with ectopic pregnancy **Exclusion Criteria** Not reported	**Tests** Index test History taking and physical examination Reference test Unclear, however it is reported that some patients were managed surgically and some medically; therefore ectopic pregnancy is likely to have been diagnosed through ultrasound or laparoscopy.	**Methods** The Department of Obstetrics and Gynaecology at the University of Pennsylvania Medical Centre has an electronic data management system. All patients at risk for an ectopic pregnancy are entered into a database and followed until definitive diagnosis. This study evaluates the database and medical records of 452 patients diagnosed with ectopic pregnancy during the study period. Historic risk factors and findings at presentation were evaluated. Data were taken from operative records, outpatient charts and inpatient charts using a uniform data collection sheet. Data were then entered into an Excel database.	**Results** **Frequency of symptoms (number with symptom/total ectopics (%))** Pain as primary complaint: 329/452 (72.8) Bleeding as primary complaint: 336/452 (74.3) Severity of bleeding at presentation: - No bleeding: 116/452 (25.7) - Mild bleeding: 270/452 (59.7) - Moderate bleeding: 60/452 (13.3) - Severe bleeding: 6/452 (1.3) **Frequency of signs on examination (number with sign/total ectopics (%)** Orthostasis on presentation: 21/452 (4.6) Ultrasound report at presentation: - Definitive EP: 90/452 (19.9) - Suspicious for EP: 152/452 (33.6)	**Limitations** Retrospective Unclear who entered the data of symptoms in to the database originally. Type or location of pain is not defined Exclusion criteria not reported **Other information** 60/452 (13.3%) of the ectopics were ruptured. **Site of ectopic** Cornual: 40/452 (8.8) Isthmic: 74/452 (16.4) Ampullary/distal: 269/452 (59.5) Fimbriae or aborting: 22/452 (4.9) Entire tube: 48/452 (10.6) Cervical, ovarian or abdominal: 8/452 (1.8) Note: this study is conducted in the same location and time period as another included study (Barnhart et al. 2006);

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
to look for differences in the patient characteristics and short-term sequelae of the disease. **Study dates** 1993 to 1998 **Source of funding** National Institutes of Health				- Nondiagnostic: 195/452 (43.1) - Non-viable IUP: 14/452 (3.1) Positive cervical cultures (Neisseria gonorrheae or Chlamydia trachomatis): 22/452 (4.9)	therefore they are likely to be the same population of ectopic pregnancies. Presenting symptoms are reported in more detail in this study and therefore are detailed here. Risk factors are analysed in more detail in the other study, and are detailed in that study.
Full citation Banerjee,S., Aslam,N., Zosmer,N., Woelfer,B., Jurkovic,D., The expectant management of women with early pregnancy of unknown location, Ultrasound in Obstetrics and Gynecology, 14, 231-236, 1999 **Ref Id** 69257 **Country/ies where the study was carried out**	**Sample size** N=127 (However only 64 were diagnosed as spontaneously resolving and 18 as ectopic pregnancy, therefore the population of interest is N=82) **Characteristics** **Final outcome (number/total (%))** Ectopic pregnancy: 18/127 (14.2) Spontaneous resolution: 64/127 (50.4) Miscarriage: 11/127 (8.7) Normal pregnancy: 34/127	**Tests** Index test History taking Reference test **Ectopic pregnancy:** diagnosed using laparoscopy or ultrasound **Spontaneous resolution:** decrease of serum hCG levels to below 20 IU/l and complete resolution of symptoms without intervention	**Methods** This is a prospective observational study of women attending an EPAU. Women were referred for ultrasound by their GP or A&E. A full history was taken, and physical examination performed in all cases. All women had a positive pregnancy test. The diagnosis of PUL was made at the initial visit in all women with no evidence of an intrauterine or extrauterine pregnancy on transvaginal scan. Women with PUL were managed expectantly on an outpatient basis. They were advised not to travel, to avoid sexual intercourse, and to return immediately if their pain increased significantly. Follow-up	**Results** (Note: where possible, ORs were calculated by the technical team, comparing odds of the risk factor or symptom in those with EP vs. odds in all other outcomes (i.e. spontaneous resolution, miscarriage and normal pregnancy) **Frequency of possible risk factors for ectopic pregnancy** **a. Number of previous elective abortions (median (range))** Ectopic pregnancy: 0 (0-2) Spontaneous resolution: 0	**Limitations** Type or location of pain is not reported Incidence of risk factors is not reported (except PID), therefore it is impossible to judge what % of women presented with the risk factor. Unclear who collected the initial signs and symptoms data n=18 for ectopic pregnancies. **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
UK **Study type** Prospective cohort study **Aim of the study** To assess the results of expectant management in women with pregnancy of unknown location and to identify diagnostic parameters that are predictive of spontaneous pregnancy resolution. **Study dates** August 1997 to March 1998 **Source of funding** Not reported	(26.8) Note: the following are only reported for spontaneously resolving pregnancies and ectopic pregnancies, as they are the population of interest for this review question. **Age/years (mean (95% CI))** Ectopic pregnancy: 29.8 (18.9-40.8) Spontaneous resolution: 29.6 (15.5-43.7) **Duration of amenorrhea/days (mean (95% CI))** Ectopic pregnancy: 52.1 (22.4-81.9) Spontaneous resolution: 51.3 (24.3-78.3) **Gravida (median (range))** Ectopic pregnancy: 3.5 (1-6) Spontaneous resolution: 2.5 (1-10) **Inclusion Criteria** Pregnancy of unknown location (defined as no		appointments were arranged for 2-3 days later, and continued until a final diagnosis was reached. **Diagnosis of final outcome** Normal pregnancy: diagnosed in women with a normally growing intrauterine gestational sac and detectable live embryo on follow-up scans Miscarriage: diagnosed histologically, following surgical evacuation, or by ultrasound Ectopic pregnancy: diagnosed at laparoscopy or at ultrasound in women that received medical treatment Spontaneous resolution: defined as a decrease of serum hCG to below 20 IU/l and complete resolution without need for any therapeutic intervention Data regarding past obstetric and gynaecological history were recorded in a database. This papers aims to identify parameters that predict spontaneous resolution by creating a logistic model. However this is not relevant to this review question, and	(0-4) Miscarriage: 0 (0-3) Normal pregnancy: 0 (0-5) **b. Number of previous miscarriages (median (range))** Ectopic pregnancy: 0 (0-3) Spontaneous resolution: 0 (0-3) Miscarriage: 1 (0-3) Normal pregnancy: 0 (0-5) **c. Number of previous caesareans (median (range))** Ectopic pregnancy: 0.5 (0-2) Spontaneous resolution: 0 (0-2) Miscarriage: 0 (0-1) Normal pregnancy: 0 (0-0) **d. Number of previous ectopic pregnancies (median (range))** Ectopic pregnancy: 0 (0-1) Spontaneous resolution: 0 (0-1) Miscarriage: 0 (0-1) Normal pregnancy: 0 (0-1) **e. Past history of PID (number/total (%))**	PUL population None of the ectopics were ruptured; location is not reported.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	evidence of an intrauterine or ectopic pregnancy on transvaginal scan) **Exclusion Criteria** Early pregnancy sac-like structure in the uterine cavity that needed follow-up for verification Adnexal mass believed to be ectopic pregnancy Clinically unstable patients Indirect signs of a specific pregnancy location Products of conception visualised on speculum examination		therefore methodological details have not been reported here. Only prevalence of risk factors and signs and symptoms will be reported here. Similarly, only data for ectopic pregnancies and spontaneous resolving pregnancies (whose location is not reported, and hence could be ectopics) will be reported.	Ectopic pregnancy: 3/18 (16.7) Spontaneous resolution: 9/64 (14.1) Miscarriage: 2/11 (18.2) Normal pregnancy: 6/34 (17.6) OR (95% CI): 1.08 (0.28 - 4.15) **Frequency of symptoms (number with symptoms/total (%))** **a. Pain** Ectopic pregnancy: 11/18 (61.1) Spontaneous resolution: 45/64 (70.3) Miscarriage: 6/11 (54.5) Normal pregnancy: 27/34 (79.4) OR (95% CI): 0.62 (0.22 - 1.76) **b. Bleeding** Ectopic pregnancy: 13/18 (72.2) Spontaneous resolution: 61/64 (95.3) Miscarriage: 5/11 (45.5) Normal pregnancy: 6/34 (17.6) OR (95% CI): 1.34 (0.44 -	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				4.03)	
Full citation Makinen,J., Nikkanen,V., Kivikoski,A., Problems and benefits in early diagnosis of ectopic pregnancy, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 16, 381-391, 1984 **Ref Id** 69499 **Country/ies where the study was carried out** Finland **Study type** Case-series **Aim of the study** To show certain features and trends characteristic of ectopic pregnancy and it's early	**Sample size** N=168 **Characteristics** **Age/years (mean (range)):** 29.7 (15-44) **Inclusion Criteria** Histologically confirmed diagnosis of ectopic pregnancy **Exclusion Criteria** Not reported	**Tests** Index test History taking Reference test Surgical confirmation	**Methods** During the study period, 168 consecutive patients with a histologically confirmed diagnosis of ectopic pregnancy were operated on at the Central Hospital of Paijat-Hame, Finland. This study is a retrospective review of available records. The diagnostic procedures used in reaching the final diagnosis include pregnancy tests, grey scale and real-time ultrasound, curettage, culdocentesis, laparoscopy and laparotomy.	**Results** **Frequency of possible risk factors (number with risk factor/total ectopics (%))** Abdominal surgery: 82/168 (48.8) Tubal surgery: 27/168 (16.1) Appendectomy: 27/168 (16.1) IUCD in situ: 56/168 (33.3) Low-dose progestogen: 1/168 (0.6) PID: 20/168 (11.9) Ectopic pregnancy: 21/168 (12.5) Infertility: 21/168 (12.5) Induced abortion: 25/168 (14.9) Miscarriage: 19/168 (11.3) Endometriosis: 6/168 (3.6)	**Limitations** Retrospective Unclear who initially recorded the signs and symptoms data, and who extracted the data from the records. Exclusion criteria are not reported. **Other information** **Type of ectopic pregnancy (number/total (%))** Tubal: 163/168 (97.0) Ovarian: 3/168 (1.8) Tubo-ovarian: 2/168 (1.2) Note: rupture of the oviduct had occurred in 79/165 (47.9%) cases 81/168 (48.2%) of patients had a positive pregnancy test (unclear if this is because of negative test results or tests not performed).

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
diagnosis, and their relation to diagnostic delay. **Study dates** January 1977 to December 1981 **Source of funding** Not reported				Sterilisation: 1/168 (0.6) No predisposing factors: 40/168 (23.8) **Frequency of symptoms (number with symptom/total ectopics (%))** Abdominal pain: 151/168 (89.9) Shoulder pain: 21/168 (12.5) Spotting: 108/168 (64.3) Profuse bleeding: 20/168 (11.9) No clear amenorrhea: 60/168 (35.7) Nausea: 26/168 (15.5) Breast tenderness: 43/168 (25.6) Note: signs and symptoms were also analysed separately for those with and without an IUCD in situ. There were no significant differences except in the % of each group with no clear amenorrhea (51.8% in those with an IUCD, compared to 27.7% in those without an IUCD).	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Hutton,J.D., Narayan,R., Is ectopic pregnancy too often diagnosed too late?, New Zealand Medical Journal, 99, 3-5, 1986 **Ref Id** 69774 **Country/ies where the study was carried out** New Zealand **Study type** Case-series **Aim of the study** To report the predisposing factors and presenting symptoms and signs of all women admitted with an ectopic pregnancy during the study period, and relate these to their outcomes, including the time to definitive diagnosis, type of surgery and need for	**Sample size** N=177 **Characteristics** The race, age and parity distributions showed no predominance when compared with patients delivering at the same hospital, except that 12% of women were aged over 35 years old. **Gestational age** - <6 weeks: 60/177 (34) - 6-7 weeks: 64/177 (36) - 8-9 weeks: 39/177 (22) **Inclusion Criteria** Tubal ectopic pregnancy **Exclusion Criteria** Not reported	**Tests** Index test History taking and physical examination Reference test Visualisation of extrauterine gestation at laparotomy or laparoscopy, in all but 2 cases (where it was felt that expulsion was complete)	**Methods** The records of all tubal ectopic pregnancies diagnosed at the National Women's Hospital in 1979 and 1980 were reviewed retrospectively. The diagnosis was established by laparotomy or laparoscopy in all but two cases. The interrelationships of various predisposing factors, presenting signs and symptoms, diagnostic investigations, treatment and outcomes were analysed using SPSS. Statistical analysis was performed using chi-squared tests or Pearson's rank correlation coefficient.	**Results** **Frequency of risk factors (number with risk factor/total ectopics (%))** **History of previous pelvic infection:** 44/177 (24.9) **Contraceptive use at point of conception** - No contraception: 144/177 (81.4) - IUCD: 19/177 (10.7) - Oral contraceptive: 7/177 (4.0) - Mini-pill: 5/177 (2.8) - Barrier methods: 2/177 (11.3) **History of infertility** - At least 2 years: 67/177 (37.9) - At least 5 years: 24/177 (13.6) **Frequency of symptoms (number with symptom/total ectopics (%))** **Lower abdominal pain:** 99 **Vaginal bleeding:** 82 **Fainting:** 28 **Shoulder-tip pain:** 23	**Limitations** Retrospective Unclear who collected the data in the first place. Unclear who reviewed the records. **Other information** 68/177 (38.4%) of the ectopics were ruptured. A urinary pregnancy test was done on admission in 121 women, of which 87 (72%) tested positive.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
a blood transfusion. **Study dates** 1979-1980 **Source of funding** Not reported				**Frequency of signs at examination (%)** **Shock:** 10 **Pelvic tenderness:** 91 **Rebound abdominal tenderness:** 86 **Palpable pelvic mass:** 19 (Note: the authors report that fainting, shoulder-tip pain and shock commonly occurred together, p<0.01)	
Full citation Jiao,L.Z., Zhao,J., Wan,X.R., Liu,X.Y., Feng,F.Z., Ren,T., Xiang,Y., Diagnosis and treatment of cesarean scar pregnancy, Chinese Medical Sciences Journal, 23, 10-15, 2008 **Ref Id** 69926 **Country/ies where the study was carried out** China	**Sample size** N=28 **Characteristics** **Age/years (mean (range)):** 31.4 (26 - 42) **Gravidity (mean (range)):** 3.3 (2 - 7) **Parity (mean (range)):** 1.2 (1 - 2) **Duration of amenorrhea/days (range):** 39 - 80	**Tests** Index test History taking Reference test Ultrasound, MRI	**Methods** During the study, 2663 ectopic pregnancies were diagnosed at Peking Union Medical College Hospital. 28 of them were diagnosed as caesarean scar pregnancies and constitute the study population. The clinical data of the patients were obtained from medical files, and analysed retrospectively. The following information was collected: age, gravidity, parity, previous history of caesarean, interval from last caesarean to diagnosis, clinical presentation, results of auxiliary examination, location of pregnancy, diagnosis, treatment and follow-up.	**Results** **Medical history linked to previous caesareans** **Number of previous caesareans (number/total (%)):** **1:** 26/28 (92.9) **>1:** 2/28 (7.1) **Interval from last caesarean section to delivery/years (mean (range)):** 5.5 (0.3 - 15) **Frequency of symptoms (number with symptoms/total ectopics (%))** **Amenorrhea:** 27/28 (96.4)	**Limitations** Retrospective Unclear who collected medical history in the first place, and who extracted it from the files. Exclusion criteria not reported. Many of the participants had undergone prior treatment for a misdiagnosis. **Other information** CAESAREAN SCAR PREGNANCIES ONLY

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Case-series **Aim of the study** To investigate the early diagnosis and treatment of caesarean scar pregnancy. **Study dates** January 1994 to April 2007 **Source of funding** Not reported	**Inclusion Criteria** Caesarean scar pregnancy **Exclusion Criteria** Not reported			**Severe vaginal bleeding:** 11/28 (39.3) (It is reported that these were the most common symptoms; no details of other presenting signs and symptoms are given)	**<u>Clinical presentations (number/total (%))</u>** Persistent vaginal bleeding after intrauterine pregnancy interruption: 10/28 (35.7) Failure of medical abortion: 6/28 (21.4) Amenorrhea followed by irregular vaginal bleeding: 5/28 (17.9) Amenorrhea without vaginal bleeding: 3/28 (10.7) Slow rise or fall in hCG after suction curettage: 3/28 (10.7) Irregular vaginal bleeding with no amenorrhea: 1/28 (3.6) Note: 19/28 were primarily diagnosed as other diseases (early intrauterine pregnancies, gestational trophoblastic tumours). Therefore, 16 of them had undergone medical abortion, curettage or chemotherapy in other facilities before admission. 9/28 were definitely diagnosed of caesarean scar pregnancies before

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					treatment, using ultrasound (n=8) or MRI (n=1).
Full citation Buckley,R.G., King,K.J., Disney,J.D., Ambroz,P.K., Gorman,J.D., Klausen,J.H., Derivation of a clinical prediction model for the emergency department diagnosis of ectopic pregnancy, Academic Emergency Medicine, 5, 951-960, 1998 **Ref Id** 70825 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To assess the value and limitations of individual clinical	**Sample size** N=486 (however only 39 were ectopic pregnancies, and hence constitute the population of interest for this review question) **Characteristics** **<u>Characteristics of patients with ectopic pregnancy</u>** **Age/years (mean (SD)):** 26.1 (6.1) **Estimated gestational age/years (mean (SD)):** 39 (18) (p<0.001 when compared to non-ectopic pregnancies) **hCG <2000 mIU/ml:** 22/39 (56%) (p<0.001 when compared to non-ectopic pregnancies) **Ultrasonography during ED visit:** 23/39 (59%) **Inclusion Criteria** Presenting with first	**Tests** <u>Index test</u> History taking and physical examination <u>Reference test</u> Visualisation of extrauterine gestation at laparotomy or laparoscopy, or ultrasound visualisation.	**Methods** This study was conducted in the emergency department of a large tertiary care teaching hospital of the US Navy. All patients are seen under the direct supervision of residency-trained, board-eligible, or board certified emergency physicians. Ultrasound is available 24 hours a day, performd in the radiology department and interpreted by a radiologist. This study included all haemodynamically stable patients presenting with abdominal pain or vaginal bleeding during the study period. Patients were included in a prospective clinical registry. 104 patients were excluded (see exclusion criteria) and 7 were lost to follow-up, leaving 486 patients available for analysis. A templated clinical data collection form was completed, and a standard blood panel (including CBC, urinalysis, blood typing, serum hCG and progesterone) was ordered. To facilitate data collection and encourage the inclusion of all eligible patients, the data forms were approved by the hospital to be used as a substitute for the written or dictated history and physical	**Results** **<u>Frequency of clinical findings (number with finding/total ectopics (%))</u>** **a. Absence of fetal heart tones:** 39/39 (100) **b. Absence of tissue at cervical os:** 39/39 (100) **c. Pain other than midline cramping:** 38/39 (97.4) **d. Any abdominal pain:** 38/39 (97.4) **e. Absence of tissue passed by history:** 38/39 (97.4) **f. Absence of open cervical os:** 38/39 (97.4) **g. Estimated gestational age <70 days:** 37/39 (94.9) **h. Any abdominal tenderness:** 33/39 (84.6) **i. Any pelvic abnormality:** 30/39 (76.9) **j. Any adnexal tenderness:** 27/39 (69.2)	**Limitations** Only includes women with pain and/or bleeding. **Other information** Note: 12/39 ectopics were ruptured

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
findings to predict the presence or absence of ectopic pregnancy. To derive a clinical prediction model that could potentially help clinicians estimate the probability of ectopic pregnancy. **Study dates** August 1994 to September 1995 **Source of funding** Not reported	trimester abdominal pain or vaginal bleeding **Exclusion Criteria** Prior documentation of an intrauterine pregnancy on ultrasound Enrolled on a previous emergency department visit Gestational age of ≥ 13 weeks (based on first day of last normal period and uterine size)		examination. To encourage blinding, physicians were encouraged to complete the history and physical examination portions of the form before obtaining lab or ultrasound results. All patients were followed longitudinally until a diagnosis was reached. The criteria for diagnosis of an ectopic pregnancy was as follows: - Direct visualisation of an extrauterine gestation on laparoscopy or laparotomy - For non-surgical cases, an empty uterine cavity on ultrasound accompanied by visualisation of an adnexal mass with significant free peritoneal fluid, adnexal ring, or an adnexal sac that contains a yolk sac or fetal pole The association between clinical variables and the presence or absence of ectopic pregnancy was assessed. Sensitivity, specificity, PPV and NPV with 95% CI were calculated.	**k. Any vaginal bleeding:** 27/39 (69.2) **l. Any cervical motion tenderness:** 13/39 (33.3) **m. Any ectopic risk factors:** 9/39 (23.1) **n. Abdominal peritoneal signs:** 9/39 (23.1) **o. Definite cervical motion tenderness:** 9/39 (23.1) **p. Discrete adnexal mass:** 2/29 (5.1) **<u>Other diagnostic accuracy measures for each clinical finding</u>** **a. Absence of fetal heart tones:** Specificity: 5.8 PPV: 8.5 NPV: 100 LR+: 1.06 LR-: 0.00 **b. Absence of tissue at cervical os:** Specificity: 2.0 PPV: 8.2 NPV: 100 LR+: 1.02 LR-: 0.00 **c. Pain other than midline**	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				cramping: Specificity: 21.3 PPV: 9.7 NPV: 99.0 LR+: 1.24 LR-: 0.12 **d. Any abdominal pain:** Specificity: 15.3 PPV: 9.1 NPV: 98.5 LR+: 1.15 LR-: 0.17 **e. Absence of tissue passed by history:** Specificity: 6.9 PPV: 8.4 NPV: 96.9 LR+: 1.05 LR-: 0.38 **f. Absence of open cervical os:** Specificity: 6.5 PPV: 8.3 NPV: 96.7 LR+: 1.04 LR-: 0.40 **g. Estimated gestational age <70 days:** Specificity: 26.6 PPV: 10.1 NPV: 98.3 LR+: 1.29 LR-: 0.19 **h. Any abdominal tenderness:**	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Specificity: 50.1 PPV: 12.9 NPV: 97.4 LR+: 1.70 LR-: 0.31 **i. Any pelvic abnormality:** Specificity: 53.5 PPV: 12.7 NPV: 96.4 LR+: 1.66 LR-: 0.43 **j. Any adnexal tenderness:** Specificity: 62.0 PPV: 13.7 NPV: 95.8 LR+: 1.82 LR-: 0.50 **k. Any vaginal bleeding:** Specificity: 26.2 PPV: 7.6 NPV: 90.7 LR+: 0.94 LR-: 1.18 **l. Any cervical motion tenderness:** Specificity: 90.8 PPV: 24.1 NPV: 94.0 LR+: 3.62 LR-: 0.73 **m. Any ectopic risk factors:** Specificity: 83.4 PPV: NR	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				NPV: 92.6 LR+: 1.39 LR-: 0.92 **n. Abdominal peritoneal signs:** Specificity: 94.9 PPV: 28.1 NPV: 93.4 LR+: 4.52 LR-: 0.81 **o. Definite cervical motion tenderness:** Specificity: 97.3 PPV: 42.9 NPV: 93.5 LR+: 8.56 LR-: 0.79 **p. Discrete adnexal mass:** Specificity: 96.4 PPV: 11.1 NPV: 92.1 LR+: 1.42 LR-: 0.98	
Full citation Condous,G., Van,Calster B., Kirk,E., Haider,Z., Timmerman,D., Van,Huffel S., Bourne,T., Clinical information does not improve the performance of mathematical models in predicting the	**Sample size** N=376 (however, only 27 were diagnosed as ectopic pregnancy, and hence constitute the main population of interest for this review)	**Tests** Index test Ultrasound, history taking Reference test **Ectopic pregnancy:** diagnosed using transvaginal ultrasound and/or	**Methods** Women were seen in an EPAU during the study period. Women classified as having a PUL (see inclusion criteria) were followed up using hCG, ultrasound and/or laparoscopy until final clinical outcomes were established. The outcomes were defined as follows: - Failing PUL: serum	**Results** **Frequency of signs and symptoms (number/total (%))** (Note: the odds ratios (OR) reported have been calculated by the technical team, for the odds of the symptom in diagnosed EP vs. the odds in any other outcome (i.e. failing PUL	**Limitations** No details of individual risk factors are reported. Location of the ectopics is not reported. **Other information** PUL population

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
outcome of pregnancies of unknown location, Fertility and Sterility, 88, 572-580, 2007 **Ref Id** 70932 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** To see if the incorporation of clinical variables can improve the diagnostic performance of logistic regression models in the prediction of pregancy of unknown location outcome. **Study dates** March 2002 to July	**Characteristics** **Final outcome (number/total (%))** Failing PUL: 203/376 (54.0) EP: 17/376 (4.5) IUP: 140/376 (3.7) Persisting PUL: 6/376 (1.6) **Inclusion Criteria** Pregnancy of unknown location, diagnosed with transvaginal ultrasound as no signs of an intra- or extra-uterine pregnancy or RPOC in a woman with a positive pregnancy test **Exclusion Criteria** Any evidence of an intrauterine sac at first scan Adnexal mass thought to be an ectopic pregnancy at initial scan Endometrial thickness of >15 mm on transvaginal scan, with the presence of heterogenous irregular tissues within the uterus (thought to be an	laparoscopy **Failing PUL:** serum progesterone at presentation <20 nmol/l, with a subsequent drop in hCG to below 5 IU/l and location remaining unknown	progesterone at presentation <20 nmol/l, with a subsequent drop in hCG to below 5 IU/l and location remaining unknown - Intrauterine pregnancy: made using transvaginal ultrasound when a gestational sac was visualised within the endometrial cavity - EP: diagnosed using ultrasound, and/or laparoscopy with confirmatory histology of the chorionic villi. Risk factors, and the presence of pain/bleeding on entry to the study were recorded. However, risk factors were only reported as a sum (i.e. the total number of risk factors in a given woman). The risk factors investigated were: PID, STI, previous EP, endometriosis, infertility, fertility treatment, past surgical history and contraceptive use. This data was used to create a model to predict the outcome of PULs. However, this model is not relevant to this review question, and methodological details and results will not be reported here. Only data on presenting signs/symptoms will be reported.	and IUP)) **a. Abdominal pain** Any EP: 20/27 (74.1) Failing PUL: 134/203 (66.0) IUP: 98/140 (70) OR (95% CI): 1.37 (0.56 - 3.33) Left iliac fossa EP: 4/27 (14.8) Failing PUL: 17/203 (8.4) IUP: 24/140 (17.1) OR (95% CI): 1.28 (0.42 - 3.89) Right iliac fossa EP: 3/27 (11.1) Failing PUL: 8/203 (3.9) IUP: 18/140 (12.9) OR (95% CI): 1.52 (0.43 - 5.40) Central lower abdominal pain EP: 13/27 (48.1) Failing PUL: 109/203 (53.7) IUP: 56/140 (40) OR (95% CI): 1.00 (0.46 - 2.19) **b. Vaginal bleeding** Any	Training and test data sets have been combined, as this dichotomy is not relevant to this review question.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
2003 **Source of funding** Research Council of the Katholieke Universiteit Leuven Flemish Government Research communities ICCoS and ANMMM Belgian Federal Government EU	incomplete miscarriage) Clinical instability or signs of intra-abdominal bleeding or haemoperitoneum on scans			EP: 20/27 (74.1) Failing PUL: 179/203 (88.2) IUP: 34/140 (24.3) OR (95% CI): 1.74 (0.72 - 4.24) <u>Without clots</u> EP: 14/27 (51.9) Failing PUL: 78/203 (38.4) IUP: 31/140 (22.1) OR (95% CI): 2.31 (1.05 - 5.09) <u>With clots</u> EP: 6/27 (22.2) Failing PUL: 101/203 (49.8) IUP: 3/140 (2.1) OR (95% CI): 0.66 (0.26 - 1.67) **<u>c. Abdominal tenderness</u>** EP: 2/27 (7.4) Failing PUL: 24/203 (11.8) IUP: 21/140 (15) OR (95% CI): 0.53 (0.12 - 2.31)	
Full citation Tsai,H.D., Chen,H.Y., Yeh,L.S., A 12-year survey of 681 ectopic pregnancies, Chung Hua i Hsueh Tsa Chih - Chinese Medical	**Sample size** N=681 **Characteristics** Age/years (range): 16 – 43	**Tests** <u>Index test</u> History taking and physical examination <u>Reference test</u>	**Methods** 681 ectopic pregnancies were encountered at the China Medical College Hospital during the study period. In all cases, the diagnosis was confirmed by histopathological examinations.	**Results** **<u>Frequency of risk factors for ectopic pregnancy (number of women/total (%))</u>** Previous PID: 196/681	**Limitations** Retrospective Unclear who extracted the data and how the cases were identified

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Journal, 55, 457-462, 1995 **Ref Id** 72121 **Country/ies where the study was carried out** Taiwan, Republic of China **Study type** Case-series **Aim of the study** Not stated **Study dates** January 1981 to December 1992 **Source of funding** Not reported	Nulliparous (number/total (%)): 81/681 (11.9) **Inclusion Criteria** Ectopic pregnancy **Exclusion Criteria** Not reported	Histopathological examination	Analysis was confined to known risk factors of ectopic pregnancy recorded during the hospital stay. Clinical management in terms of diagnostic procedures and surgical treatment was analysed.	(28.8) (Note: this is defined as previous antibiotic therapy for PID) Previous pelvic operation: 138/681 (20.3) Previous D&C: 106/681 (15.6) IUCD in situ: 63/681 (9.3) **Frequency of symptoms (number of women/total (%))** Abdominal pain: 667/681 (97.9) Amenorrhea: 613/681 (90.0) Vaginal bleeding: 436/681 (64.0) Pregnancy symptoms: 279/681 (41.0) (Note: includes nausea, vomiting, breast engorgement and colostrum) Fainting and syncope: 32/681 (4.7) Back pain: 18/681 (2.6) (Note: all of these patients had ruptured EP with a large amount of	Exclusion criteria not reported % of ruptured EP not reported **Other information** **Location of ectopic (number (%))** Tubal: 647 (95.0) Cornual: 11 (1.6) Ovarian: 10 (1.5) Cervical: 5 (0.7) Abdominal: 4 (0.6) Rudimentary horn: 4(0.6)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				haemoperitoneum)	
Full citation Jabbar,F.A., Al-Wakeel,M., A study of 45 cases of ectopic pregnancy, International Journal of Gynaecology and Obstetrics, 18, 214-217, 1980 **Ref Id** 77352 **Country/ies where the study was carried out** Saudia Arabia **Study type** Case-series **Aim of the study** To discuss the clinical presentation of ectopic pregnancy and explore the most common predisposing factors among Saudi women. **Study dates**	**Sample size** N=68 (however only 45 of these were diagnosed as ectopic pregnancies, and hence constitute the population of interest for this review question) **Characteristics** **Age/years (number/total (%))** **15-20:** 5/45 (11.1) **20-30:** 27/45 (60) **30-40:** 13/45 (28.9) **Parity** **0:** 1/45 (2.2) **1-5**: 39/45 (86.7) **>5:** 5/45 (11.1) **Inclusion Criteria** Diagnosed ectopic	**Tests** Index test History taking and physical examination Reference test Visualisation of extrauterine gestation at laparoscopy and/or laparotomy.	**Methods** At the Riyadh Maternity Hospital, the medical records of 68 cases of suspected ectopic pregnancy were reviewed. Only 45 of the 68 were finally diagnosed as ectopic pregnancies, and constitute the study population.	**Results** **Frequency of possible risk factors (number with risk factor/total ectopics (%))** History of pelvic infection: 20/45 (44.4) History of pelvic or abdominal surgery: 18/45 (40) History of infertility: 21/45 (46.7) IUD in situ: 1/45 (2.2) Recurrent ectopic pregnancy: 1/45 (2.2) **Frequency of symptoms (number with symptom/total ectopics (%))** Amenorrhea: 43/45 (95.6) Lower abdominal pain:	**Limitations** Retrospective Unclear who was responsible for recording signs and symptoms in the first place. Unclear who extracted the data from the medical records. **Other information** 21/40 (52.5%) of the tubal pregnancies had ruptured by the time of laparotomy. **Type of ectopic pregnancy (number/total (%))** Tubal: 40/45 (88.9) Cervical: 2/45 (4.4) Ovarian: 1/45 (2.2) Rudimentary horn pregnancy: 2/45 (4.4)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
1977-1979 (Note: this is reported in Islamic calendar years in the paper, 1397-1399) **Source of funding** Not reported	pregnancy **Exclusion Criteria** Not reported			42/45 (93.3) Vaginal bleeding: 23/45 (51.1) Fainting attacks: 4/45 (8.9) Shoulder tip pain: 14/45 (31.1) **Frequency of signs at physical examination (number with sign/total ectopics (%))** Acute collapse: 5/45 (11.1) Tachycardia (100 bpm): 34/45 (75.6) Hypotension (<100/60 mmHg): 12/45 (26.7)	
Full citation Michelas,S., Creatsas,G., Fakas,G., Kaskarelis,D., Ectopic pregnancy: outcome of 152 cases, International Surgery,	**Sample size** N=152 **Characteristics** Primigravida (n (%)): 20 (13)	**Tests** Index test History taking Reference test Culdocentesis or laparoscopy	**Methods** This study reports the ectopic pregnancies occurring during the study period at the Alexandra State and University Maternity Hospital, Athens, Greece.	**Results** Frequency of risk factors for ectopic pregnancy (n (%)) Previous ectopic pregnancy: 19 (13) Previous miscarriage: 50 (33)	**Limitations** Retrospective Method of data collection not reported Unclear who was responsible for collecting

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
65, 355-358, 1980 **Ref Id** 77452 **Country/ies where the study was carried out** Greece **Study type** Case-series **Aim of the study** Not stated **Study dates** January 1976 to December 1978 **Source of funding** Not reported	At least one previous delivery (n (%)): 92 (61) Age/years (range): 16 - 48 <u>Duration of amenorrhea (n (%))</u> < 4: 9 (6) 6 - 10: 80 (53) 11 - 14: 60 (39) 28 - 40: 3 (2) **Inclusion Criteria** Ectopic pregnancy **Exclusion Criteria** Not reported			Previous induced abortion: 72 (47) Previous caesarean: 18 (12) History of appendectomy at least one year before pregnancy: 68 (45) Laparotomy for gynaecological reasons: 3 (2) Chronic inflammation of fallopian tubes: 50 (33) <u>Frequency of symptoms (n (%))</u> Pelvic pain: 152 (100) Vaginal bleeding: 120 (79) Weakness, syncope, dizziness: 74 (49) Nausea: 28 (18) <u>Frequency of signs (n (%))</u> Shock: 35 (23)	data in the first place **Other information** The % of ruptured ectopics is not reported. <u>Location of pregnancy (n (%))</u> Tubal: 141 (93) Fimbrial: 3 (2) Interstitial: 3 (2) Abdominal: 3 (2) Cervical: 2 (1)
Full citation Raziel,A., Schachter,M., Mordechai,E., Friedler,S., Panski,M.,	**Sample size** N=19	**Tests** <u>Index test</u> History taking and physical	**Methods** This study reviewed the medical records of 19 patients with ovarian pregnancy at Assaf Harofeh Medical Centre, Zerifin,	**Results** **<u>Frequency of possible risk factors (number with risk factor/total ectopics</u>**	**Limitations** Retrospective Unclear who was collected

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ron-El,R., Ovarian pregnancy-a 12-year experience of 19 cases in one institution, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 114, 92-96, 2004 **Ref Id** 77529 **Country/ies where the study was carried out** Israel **Study type** Case-series **Aim of the study** To report the prevalence, presentation, diagnostic modalities, and treatment of ovarian pregnancy in one institution. **Study dates** 1990 to 2001	**Characteristics** **Age/years (mean (range)):** 32.3 (24-43) **Gravidity (mean):** 2.8 **Parity (mean):** 2.1 **hCG/mIU/l (range):** 256 - 12834 **Inclusion Criteria** Ovarian pregnancy **Exclusion Criteria** Not reported	examination Reference test Laparoscopy (n=18) or ultrasound (n=1)	Israel during the study period. The medical centre is a major medical facility for obstetrics and gynaecology in the surrounding area. During the time period there were 63330 deliveres and 694 ectopic pregnancies at the institution. 19 were ovarian pregnancies. All records coded as "ectopic pregnancy" during the same period were also reviewed to ensure that all the diagnoses of ovarian pregnancy were correctly assigned. Diagnosis of ovarian pregnancy was confirmed by review of the pathological reports from surgical material in all ectopic pregnancies. In cases in which ovarian tissue was available, the final diagnosis was established by histo-pathologic examination showing that the pregnancy was limited to the ovary.	**(%))** **a. Previous abdominal surgery:** 2/19 (10.5) (Note: one appendectomy, one diagnostic laparoscopy) **b. Previous caesarean section:** 2/19 (10.5) (Note: 1 of these patients also had previous other abdominal surgery) **c. IUD present:** 13/19 (68.4) **d. History of elective abortion:** 3/19 (15.8) **e. History of miscarriage:** 3/19 (15.8) **Frequency of signs and symptoms (number with sign or symptom/total ectopics (%))** **a. Abdominal pain:** 17/19 (89.5) **b. Menstrual irregularities:** 14/19 (73.7) **c. Circulatory collapse:**	data on signs and symptoms in the first place. Unclear who extracted the data from the charts. **Other information** OVARIAN PREGNANCIES

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Not reported				4/19 (21.1)	
Full citation Al-Suleiman,S.A., Khwaja,S.S., Ectopic pregnancy, Journal of Obstetrics and Gynaecology, 12, 254-257, 1992 **Ref Id** 90845 **Country/ies where the study was carried out** Saudia Arabia **Study type** Case-series **Aim of the study** To determine the incidence of ectopic pregnancy in the hospital population and to assess the possible risk factors and clinical features of ectopic pregnancy. **Study dates**	**Sample size** N=104 **Characteristics** **Ethnic origin (number/total (%))** Saudi: 45/104 (43.3) Other Arabs: 35/104 (33.7) Non-Arabs: 24/104 (23.1) **Age/years (number/total (%))** <19: 7/104 (6.7) 20-24: 27/104 (26.0) 25-29: 31/104 (29.8) 30-34: 31/104 (29.8) >35: 8/104 (7.7) **Parity (number/total (%))** 0: 23/104 (22.1) 1-2: 46/104 (44.2) 3-5: 26/104 (25) >5: 9/104 (8.7) **Inclusion Criteria**	**Tests** Index test History taking and physical examination Reference test Surgical confirmation and histological examination of specimen	**Methods** The case records of 104 patients with ectopic pregnancies during the study period were studied. All patients underwent laparotomy and the operative diagnosis of ectopic gestation was confirmed by histological examination of the specimens. The hospital is a referral hospital that receives patients from primary health care centres and other hospitals in the area, in addition to emergency cases brought straight to the emergency department. The population includes patients of all nationalities, but the majority are Arab. Real time transabdominal ultrasound was available from 1982 onwards on a limited scale, and since 1988, resident obstetricians were trained and scanning was possible at any time. The ultrasound findings suggestive of ectopic pregnancy included absence of an intrauterine gestation sac, presence of an adnexal mass, and presence of fluid in the cul-de-sac. hCG assay kits were	**Results** **Frequency of possible risk factors (number with risk factor/total ectopics (%))** History of infertility: 25/104 (24.0) History of PID: 22/104 (21.2) IUCD in situ: 3/104 (2.9) Prior use of IUCD: 3/104 (2.9) Prior EP and salpingectomy: 3/104 (2.9) Prior tubal or ovarian surgery: 5/104 (4.8) Appendicectomy: 7/104 (6.7) Prior caesarean: 7/104 (6.7) Prior caesarean and tubal sterilisation: 1/104 (1.0)	**Limitations** Retrospective Unclear who initially collected history, and unclear who extracted data from the medical records. Exclusion criteria not reported. **Other information** 39% of the ectopic pregnancies were ruptured.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
1981 to 1989 **Source of funding** Not reported	Ectopic gestation **Exclusion Criteria** Not reported		available twice a week. Specimens were stored for testing if sent on other days.	**Frequency of symptoms (number with symptom/total ectopics (%))** Abdominal pain: 98/104 (94.2) Abnormal uterine bleeding: 77/104 (74.0) Amenorrhoea: 67/104 (64.4) Dizziness: 20/104 (19.2) Syncope: 19/104 (18.3) Nausea or vomiting: 17/104 (16.3) Passage of tissue: 13/104 (12.5) Diarrhoea: 2/104 (1.9) Urinary symptoms: 9/104 (8.7) **Frequency of signs at physical examination (number with sign/total ectopics (%))**	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Abdominal tenderness: 86/104 (82.7) Rebound tenderness: 38/104 (36.5) Cervical excitation: 90/104 (86.5) Adnexal tenderness: 88/104 (84.6) Enlarged uterus: 34/104 (32.7) Adnexal mass: 28/104 (26.9)	
Full citation Dimitry,E.S., A ten year survey of 193 ectopic pregnancies, Journal of Obstetrics and Gynaecology, 9, 309-313, 1989 **Ref Id** 91199 **Country/ies where the study was carried out**	**Sample size** N=193 **Characteristics** **Age/years (number/total (%))** 15-19: 7/193 (3.6) 20-24: 42/193 (21.7) 25-29: 66/193 (34.2) 30-34: 58/193 (30.1) 35-39: 16/193 (8.3) 40-44: 4/193 (2.1)	**Tests** Index test History taking and physical examination Reference test Surgical confirmation.	**Methods** The study is based on the case records of patients with ectopic pregnancy seen and treated in the Medway District Hospital. Cases were identified from registers kept in the histopathology department, operating theatre and gynaecological ward, and the Hospital Activity Analysis records. Every woman who underwent surgery for ectopic pregnancy during the study period was identified, which was a total of 193 cases.	**Results** **Frequency of possible risk factors (number with risk factor/total ectopics (%))** Previous appendicectomy: 47/193 (24.4) Previous investigations for infertility: 36/193 (18.7) Use of an IUD at time of diagnosis: 29/193 (15.0)	**Limitations** Retrospective Only includes women who underwent surgery to treat an ectopic Unclear who extracted data from records, and who made the records in the first place. **Other information** 66/193 (34%) had a negative pregnancy test.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
UK **Study type** Case-series **Aim of the study** To review the incidence, trend, diagnosis and management of ectopic pregnancy. **Study dates** 1977-1986 **Source of funding** Not reported	**Parity (number/total (%))** 0 + 0: 43/193 (22.3) 0 + >=1: 25/193 (13.0) >=1 + 0: 52/193 (26.9) >=1 + >= 1: 73/193 (37.8) **Inclusion Criteria** Undergoing surgery for ectopic pregnancy **Exclusion Criteria** Not reported			Previous PID: 24/193 (12.4) Previous abdominal surgery (excluding appendicectomy): 17/193 (8.8) Previous ectopic pregnancy: 14/193 (7.3) Previous reconstructive tubal surgery: 10/193 (5.2) Previous tubal sterilisation: 8/193 (4.1) Use of progestagen-only contraception: 8/193 (4.1) No risk factors: 32% **Frequency of symptoms (%)** Abnormal vaginal bleeding: 82 Amenorrhea: 73 Abdominal pain: 96 Dizziness: 23	61% were unruptured. **Type of ectopic pregnancy (number/total (%))** Tubal: 184/193 (95.3) Ovarian: 4/193 (2.1) Abdominal: 4/193 (2.1) Cervical: 1/193 (0.5)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Shoulder pain: 19 Rectal pressure: 9 **<u>Frequency of signs at physical examination (%)</u>** Abdominal tenderness: 91 Adnexal tenderness: 82 Cervical excitation pain: 48 Rebound abdominal tenderness: 46 Adnexal mass: 40 Enlarged uterus: 24 Tachycardia >100 bpm or hypotension <90/60 mmHg: 21	
Full citation Easley,H.A., Olive,D.L., Holman,J.F., Contemporary evaluation of suspected ectopic pregnancy, Journal of Reproductive	**Sample size** N=119 (Note: this is the population of the entire study, however only 68 were finally diagnosed with an ectopic pregnancy and hence constitute the	**Tests** <u>Index test</u> History taking and physical examination <u>Reference test</u>	**Methods** The records of 119 patients undergoing surgery for suspected ectopic pregnancy were reviewed retrospectively. Each patient was evaluated in either the emergency room or the outpatient gynaecology clinic. Histories were taken and recorded by obstetrics	**Results** (Note: the stated odds ratios (OR) have been calculated by the technical team, for those with ectopic pregnancy (n=68) vs. those without an ectopic pregnancy (n=51))	**Limitations** Retrospective Unclear who extracted the data from the charts. Exclusion criteria not

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Medicine, 32, 901-906, 1987 **Ref Id** 91220 **Country/ies where the study was carried out** USA **Study type** Case-series **Aim of the study** To identify the factors that might be important in the differential diagnosis of ectopic pregnancy. **Study dates** June 1981 to June 1983 **Source of funding** Not reported	main population of interest for this review question) **Characteristics** **Final diagnosis (number/total (%))** Ectopic pregnancy: 68/119 (57.1) Non-ectopic: 51/119 (42.9) - Ruptured ovarian cyst: 13/119 (10.9) - Unruptured ovarian cyst: 8/119 (6.7) - Miscarriage: 11/119 (9.2) - PID: 7/119 (5.9) - IUP: 1/119 (0.8) - Other: 11/119 (9.2) **Characteristics of those with ectopic pregnancy (n=68)** a. Time since last menstrual period/weeks (mean): 6.8 b. Duration of pain/days (mean): 8.0 c. Duration of bleeding/days (mean): 8.0 d. Presence of	Surgical confirmation.	and gynaecology residents. Physical examinations were initially performed by first year residents, and then repeated by more advanced clinicians. If there were differences in findings, those recorded by the most advanced resident were used. This study included both patients who did and did not undergo serum pregnancy tests. Culdocentesis was performed usually by first and second year residents. Patients were selected for the procedure without a specific protocol. Ultrasound scanning of the pelvis was performed by trained ultrasound technicians or radiology residents using realy time scanning, and was reviewed by an attending radiologist. Ultrasound was ordered without any specific protocol. Test results in women with ectopic pregnancy (N=68) were compared to those without ectopic pregnancy, and those with a ruptured ectopic were compared to those with an unruptured pregnancy. Results were analysed using chi-squared and student's t-tests.	**Frequency of symptoms (number with symptom/total ectopics (%))** Abdominal pain only: 22/68 (32.4) OR (95% CI): 0.54 (0.25 - 1.14) Vaginal bleeding only: 6/68 (8.8) OR (95% CI): 1.14 (0.30 - 4.26) Abdominal pain and vaginal bleeding: 37/68 (54.4) OR (95% CI): 1.34 (0.65 - 2.78) **Frequency of signs at physical examination (number with sign/total ectopics (%))** Rebound: 24/68 (35.3) OR (95% CI): 2.55 (1.06 - 6.11) Abdominal tenderness: 24/68 (35.3) OR (95% CI): 0.57 (0.27 - 1.19) Unilateral abdominal tenderness: 40/68 (58.8) OR (95% CI): 0.54 (0.25 -	reported. **Other information** TUBAL ECTOPICS (indirectly reported in the discussion) Unclear why a total of 68 ectopics were reported, but it is reported that 27 were ruptured and 40 were unruptured.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	haemoperitoneum: 52/119 (43.7) **Inclusion Criteria** Patients undergoing surgery with a pre-operative diagnosis of suspected ectopic pregnancy **Exclusion Criteria** Not reported			1.18) Adnexal mass: 33/68 (48.5) OR (95% CI): 0.66 (0.32 - 1.37) Orthostatic hypotension: 12/68 (17.6) OR (95% CI): 3.43 (0.91 - 12.87) **Signs and symptoms, split by ruptured status (number with sign or symptom/total ectopics (%))** **a. Abdominal pain only** Ruptured: 13/27 (48.1) Unruptured: 9/40 (22.5) ($p<0.05$) **b. Vaginal bleeding only** Ruptured: 2/27 (7.4) Unruptured: 4/40 (10) (NS) **c. Abdominal pain and vaginal bleeding** Ruptured: 12/27 (44.4) Unruptured: 24/40 (60) (NS)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				d. Rebound Ruptured: 16/27 (59.3) Unruptured: 7/40 (17.5) (P<0.001) **e. Abdominal tenderness** Ruptured: 6/27 (22.2) Unruptured: 18/40 (45) (NS) **f. Unilateral abdominal tenderness** Ruptured: 14/27 (51.9) Unruptured: 25/40 (62.5) (NS) **g. Adnexal mass** Ruptured: 12/27 (44.4) Unruptured: 20/40 (50) (NS)	
Full citation Wong,E., Suat,S.O., Ectopic pregnancy--a diagnostic challenge in the emergency department, European Journal of Emergency Medicine, 7, 189-194, 2000	**Sample size** N=207 **Characteristics** Age/years (mean (range)): 30.6 (18 - 43)	**Tests** Index test History taking and physical examination Reference test	**Methods** This study is a retrospective descriptive study of 207 cases of ectopic pregnancy seen at a tertiary teaching hospital. The cases were identified from the hospital's computer database using the ICD coding. The cases were then traced by the Medical	**Results** **Frequency of possible risk factors (number with risk factor/total on whom data is available (%))** Previous elective abortion: 34/183 (18.6)	**Limitations** Retrospective Exclusion criteria not reported Unclear who collected signs and symptoms data in the first place, and who

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 92207 **Country/ies where the study was carried out** Singapore **Study type** Case-series **Aim of the study** To investigate the clinical presentation of ectopic pregnancy in the emergency department, and highlight the atypical presentations and pitfalls in its diagnosis. **Study dates** 1992 to 1995 **Source of funding** Not reported	Gravidity (mean): 2.68 Parity (mean): 1.04 Duration of amenorrhea/weeks (mean): 6.3 **Inclusion Criteria** Ectopic pregnancy, classified by ICD coding in hospital records **Exclusion Criteria** Not reported	Ultrasound (n=123), laparoscopy (n=37), or laparotomy (n=47)	Records Office, and information was extracted from the admission and clerking notes.	Previous miscarriage: 30/183 (16.4) Subfertility: 26/179 (14.5) Previous ectopic pregnancy: 16/183 (8.7) History of tubal ligation: 10/205 (4.9) Ovarian induction agents: 8/162 (4.9) IUCD: 6/89 (6.7) History of PID: 3/15 (20) With risk factors: 105/182 (57.7) **Frequency of symptoms (number with symptom/total on whom data is available (%))** Abdominal pain: 171/196 (87.2) Amenorrhea: 169/195 (86.7) Vaginal bleeding: 144/188 (76.6) Vomiting: 22/64 (34.4) Diarrhoea: 22/60 (36.7)	then extracted it from medical records. Data is missing on certain risk factors and signs/symptoms; sometimes up to 192/207 have missing data **Other information** 84/199 (42.2%) of the ectopics were ruptured. Site of ectopics is not reported.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Non-specific dizziness: 16/19 (84.2) Syncope: 14/53 (26.4) Shoulder tip pain: 13/37 (35.1) Urinary symptoms: 10/43 (23.3) Rectal bleeding: 1 (denominator or % not reported) Epigastric/central abdominal pain: 3 (denominator or % not reported) **Frequency of signs at examination (number with sign/total ectopics (%))** Abdominal tenderness: 140/200 (70) Positive cervical motion tenderness: 94/148 (63.5) Haemoglobin <11 g%: 77/192 (40.1) Rebound tenderness: 74/145 (51.0) Adnexal tenderness: 71/83 (85.5)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Blood in the vagina: 51/76 (67.1) Guarding: 50/158 (31.6) Hypotension (systolic BP <100mmHg): 46/200 (23) Pallor: 43/97 (44.3) Shifting dullness: 34/61 (55.7) Abdominal distension: 31/55 (56.4) Tachycardia (>100 bpm): 20/193 (10.4) Palpable pelvic mass: 8/65 (12.3) Shock: 46/200 (23) **Frequency of combinations of abdominal pain, amenorrhea and bleeding in 174 cases (number/total (%))** a. Pain + Amenorrhea + Bleeding: 98/174 (56.3) b. Amenorrhea + Pain only: 35/174 (20.1) c. Amenorrhea + Bleeding only: 20/174 (11.5) d. Pain + Bleeding only:	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				12/174 (6.9) e. Pain alone: 6/174 (3.4) f. Amenorrhea alone: 2/174 (1.2) g. Bleeding alone: 1/174 (0.6)	
Full citation Gonzalez,F.A., Waxman,M., Ectopic pregnancy. A retrospective study of 501 consecutive patients, Diagnostic Gynecology and Obstetrics, 3, 181-186, 1981 **Ref Id** 95822 **Country/ies where the study was carried out** USA **Study type** Case-series **Aim of the study** To examine retrospectively the anamnestic, clinical and pathologic data in patients with known	**Sample size** N=501 **Characteristics** Age/years (mean (range)): 28.1 (15 - 45) Previous pregnancy (mean (range)): 2.5 (1 - 8) Ethnicity (% black): 80.6 Duration of amenorrhea/weeks (mean (range)): 7.8 (0 - 22) **Inclusion Criteria** Diagnosis of ectopic pregnancy during the study period **Exclusion Criteria** Not reported	**Tests** Index test History taking and physical examination Reference test Culdocentesis, ultrasound, laparoscopy	**Methods** This was a retrospective review of all 501 patients with an ectopic pregnancy treated at Kings County Hospital during the study period. Complete information was available on 448 patients, and incomplete data was available on 53 patients from the files of Surgical Pathology. The following data were recorded and analysed: age, race, gravidity, parity, past health, history of present illness, physical exam on admission, and diagnostic and therapeutic procedures performed. Histologic slides of the tubes were reviewed for 394 patients, in an effort to identify tubal pathology such as salpingitis, diverticula, endometriosis, or tumour.	**Results** Frequency of risk factors for ectopic pregnancy (n (%)) Previous induced abortion: 149 (29.7) Previous miscarriage: 93 (18.6) Previous ectopic: 34 (6.8) History of pelvic infection: 71 (14.2) Abdominal surgery: 71 (14.2) Use of birth control pills: 75 (15.0) Use of an IUCD: 47 (9.4) Tuboplasty: 24 (4.8) Tubal ligation: 10 (2.0) Frequency of presenting symptoms (number/total (%)) Amenorrhea: 98%	**Limitations** Retrospective Abdominal tenderness and rebound abdominal tenderness refer to at least moderate tenderness. Unclear who extracted data, or was responsible for collecting data originally. Some signs and symptoms have only reported a value for n, without a denominator or %. However, as denominators differing from 501 are reported for some findings, the technical team have assumed that those without a stated different value have a denominator of 501. **Other information** 339/501 (67.6%) of ectopics were ruptured at the point of laparotomy.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
ectopic pregnancy **Study dates** January 1st 1973 to December 31st 1977 **Source of funding** Not reported				(denominator NR) Abdominal pain: 439/449 (98) Vaginal bleeding: 230/438 (52.5) Nausea and vomiting: 141 (denominator NR, 28% assuming N=501) Dizziness: 184 (denominator NR, 37% assuming N=501) Fainting: 128 (denominator NR, 26% assuming N=501) Dysuria: 26/441 (5.9) Tenesmus: 35/500 (7) Breast tenderness: 39/438 (8.9) <u>Frequency of signs on physical examination (number/total (%))</u> Systolic BP < 90 mmHg: 68/501 (13.6) Moderate to severe abdominal tenderness: 342/439 (77.9) Moderate rebound abdominal tenderness: 249/401 (62.1)	<u>Location of ectopic pregnancy (n (%))</u> Fimbria: 49 (9.8) Ampulla: 260 (51.9) Isthmus: 68 (13.6) Cornua: 42 (8.4) Ovary: 1 (0.2) Unknown: 81 (16.1)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Cyanotic cervix: 177/458 (38.6) Cervical motion pain: 321/448 (71.6) Adnexal fullness: 268/481 (55.7) Enlarged uterus: 39/253 (15.4)	
Full citation Powers,D.N., Ectopic pregnancy: a five-year experience, Southern Medical Journal, 73, 1012-1015, 1980 **Ref Id** 101705 **Country/ies where the study was carried out** USA **Study type** Case-series	**Sample size** N=204 **Characteristics** **Age/years (minimum-maximum):** 17 - 45 **Parity (number/total (%))** 0: 77/204 (37.7) 1: 66/204 (32.4) >=2: 61/204 (29.9) **Duration of amenorrhea/weeks (average):** 7.4 **Duration of bleeding/days (minimum-**	**Tests** Index test History taking and physical examination Reference test Ultrasound or laparoscopy	**Methods** During a five year period, 204 patients with ectopic pregnancies were treated at Fairfax Hospital. The charts of these patients were reviewed, and data were analysed as to incidence, age, parity, etiology, medical history, symptoms, physical findings, diagnosis and treatment, pathologic findings and morbidity.	**Results** **Frequency of possible risk factors (number with risk factor/total ectopics (%))** Previous elective abortion: 64/204 (31.4) Previous ectopic: 14/204 (6.9) Past pelvic surgery: 46/204 (22.5) Tubal ligation: 8/204 (3.9) History or record of salpingitis: 27/204 (13.2)	**Limitations** Retrospective Exclusion criteria not reported Unclear who initially collected signs and symptoms data, and who was responsible for extracting it from the charts. **Other information** **Location of ectopic (number/total (%))** Tubal: 200/204 (98.0) Ovarian: 1/204 (0.5)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To review historic and physical findings, diagnostic procedures. etiological factors and treatment in patients presenting with an ectopic gestation at Fairfax Hospital. **Study dates** January 1974 to December 1978 **Source of funding** Not reported	**maximum):** 1 - 84 **Inclusion Criteria** Ectopic pregnancy **Exclusion Criteria** Not reported			Past use of IUCD: 18/204 (8.8) IUCD in situ: 21/204 (10.3) **Frequency of symptoms (number with symptom/total ectopics (%))** Abdominal pain: 194/204 (95.1) Nausea and/or vomiting: 56/204 (27.5) Syncope: 20/204 (9.8) Amenorrhea: 146/204 (71.6) No missed period: 52/204 (25.5) Atypical uterine bleeding: 130/204 (63.7) **Frequency of signs at examination (number with sign/total ectopics (%))** Abdominal tenderness: 186/204 (91.2)	Abdominal: 2/204 (1.0) Heterotopic: 1/204 (0.5) **Status of ectopic at time of surgery (number/total (%))** Ruptured: 150/204 (73.5) Unruptured: 48/204 (23.5) Aborting: 6/204 (2.9)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				- Unilateral: 69/204 (33.8) - Bilateral: 117/204 (57.4) Rebound tenderness: 92/204 (45.1) Abdominal distention: 35/204 (17.2) Diminished bowel sounds: 40/204 (19.6) Absent bowel sounds: 4/204 (2.0) Cullen's sign: 0/204 (0) Adnexal tenderness: 193/204 (94.6) Cervical tenderness: 107/204 (52.5) Adnexal fullness: 101/204 (49.5) Adnexal mass: 52/204 (25.5) Uterine enlargement: 36/204 (17.6) Shock: 36/204 (17.6)	
Full citation Diamond,M.P., Wiser-	**Sample size**	**Tests**	**Methods**	**Results**	**Limitations**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Estin,M., Jones,E.E., DeCherney,A.H., Failure of standard criteria to diagnose nonemergency ectopic pregnancies in a noninfertility patient population, Journal of the American Association of Gynecologic Laparoscopists, 1, 131-134, 1994 **Ref Id** 101769 **Country/ies where the study was carried out** USA **Study type** Case-series **Aim of the study** To examine the utility of the same diagnostic criteria for identifying and ectopic pregnancy in different patient populations in the same institution (women in an infertility clinic and a	N=60 **Characteristics** Not reported **Inclusion Criteria** Surgically proved ectopic pregnancy treated in the same hospital (either at the infertility clinic or the residents' clinic) A minimum of two β-hCG measurements **Exclusion Criteria** Ectopic pregnancy managed by private practitioner Women who were first evaluated in the emergency room and were diagnosed at that time to have an ectopic pregnancy	<u>Index test</u> History taking <u>Reference test</u> Laparoscopy or laparoscopy	<u>Data collection</u> Retrospective analysis of patients' records. The population included women from the Reproductive Endocrinology and Infertility Clinic (n=38), and those from the Obstetrics and Gynaecology Clinic (n=22). <u>Diagnostic tests</u> Clinically stable patients were followed with serial β-hCG titres until the titre reached 6500mIU/ml at which point they had an ultrasound. Abdominal ultrasound was supplemented with vaginal ultrasound if the first one failed to identify an intrauterine pregnancy. With the exception of haemodynamically unstable patients, ectopic pregnancies were identified definitely by laparoscopy. Where possible, treatment was also by laparoscopy.	<u>Frequency of symptoms at presentation (number of women and %) (N=60)</u> Asymptomatic: 5 (8.3) Abdominal pain: 40 (66.7) Spotting/bleeding > 3 days: 16 (26.7) Dizziness: 4 (6.7) Shoulder pain: 3 (5.0) <u>Frequency of signs (number of women and %) (N=60)</u> Orthostasis: 2 (3.3)	Retrospective study Unclear who reviewed patients' records Unclear who collected data on symptoms in the first place 63% of the study population are patients at an infertility clinic, although it is unclear whether they conceived as a result of infertility treatment Specific characteristics of abdominal pain not recorded **Other information** 11/60 (18.3%) of ectopic pregnancies were ruptured. The two populations in the study have been grouped and reported as one case series for the purposes of this review.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
residents' Obstetrics and Gynaecology clinic) **Study dates** May 1988 to July 1990 **Source of funding** Not stated					
Full citation Aboud,E., Chaliha,C., Nine year survey of 138 ectopic pregnancies, Archives of Gynecology and Obstetrics, 261, 83-87, 1998 **Ref Id** 102060 **Country/ies where the study was carried out** UK **Study type** Case-series	**Sample size** N=138 **Characteristics** Not stated **Inclusion Criteria** Patients treated for ectopic pregnancy at a North London Hospital **Exclusion Criteria** Not stated	**Tests** Index tests History taking and physical examination Reference tests Unclear, however all patients had a laparotomy.	**Methods** Data collection This is a retrospective review of the case records of patients treated for ectopic pregnancy during the study period. Cases were identified from Registers in the Histopathology Department, operating theatres and Gynaecology ward.	**Results** **Frequency of possible risk factors (number of women and %) (N=138)** Past investigations for infertility: 24 (17) Previous use of IUCD: 18 (13) Previous ectopic pregnancy: 15 (11) Previous appendectomy: 13 (9.5) Previous PID: 11 (8)	**Limitations** Retrospective study Unclear who reviewed the case records Unclear who collected data on risk factors and signs and symptoms in the first place Unclear how many patients had an ultrasound, and what kind of ultrasound was used Pyrexia not defined

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study Not stated **Study dates** 1986 to 1994 **Source of funding** Not stated				Previous tubal surgery: 8 (6) Endometriosis: 7 (5) Use of progesterone only pill: 6 (4) Past history of tubal ligation: 2 (1) **Frequency of symptoms at presentation (number of women and %) (N=138)** Abdominal pain: 132 (96) Vaginal bleeding preceding pain: 82 (59.4) Nausea and vomiting: 30 (22) Dizziness: 22 (16) Shoulder tip pain: 11 (8) Asymptomatic: 4 (2.9) **Frequency of signs on examination (number of women and %) (N=138)** Abdominal tenderness: 121 (88)	**Other information** At laparotomy, 64% of the ectopics were intact and had not ruptured. 35% of the ectopics had ruptured. Asymptomatic patients were diagnosed by pelvic ultrasound scan carried out for early pregnancy dating The majority of patients were referred to hospital by their GP (62%). 32% were self referrals into A&E and 6% were referred to the Gynaecology Department from other specialties within the hospital 11 patients (8%) had a negative urine pregnancy test and in 39 patients (28.3%) it was inconclusive or not documented Serum β hCG was performed on 21 patients and only two of them required quantitative serial measurements 134 pregancies were tubal, 3 ovarian and 1 cervical

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Adnexal tenderness: 79 (57) Cervical excitation: 58 (42) Abdominal tenderness with rebound and guarding: 57 (41) Enlarged uterus: 46 (33) Adnexal mass: 14 (10) Tachycardia over 100 beats/min: 21 (15) Hypotension (< 90/60 mmHg): 20 (14.5) Pyrexia: 10 (7)	
Full citation Barnhart,K.T., Sammel,M.D., Gracia,C.R., Chittams,J., Hummel,A.C., Shaunik,A., Risk factors for ectopic pregnancy in women with symptomatic first-trimester pregnancies, Fertility and Sterility, 86, 36-43, 2006	**Sample size** N=2026 (367 cases of ectopic pregnancy, 1659 controls) **Characteristics** **<u>Age/years</u>** < 20: 43 (11.8) 20 - 25: 87 (23.8) 25 - 30: 112 (30.7)	**Tests** <u>Index test</u> History taking <u>Reference tests</u> - Spontaneous miscarriage: histopathology of products of conception on suction D & C or spontanous decline of hCG level to ≤5 mIU/mL	**Methods** A database of all women who present with pain and/or bleeding at the University of Pennsylvania is maintained, with data entered directly by clinical staff caring for the patients. Potential risk factors for ectopic pregnancy were identified from the history, clinical presentation and diagnostic tests. Women were followed in the database until they were definitely diagnosed with either	**Results** **<u>Frequency of possible risk factors in cases only (number with risk factor (%))</u>** **<u>Prior elective abortion</u>** 0: 294 (82.4) 1: 33 (9.2) 2 or more: 30 (8.4) **<u>History of miscarriage</u>**	**Limitations** Retrospective Only includes women presenting with pain and/or bleeding **Other information** Note: this study was conducted during the same

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 102279 **Country/ies where the study was carried out** USA **Study type** Case-control study **Aim of the study** To evaluate the association between ectopic pregnancy and clinical and historical factors among women presenting with pain and/or bleeding in early pregnancy **Study dates** January 1st 1990 to July 31st 1999 **Source of funding** National Institutes of Health (Bethesda, MD) grant R01: HD-36455-05	≥ 35: 39 (10.7) **Race** African-American: 229 (62.6) Other: 12 (3.3) **Prior live births:** 192 (52.3) **Parity** 0: 174 (47.4) 1: 94 (25.6) 2: 45 (12.3) 3: 29 (7.9) 4 or more: 25 (6.8) **Inclusion Criteria** All women in their first trimester of pregnancy (positive pregnancy test or history of a missed period) presenting with pain and/or bleeding **Exclusion Criteria** Not stated	- Normal intrauterine pregnancy: ongoing progression of the pregnancy by ultrasound visualisation of an intrauterine yolk sac, fetal pole or the presence of heartbeat - Ectopic pregnancy: confirmed by the presence of chorionic viili in the fallopian tube, or by visualisation of an extrauterine gestational sac (with yolk sac or cardiac activity) for those treated medically, or by a rise in hCG level after dilatation and evacuation, with no evidence of chorionic villi in the endometrial curettage samples.	an ectopic pregnancy or an intrauterine pregnancy (either viable ongoing pregnancy or miscarriage). See "tests" section for diagnostic criteria. Data were analysed as a nested case-control study. The cases were defined as women who were definitively diagnosed with an ectopic pregnancy. Controls were defined as those presenting with the same symptoms but who were eventually diagnosed with an intrauterine pregnancy (Note: the controls consist of 1659 women diagnosed with an IUP (of which 467 had an ongoing pregnancy and 1192 had a miscarriage) Firstly, univariate associations were evaluated using student's t-test or chi-squared. Stratified analyses were then performed to test for confounding and effect modification. Historical and clinical presentation variables were first tested to check for interaction. For the purposes of analysis of categorial variables, one category was chosen as the reference standard. Reference categories included age 25 - 29 years and hCG of < 500 mIU/l. When no interaction was noted, both historical and clinical variables were combined. A logistic regression model was	0: 269 (83.8) 1: 36 (11.2) 2 or more: 16 (5) **History of ectopic pregnancy** 0: 306 (83.4) 1: 48 (13.1) 2 or more: 13 (3.5) **History of pelvic surgery (excluding CS):** 88 (24) **History of prior caesarean** 0: 342 (93.2) 1: 16 (4.4) 2 or more: 9 (2.4) **Past use of IUCD:** 20 (5.5) **History of PID:** 90 (24.5) **History of outpatient treatment for gonorrhea and/or chlamydia** 0: 289 (79) 1: 60 (16.4) 2: 18 (4.9) 3 or more: 0 (0) **Current gonorrhea and/or chlamydia cervical infection:** 22 (6.9)	time period in the same hospital as another included study (Barnhart et al. 2003). This paper has more details on risk factors but less on presenting symptoms; therefore details of risk factors have been reported here, and details of prevalence of symptoms are reported for the other paper (with the exception of the odds ratios for pain and bleeding, which have been reported in this study)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			then generated using manual selection of confounding variables and backward stepwise selection of variables. At each step, the largest p value variable was removed from the table and this process was repeated until alll variables had a p value of ≤ 0.05. A variable was retained in the model as a confounder if it significantly affected the coefficient estimates of other variables by at least 15%.	**Risk factors associated with ectopic pregnancy (adjusted odds ratio (95% CI), p value)** **a. Age/years** < 20: 0.34 (0.22 - 0.52), p<0.0001 20 - 24: 0.59 (0.41 - 0.85), p=0.01 25 - 29: Reference 30 - 34: 1.18 (0.79 - 1.76), p=0.42 ≥ 35: 1.00 (0.61 - 1.64), p=0.99 **b. Prior elective abortion** 0: Reference 1: 0.58 (0.38 - 0.90), p=0.02 2 or more: 0.99 (0.61 - 1.6), p=0.96 **c. History of ectopic pregnancy** 0: Reference 1: 2.98 (1.88 - 4.73), p<0.0001 2 or more: 16.04 (5.39 - 47.72), p<0.0001 **d. History of PID** Yes: 1.50 (1.11 - 2.05),	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				p=0.01 **<u>e. Parity</u>** 0: Reference 1: 1.71 (1.21 - 2.42), p=0.003 2: 1.13 (0.72 - 1.78), p=0.60 3: 0.95 (0.56 - 1.59), p=0.83 4 or more: 1.26 (0.68 - 2.36), p=0.46 **<u>f. hCG at presentation</u>** 0 - 500: Reference 501 - 2000: 1.73 (1.24 - 2.42), p=0.001 2001 - 4000: 1.38 (0.88 - 2.16), p=0.16 ≥ 4000: 0.97 (0.67 - 1.39), p=0.86 Note: History of 2 treatments for gonorrhea and/or chlamydia and current gonorrhea/chlamydia infection were significantly associated in the univariate analysis but not in the adjusted analysis. The remaining risk factors were not significant in either univariate or adjusted analyses. **<u>Association of symptoms with ectopic pregnancy</u>**	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				vs. controls (OR (95% CI)) a. Pain as the presenting symptom Unadjusted OR: 1.16 (0.92 - 1.48) Adjusted OR: 1.42 (1.06 - 1.92) b. Bleeding (moderate to severe) at presentation Unadjusted OR: 1.34 (1.04 - 1.78) Adjusted OR: 1.42 (1.04 - 1.93)	
Full citation Menon,S., Sammel,M.D., Vichnin,M., Barnhart,K.T., Risk factors for ectopic pregnancy: a comparison between adults and adolescent women, Journal of Pediatric and Adolescent Gynecology, 20, 181-185, 2007 **Ref Id** 102281 **Country/ies where the study was**	**Sample size** N=2721 (However, only 509 of these were diagnosed with ectopic pregnancy and hence constitute the population of interest for this review question. No data or outcomes have been reported for the remaining 2212 women) **Characteristics** **Breakdown of final diagnosis by age (number (%))** Total	**Tests** Index test History taking and physical examination Reference test Ectopic pregnancy: Diagnosed if products of conception were detected within the fallopian tube, ultrasound documeneted an extra uterine gestational sac, or a rise in hCG was seen following dilation and evacuation. Viable pregnancy: Diagnosed by ultrasound visualisation of	**Methods** A database of all pregnant women presenting with complaints of pain or bleeding is kept at the University of Pennsylvania. The database contains information on women since 1990. Only women requiring a follow-up ultrasound or hCG measurements were included in the database. Information about women undergoing a salpingostomy for ectopic pregnancy treatment was entered into the database; those undergoing emergency salpingectomy were excluded. 2721 presented to the emergency department during the first trimester of pregnancy, of which 649 were adolescents. A total of	**Results** **Frequency of possible risk factors in those with ectopic pregnancy, split by age (% (n for whom data was available)** **a. Prior ectopic pregnancy** Adolescents: 1.61 (n=62) Adults: 20.22 (n=445) ($p < 0.01$) **b. Prior surgery** Adolescents: 1.59 (n=63) Adults: 24.44 (n=446) ($p < 0.01$) **c. Prior PID**	**Limitations** Retrospective Unclear what type of surgery is reported as a risk factor Only includes women with pain and/or bleeding Unclear what was adjusted for to calculate adjusted ORs **Other information** This study population has

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
carried out USA **Study type** Case-series **Aim of the study** To compare the prevalence of classical risk factors and presenting signs and symptoms between adolescents and adults with ectopic pregnancy. **Study dates** 1990 onwards (no further details given) **Source of funding** Not reported	Adolescents: 649 Adult: 2072 <u>Ectopic pregnancy</u> Adolescents: 63 (9.7) Adults: 446 (21.7) <u>Intrauterine pregnancy</u> Adolescents: 172 (26.5) Adults: 505 (24.4) <u>Miscarriage</u> Adolescents: 414 (63.8) Adults: 1121 (53.9) 95% of the population were black, with no difference between adolescent and adult populations. **Inclusion Criteria** Pregnant women in the first trimester presenting with pain or bleeding Requirement for follow-up ultrasound or serial hCG measurements **Exclusion Criteria** Emergency salpingectomy	a yolk sac, fetal pole or fetal cardiac activity within the uterus Miscarriage: Diagnosed when hCG fell to <5 mIU/ml or by pathologic confirmation of products of conception after suction dilation and curettage	509 patients were eventually diagnosed with an ectopics pregnancy, of which 63 were in adolescents and 446 were in adults. Transvaginal ultrasounds were routinely performed at initial presentation. Results were categorised as likely IUP, non-diagnostic, suspicious for EP, definite EP, and non-viable IUP. Age, obstetric history, previous STIs and surgical history were recorded in the database. Symptoms at time of presentation to the emergency room were also recorded. Both research and clinical staff caring for the patient were responsible for entry of information in to the database. Diagnoses were confirmed for each woman (see "Tests" section). A retrospective cross-sectional study was designed to analyse the incidence of ectopic pregnancies in a teenage population. The database was first split into adolescent (<20 years old) and adult (≥20 years old). Descriptive statistics were used to compare the presentation and risk factor association of ectopics in adults versus adolescents.	Adolescents: 22.22 (n=63) Adults: 19.73 (n=446) (p=0.64) **<u>d. Prior gonorrhea or chlamydia infection</u>** Adolescents: 30.65 (n=62) Adults: 26.68 (n=446) (p=0.51) **<u>e. Use of an IUCD</u>** Adolescents: 0 (n=62) Adults: 4.93 (n=446) (p=0.07) **<u>f. Parous</u>** Adolescents: 22.22 (n=62) Adults: 62.33 (n=446) (p < 0.01) **<u>Frequency of symptoms in those with ectopic pregnancy, split by age (% (n for whom data was available))</u>** **<u>a. Bleeding</u>** Adolescents: 77.42 (n=62) Adults: 75.36 (n=418) (p=0.72) **<u>b. Pain</u>** Adolescents: 79.37 (n=63) Adults: 66.82 (n=446)	also been reported in other included studies (Barnhart et al. 2003, Barnhart et al. 2006). However, it has been included here due to its consideration of the differing presentations of ectopic pregnancy in adolescents and adults.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				(p=0.045) **<u>c. Current gonorrhea or chlamydia infection</u>** Adolescents: 22.22 (n=63) Adults: 4.07 (n=393) (p < 0.01) **<u>d. Pain among those without gonorrhea/chlamydia</u>** Adolescents: 83.3 (n=42) Adults: 68.2 (n=377) (p=0.043) **<u>e. Pain among those with gonorrhea/chlamydia</u>** Adolescents: 58.3 (n=12) Adults: 81.3 (n=16) (p=0.183) **<u>Adjusted associations comparing risk factors and symptoms between adolescents and adults (OR (95% CI), p value)</u>** (Note: OR < 1 indicates that the risk factor or symptom is less prevalent in adolescents compared to adults) Parous: 0.35 (0.206 - 0.577), p<0.0001	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Previous ectopic: 0.11 (0.013 - 0.859), p=0.035 History of surgery: 0.10 (0.013 - 0.791), P=0.029 Neither pain or infection: 1.00 (Reference) Pain only: 2.55 (6.562 - 402.676), p=0.035 (Note: it is unclear why reported OR is not within 95% CI) Infection only: 0.08 (0.007 - 0.800), p=0.0002 Pain and infection: 3.94 (1.271 - 12.186), p=0.018	
Full citation Bouyer,J., Coste,J., Fernandez,H., Pouly,J.L., Job-Spira,N., Sites of ectopic pregnancy: A 10 year population-based study of 1800 cases, Human Reproduction, 17, 3224-3230, 2002 **Ref Id** 102345 **Country/ies where the study was carried out** France	**Sample size** N=1679 **Characteristics** <u>Age/years (number of women and %)</u> < 25: 210 (12.5) 25 - 34: 977 (58.2) ≥ 35: 490 (29.2) Prior delivery (n (%)): 1164 (69.7) **Inclusion Criteria** All women between 15 and 44 years of age who live permanently in the target area and who had	**Tests** <u>Index test</u> History taking <u>Reference test</u> Surgical visualisation (unclear whether laparoscopy or laparotomy)	**Methods** <u>Data collection</u> An ectopic pregnancy register was established in three districts of the Auvergne region. In each medical centre in the recruitment area (15 public or private maternity hospitals and 12 surgical units) a trained investigator, either a midwife or a physician, was responsible for case identification, follow-up and data collection.	**Results** <u>Frequency of potential risk factors (number of women and %) (n=1679)</u> Smoker: 767 (48.1) Current IUCD: 424 (25.5) Prior spontaneous miscarriage: 428 (25.6) Prior EP: 210 (12.6) Prior STI: 318 (19.7) Prior tubal surgery: 312 (18.7)	**Limitations** **Other information** 259/1679 (15.4%) of ectopics had tubal rupture. Only 4.5% extratubal EPs (ovarian (n=54) and abdominal (n=22)) were observed and about three-quarters of the tubal pregnancies (1175/1603=73%) were ampullary. No cervical pregnancies were observed

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Case-series **Aim of the study** To investigate the distribution of ectopic pregnancy sites in a population-based sample and its variation over time To study the immediate complications and factors determining the site of ectopic pregnancy (this data was not extracted, as it is not relevant to this review question). **Study dates** January 1992 to December 2001 **Source of funding** National Institute Committee (Comite National des Registres-INSERM-InVS), France	had surgical treatment for ectopic pregnancy **Exclusion Criteria** Women who had medical treatment only because the site of implantation could not be determined with certainty. Women who had surgical treatment but for whom precise information concerning the distribution of ectopic pregnancy implantation was not provided				

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Clancy,M.J., Illingworth,R.N., The diagnosis of ectopic pregnancy in an accident and emergency department, Archives of Emergency Medicine, 6, 205-210, 1989 **Ref Id** 102446 **Country/ies where the study was carried out** UK **Study type** Case-series **Aim of the study** To determine the accuracy of ectopic pregnancy in an accident and emergency department and consider how it could be improved **Study dates**	**Sample size** N=60 **Characteristics** **Age/years (mean (range)):** 28 (17-45) **Previous, recent contact with medical facilities (number/total (%))** **-** Referred from GP: 26/60 (43.3) - Recently seen in another A&E: 2/60 (3.3) - Recently seen in gynaecology departments: 8/60 (13.3) **Inclusion Criteria** Discharged with a diagnosis of ectopic pregnancy Initially attended A&E department **Exclusion Criteria** Not reported (however they state that 2 patients' records could not be traced)	**Tests** Index test History taking and physical examination Reference test All patients had laparotomy.	**Methods** Patient's discharged from St. James's University Hospital Leeds with a diagnosis of ectopic pregnancy were identified from hospital computer records. The notes of the patients who had initially attended the A&E department were analysed for factors associated with ectopic pregnancy, presenting signs and symptoms, initial diagnosis and investigations, and subsequent outcome. The notes of 60 patients were available.	**Results** **Frequency of possible risk factors (number with risk factor/total ectopics (%))** Investigations for infertility: 10/60 (16.7) Previous abdominal surgery: 9/60 (15) IUCD used within previous year: 8/60 (13.3) Previous ectopic pregnancy: 4/60 (6.7) Previous pelvic infection: 4/60 (6.7) Progestogen-only contraceptive pill: 4/60 (6.7) Tubal ligation or diathermy: 3/60 (5) None of these risk factors: 31/60 (51.7) **Frequency of symptoms (number with symptom/total ectopics (%))** Abdominal pain: 57/60 (95) Amenorrhea: 41/60 (68.3)	**Limitations** Retrospective Unclear who extracted the data from the records, or who exactly was responsible for reporting signs and symptoms in the first place. The location of the ectopic pregnancies is not reported. **Other information** 45 patients had results of a pregnancy test reported, of which 20/45 (44%) were negative.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
1983 to 1986 **Source of funding** Not reported				Vaginal bleeding: 45/60 (75) - Vaginal bleeding for more than a week: 21/60 (35) Nausea and vomiting: 29/60 (48.3) Breast tenderness: 19/60 (31.7) Faintness, dizziness or vomiting: 18/60 (30) Chest or shoulder pain: 9/60 (15) Pain on defecation: 4/60 (6.7) **Frequency of signs at physical examination (number with sign/total ectopics (%))** Abdominal tenderness: 42/60 (70) Adnexal tenderness: 32/60 (53.3) Cervical excitation: 25/60 (41.7) Adnexal mass: 11/60 (18.3) Uterine enlargement: 22/60 (36.7)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Hypovolaemic shock: 7/60 (11.7) Pyrexia (37.5° or higher): 6/60 (10)	
Full citation Larrain,D., Marengo,F., Bourdel,N., Jaffeux,P., ublet-Cuvelier,B., Pouly,J.L., Mage,G., Rabischong,B., Proximal ectopic pregnancy: a descriptive general population-based study and results of different management options in 86 cases, Fertility and Sterility, 95, 867-871, 2011 **Ref Id** 118771 **Country/ies where the study was carried out** France **Study type** Population-based study	**Sample size** N = 86 **Characteristics** Age/years (mean (range)): 31 (18 - 44) Gestational age at diagnosis/days (mean (range)): 48.2 (12 - 89) hCG level (mean): 10759 (95% CI 6189 - 15328) **Inclusion Criteria** Proximal ectopic pregnancy, defined as either cornual or interstitial Aged 15 - 45 Treated for ectopic pregnancy **Exclusion Criteria** None reported	**Tests** **Index test** History taking **Reference test** Transvaginal ultrasound (44%), abdominal ultrasound (8%), laparoscopy (45%), emergency laparotomy	**Methods** **Data collection** In the Auvergne region, all women aged 15 to 45 who are treated for ectopic pregnancy are registered on the Auvergne Ectopic Pregnancy Registry, and then followed up prospectively until the age of 45. The authors identified all of the women diagnosed with a proximal ectopic prengancy, located either in the intramyometrial portion of the fallopian tube (interstitial) or in the uterine horns (cornual). (Note: the authors also report details around the management of the ectopics, but the data is not relevant to this review question and therefore will not be reported here)	**Results** **Frequency of risk factors for ectopic pregnancy (number/total (%))** Smoking: 47/79 (59.5) History of PID: 27/83 (32.5) Previous surgery: 59/86 (68.6) (Note: type of surgery is not reported) History of adhesiolysis: 11/82 (13.4) Previous salpingectomy: 15/82 (18.2) Previous tubal surgery: 3/82 (3.7) History of endometriosis: 3/84 (3.6) In utero diethylstilbestrol exposure: 2/38 (5.2) History of oral contraception: 42/65 (64.6) History of IUCD use: 16/65	**Limitations** There is missing data for a lot of the risk factors (more than 50% for in utero diethylstilbestrol exxposure) and the denominator is not reported for the symptoms. **Other information** This study population is likely to partially incorporate the interstitial pregnancies reported in Bouyer et al., 2002; however, this only affects risk factors. It is not possible to deal with the cross over, as Bouyer et al. does not report proximal pregnancies in this way.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To summarise the presence of pre-disposing faactors for proximal ectopic pregnancy and outcomes of different treatments among patients with proximal ectopic pregnancy in the population **Study dates** January 1992 to December 2008 **Source of funding** None stated				(24.6) Previous EP: 24/86 (27.9) **Frequency of symptoms (%)** Abdominal pain: 87 Vaginal bleeding: 56	
Full citation Kazandi,M., Turan,V., Ectopic pregnancy; risk factors and comparison of intervention success rates in tubal ectopic pregnancy, Clinical and Experimental Obstetrics and Gynecology, 38, 67-70, 2011 **Ref Id**	**Sample size** N = 254 **Characteristics** None reported **Inclusion Criteria** Ectopic pregnancy **Exclusion Criteria**	**Tests** **Index test** Clinical history taking **Reference test** Combination of transvaginal ultrasound and quantitative serum hCG levels	**Methods** **Data collection** 254 ectopic pregnancies were retrospectively reviewed. The presenting symptoms of the patients, the location of the ectopic and the management of the patient were evaluated. (However, any outcomes relating to treatment are not relevant to this review and therefore will not be reported here)	**Results** **Frequency of risk factors reported (%)** a. History of pelvic surgery: 12 b. Previous ectopic: 6% c. Use of IUCD: 6% d. History of infertility: 5.5% e. History of PID: 4%	**Limitations** Retrospective Exclusion criteria not reported Unclear whether there was any missing data, and therefore what the denominator was for each of these symptoms and risk factors Not reported how the data

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
123280 **Country/ies where the study was carried out** Turkey **Study type** Case-series **Aim of the study** The assessment of ectopic pregnancy, its risk factors, and a comparison of the treatment modes **Study dates** January 2002 to July 2009 **Source of funding** None stated	None reported			**<u>Frequency of symptoms reported (%)</u>** a. Abdominopelvic pain: 77% b. Vaginal bleeding: 14% c. Vaginal bleeding and pelvic pain: 7%	was collected and who by **Other information** 243 (95%) ectopics were tubal; with the remainder split among cornual (n=3), cervical (n=3), rudimentary horn (n=3), ovarian (n=1) and abdominal (n=1)
Full citation Shaunik,A., Kulp,J., Appleby,D.H., Sammel,M.D., Barnhart,K.T., Utility of dilation and curettage in the diagnosis of pregnancy of	**Sample size** N = 173 (However, only 107 of these were ultimately diagnosed with an ectopic pregnancy and therefore form the population of	**Tests** **<u>Index test</u>** Clinical history **<u>Reference test</u>** Unclear, but women seem to	**Methods** **<u>Data collection</u>** This was a cohort study including all women with a non-viable PUL meeting the inclusion criteria. Potential predictors of clinical outcome were identified from	**Results** **<u>Frequency of symptoms reported (n/total (%))</u>** a. Pain: 58/107 (54.2%) b. Bleeding: 68/107 (63.6%)	**Limitations** Type or location of pain is not reported Exclusion criteria is not reported

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
unknown location, American Journal of Obstetrics and Gynecology, 204, 130-130, 2011 **Ref Id** 130830 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To determine the usefulness of dilatation and curettage for diagnosis of non viable pregnancy of unknown location (PUL) **Study dates** December 2003 to July 2007 **Source of funding**	interest for this review) **Characteristics** Median initial hCG (mIU/ml): 344 (range 142 - 926) **Inclusion Criteria** Women with a non-viable PUL Clinically stable with either: - initial hCG ≥ 2000 and a non-diagnostic ultrasound - initial hCG < 2000 and an abnormal rise/fall/plateau of levels **Exclusion Criteria** None reported	have received a uterine evacuation (the authors state that this was standard clinical practice before beginning medical treatment for a presumed ectopic)	medical and surgical history, clinical presentation, and diagnostic tests. Women were followed up in the clinical database until the were definitively diagnosed with an ectopic or non-viable IUP.		**Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Grant from National Institutes of Health					
Full citation Choi,H.J., Im,K.S., Jung,H.J., Lim,K.T., Mok,J.E., Kwon,Y.S., Clinical analysis of ovarian pregnancy: a report of 49 cases, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 158, 87-89, 2011 **Ref Id** 152753 **Country/ies where the study was carried out** South Korea **Study type** Case-series **Aim of the study** To clinically analyse cases of ectopic ovarian pregnancy and to generate data regarding the evaluation and management of	**Sample size** N = 49 **Characteristics** Age/years (mean (SD)): 30.7 (4.4) **Inclusion Criteria** Ovarian pregnancy **Exclusion Criteria** None reported	**Tests** **Index test** Clinical history taking **Reference test** Review of pathology reports	**Methods** **Data collection** The authors retrospectively reviewed the medical records of 49 cases of ovarian pregnancy diagnosed and treated in one hospital during the study period. They collected data on patient characteristics, as well as complaints, risk factors, and diagnosis.	**Results** **Frequency of risk factors reported (n/total (%))** a. Previous ectopic: 6/49 (12.2) b. Present IUD use: 2/49 (4.1) c. History of abdominal surgery: 19/49 (38.8) d. Endometriosis: 16/49 (32.7) e. PID: 4/49 (8.2) f. Ovulation induction: 4/49 (8.2) g. IVF: 8/49 (16.3) h. No risk factors: 12/49 (24.5) **Frequency of symptoms reported (n/total (%))** a. Abdominal pain: 21/49 (42.9) b. Vaginal bleeding: 14/49 (28.6)	**Limitations** Retrospective Exclusion criteria not reported **Other information** All ovarian pregnancies

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
suspected ectopic ovarian pregnancies **Study dates** January 1996 to December 2009 **Source of funding** None stated				c. Adnexal mass: 3/49 (6.1) d. Shock: 1 (2.0) e. Vomiting: 1/49 (2.0) f. Asymptomatic: 9/49 (18.4) g. Skipped menstruation: 4/49 (8.2)	
Full citation Downey,L.V., Zun,L.S., Indicators of potential for rupture for ectopics seen in the emergency department, Journal of Emergencies Trauma and Shock, 4, 374-377, 2011 **Ref Id** 152776 **Country/ies where the study was carried out** USA **Study type** Case-series	**Sample size** N = 187 **Characteristics** **Inclusion Criteria** Women aged at least 18 years old Presenting with abdominal pain or vaginal bleeding to the emergency department (ED) Determined to have an ectopic pregnancy **Exclusion Criteria** < 18 years old Presenting with complaints other than abdominal pain	**Tests** <u>Index test</u> Medical history, physical examination and lab values <u>Reference test</u> Unclear	**Methods** <u>Data collection and analysis</u> A retrospective chart review was conducted of all women with an ectopic who presented to the ED during the study period. Data was collected from the ED, hospitalisation records, and outpatient clinics, using a data collection sheet that included basic demographic information, history of the patient (medical, surgical, obstetric, gynecological, sexual, social), findings on physical examination and lab values (urine pregnancy test, beta-hCG values and complete blood count). The data was entered into SPSS and multivariate regression and frequency distributions were performed. Out of 249 patients with ectopic, 187 had complete data available for analysis.	**Results** <u>Frequency of risk factors (%)</u> Previous ectopic pregnancy: 16.0 <u>Frequency of symptoms (%)</u> Abdominal pain: 75.7 Vaginal bleeding: 51.9 Nausea: 20.6 Vomiting: 16.4 <u>Frequency of signs on clinical examination (%)</u> Abdominal tenderness: 60.8	**Limitations** Retrospective Only includes women with pain or bleeding Unclear what gold standard was used to confirm the diagnosis of ectopic pregnancy Individual denominators for each symptom or sign are not reported; therefore only % can be calculated Unclear who collected the data **Other information** Out of those presenting to the ED: 49% had rupture, 26% did not, 4% were not recorded, and 17% were

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To evaluate the indicators for rupture in patients who present to the emergency department with an ectopic pregnancy **Study dates** 2000 to 2005 **Source of funding** The authors state that they did not receive any support	or vaginal bleeding Found to have other diagnosis Significant data missing from charts				not diagnosed with an EP at the ED visit. Risk factors were reported; however, their prevalence was not reported (only association with rupture), and therefore they cannot be reported here
Full citation Goksedef,B.P., Kef,S., Akca,A., Bayik,R.N., Cetin,A., Risk factors for rupture in tubal ectopic pregnancy: definition of the clinical findings, European Journal of Obstetrics, Gynecology, and Reproductive Biology, 154, 96-99, 2011 **Ref Id**	**Sample size** N = 232 **Characteristics** **Status of ectopic (n/total (%))** Ruptured: 88/232 (37.9%) Unruptured: 144/232 (62.1%) **Age (mean (SD))** Ruptured: 29.6 (5.6) Unruptured: 28.9 (5.6) (p = 0.97)	**Tests** **Index test** Clinical history **Reference test** Laparotomy or laparoscopy	**Methods** **Data collection** This was a retrospective review of diagnosed ectopic pregnancies, and risk factors were identified and recorded. Patients with tubal rupture who needed emergency laparotomy and blood transfusion were identified. **Analysis** Student's t-test, Mann-Whitney-Wilcoxon test for independent samples, Pearson's chi-square	**Results** **Frequency of risk factors, overall and split by rupture status (n/total (%))** **a. IUD use** - All women: 16/232 (6.9) - Ruptured: 6/88 (6.8) - Unruptured: 10/144 (6.9) (p = 0.97) **b. Smoking** - All women: 44/232 (19.0) - Ruptured: 18/88 (20.5) - Unruptured: 26/144 (18.1) (p = 0.61)	**Limitations** Retrospective 38% of ectopics were ruptured Unclear what the source of the data was (i.e. who collected it and retrieved it) and how cases were identified **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
152810 **Country/ies where the study was carried out** Turkey **Study type** Case-series **Aim of the study** To determine risk factors for rupture of an ectopic pregnancy and therefore identify those at greatest risk **Study dates** January 2003 to September 2009 **Source of funding** None stated	**Gestational age (mean (SD))** Ruptured: 7.8 (1.09) Unruptured: 6.4 (1.2) ($p < 0.0001$) **hCG levels/IU/ml (mean (SD))** Ruptured: 8735.3 (11317.8) Unruptured: 4506 (5673.7) **Inclusion Criteria** Cases of tubal ectopic pregnancy operated on by laparotomy or laparoscopy **Exclusion Criteria** None stated		and Fisher's exact test were applied for the comparison of groups, where appropriate. Multivariate logistic regression analysis was used to identify predictors of the outcome of the EP (variables with a p-value of < 0.05 from the univariate analysis were entered into the multivariate analysis)	**c. Previous ectopic** - All women: 23/232 (9.9) - Ruptured: 10/88 (11.4) - Unruptured: 13/144 (9.0)* ($p = 0.33$) **d. History of PID** - All women: 17/232 (7.3) - Ruptured: 9/88 (10.2) - Unruptured: 8/144 (5.6) ($p = 0.18$) **e. Endometriosis** - All women: 11/232 (4.7) - Ruptured: 4/88 (4.5) - Unruptured: 7/144 (4.9) ($p = 0.91$) *this % does not match that stated in the paper, and it is unclear why, because to get a denominator of 8.6% (as stated), you would need a larger study population than that which is reported. Note: in the multivariate analysis, only gestational age and hCG were important risk factors for tubal rupture.	

What is the diagnostic value of ultrasound for determining a viable intrauterine pregnancy?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Steinkampf,M.P., Guzick,D.S., Hammond,K.R., Blackwell,R.E., Identification of early pregnancy landmarks by transvaginal sonography: analysis by logistic regression, Fertility and Sterility, 68, 168-170, 1997 **Ref Id** 59236 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To assess the feasibility of logistic regression analysis for determining the gestational ages at which detection of early pregnancy landmarks first can be observed	**Sample size** N=82 (82 women had a total of 215 scans) **Characteristics** **Age/years (mean (range)):** 32.3 (25-44) **Fertility treatment received during conception cycle (number of women/total (%))** **Clomiphene citrate:** 5/82 (6.1) **Ovulation induction with gonadotrophins:** 64/82 (78.0) **GIFT or IVF:** 10/82 (12.2) (Note: details of the remaining three patients are not given) **Inclusion Criteria** First trimester ultrasound examination performed Pregnancy continuing	**Tests** Transvaginal ultrasound	**Methods** This was a retrospective review of 215 scans of all first trimester ultrasound exams performed on 82 women, in whom ovulation was achieved by hCG injection and in whom pregnancy continued beyond 20 weeks gestation. All scans were performed as part of early pregnancy surveillance in a reproductive endocrinology private practice over a 2-year period. All scans were performed under the supervision of one of the authors using a 5-MHz transvaginal probe. Pregnancy outcome was confirmed by repeat scanning after the first trimester and/or obstetric delivery records. Gestational age was calculated with the date of ovulation defined as 2 days after the administration of hCG. It was expressed in terms of menstrual weeks (i.e. interval from ovulation day + 14). Logistic regression was used to estimate the probability of detecting a gestational sac or	**Results** **Visualisation of fetal heart motion, by % probability** Note: Data for the 25%, 50% and 75% probabilities were calculated by the technical team using the graphs. Data for the 95% and 99% probabilities and 5-95% intervals were reported by the authors in the text. **a. By gestational age/days** 25% probability: 41 days 50% probability: 42 days 75% probability: 43 days 95% probability: 44.5 days >99% probability: 45.5 days Interval between 5% and 95% probability: 4.9 days **b. By mean gestation sac diameter/cm** 25% probability: 0.95 cm 50% probability: 1.1 cm 75% probability: 1.3 cm	**Limitations** **Retrospective** This is a retrospective review of ultrasound scans. **Exclusions** Exclusions from the study, and any exclusion criteria used, are not reported. **Other minor issues:** - The study dates are not reported, therefore judging the quality of the ultrasound equipment is more problematic. - The authors report the point at which fetal heart motion or gestational sac can be seen with 95% and 99% probability, but no other details are given. Therefore, these values had to be calculated by the technical team from the logistic regression graph. **Other information** This study population are all women whose pregnancy continued beyond 20 weeks

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Study dates Not reported, however the study was conducted over a 2 year period. **Source of funding** Not reported	beyond 20 weeks gestation Ovulation achieved by hCG injection **Exclusion Criteria** Not reported		fetal heart motion as a function of gestational age. Logistic regressions were also run to estimate the probability of fetal heart motion as a function of sac size. All logistic estimates were obtained using a PC-based program. The authors report that for actual probabilities within the 1st and 99th percentiles, all predicted gestational ages fell within one day of the corresponding actual gestational age.	95% probability: 1.6 cm 99% probability: 1.9 cm	gestation
Full citation Pennell,R.G., Needleman,L., Pajak,T., Baltarowich,O., Vilaro,M., Goldberg,B.B., Kurtz,A.B., Prospective comparison of vaginal and abdominal sonography in normal early pregnancy, Journal of Ultrasound in Medicine, 10, 63-67, 1991 **Ref Id** 67896 **Country/ies where the study was carried out** USA **Study type**	**Sample size** N=175 **Characteristics** **<u>Outcome of pregnancy (number/total (%))</u>** **Delivery:** 163/175 (93.1) **Elective abortion:** 12/175 (6.9) **<u>Characteristics using each type of ultrasound (range)</u>** **<u>a. Crown-rump length/mm</u>**	**Tests** Vaginal ultrasound Abdominal ultrasound	**Methods** During the study period, 309 women were referred by clinicians for indicated first trimester ultrasound scans. They were scanned using vaginal and abdominal ultrasound in a double-blind protocol. 105 patients were excluded (see exclusion criteria). Of the 224 patients with adequate clinical follow-up, and abdominal and vaginal scans performed according to protocol, there were 175 patients with a sonographically visible intrauterine gestation sac using both vaginal and abdominal techniques that also had a normal outcome proven (by delivery of a normal infant, or performance of elective abortion). Where there were	**Results** **<u>Embryo size (in mm) at which 100% of embryos had a visualised heartbeat, split by ultrasound type</u>** **Vaginal:** 5 mm or larger **Abdominal:** 9 mm or larger **<u>Note:</u>** - 149/168 embryos had a size of **≥** 5 mm. 18 embryos had a CRL of < 5 mm on vaginal scan, of which 12 (67%) had visualised cardiac activity - 132/146 embryos had a size of **≥** 9 mm. 14 embryos had a CRL of < 9 mm on abdominal scan, of which 11 (79%) had visualised cardiac activity	**Limitations** **Other information** The 175 study participants only included those with a gestation sac visualised on both abdominal and vaginal ultrasound.

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Prospective cohort study **Aim of the study** To compare vaginal and abdominal sonography independently using a large group of consecutive normal patients to establish the best crown-rump length or sac size for both approaches. **Study dates** February to June 1987 **Source of funding** Not reported	**Vaginal ultrasound:** 1-60 **Abdominal ultrasound:** 3-62 **<u>b. Average sac size/mm</u>** **Vaginal ultrasound:** 7-69 **Abdominal ultrasound:** 8-70 **Inclusion Criteria** Referred for indicated first trimester ultrasound Normal outcome Gestation sac visualised on both vaginal and abdominal ultrasound **Exclusion Criteria** The criteria are not stated directly, but patients were excluded from the study for the following reasons: - No clinical diagnosis (n=40) (Note: this refers to patients who did not return to their referring physician and were unavailable when the authors attempted to		multiple studies done, only the results of the first were used. All patients were examined by both abdominal and vaginal ultrasound, using separate examiners who were blinded to the results of the other scan. The protocol was as follows: - A routine pelvic examination, scanned from the anterior abdominal wall, was performed using a full urinary bladder - After this study was considered adequate, the patient voided and a vaginal examination was performed by a second radiologist with no knowledge of the abdominal ultrasound findings. - Knowledge of the clinical history was available to both examiners. The ultrasound equipment used was generally a 5.0-MHz transducer in the case of abdominal scanning, with a 3.5-MHz transducer occasionally used for larger patients. For vaginal scans, both 5.0- and 7.5-MHz probes were used. The probes were of several configurations, using end-view sector, curved linear and angled phased array transducers. For the vaginal examinations,		

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	contact them) - Multiple tests (all but the first test were excluded) (n=18) - No sac on abdominal scan (n=18) - Twins (n=9) - Ectopic pregnancy (n=8) - Inadequate test (n=3) - Not pregnant (n=3) - Other abnormality (n=2) - Incomplete follow-up (n=2) - Mole (n=1) - Not per protocol (n=1)		after emptying of the bladder, the patient was positioned supine on the table, and a condom-covered probe was inserted. Both transverse and longitudinal views were obtained of the uterus and its contents and the adnexa. The measurements were recorded using calipers during the real-time examination. The average of three measurements for CRL was utilised. The gestational sac measurements were taken as an average of three dimensions. The long axis measurement and the anteroposterior measurement, perpendicular to it, were obtained from the longitudinal image of the uterus. The width measurement was obtained from the transverse or coronal view. For the abdominal and vaginal studies, all CRL and gestation sacs were analysed to determine the size below which normal embryos do not consistently show a heartbeat and normal sacs do not show an embryo.		
Full citation Abaid,L.N., As-Sanie,S., Wolfe,H.M., Relationship	**Sample size**	**Tests** Transvaginal	**Methods** This is a retrospective study. A	**Results** **<u>Visualisation of cardiac activity</u>**	**Limitations** **<u>Retrospective</u>**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
between crown-rump length and early detection of cardiac activity, Journal of Reproductive Medicine, 52, 375-378, 2007 **Ref Id** 70156 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To investigate whether improvements in ultrasound technology would allow accurate detection of embryonic demise at a crown-rump length < 5 mm **Study dates** January 2000 to February 2003 **Source of funding** Not reported (but the authors state that	N=179 **Characteristics** **Maternal age/years (mean (SD)):** All women (N=179): 29.8 (6.2) Women with viable pregnancy (n=113): 28.9 (6.0) Women with embryonic demise (n=66): 31.4 (6.3) Note: those with embryonic demise were an average of 2.5 years older (p=0.01) **Crown-rump length/mm (mean (range)):** 3.6 (2-5) **Most common indications for ultrasound (%)** Confirmation of viability: 35 Vaginal bleeding: 26 Note: 48/179 presented with bleeding **Inclusion Criteria** Singleton pregnancy	ultrasound	computerised ultrasound database was queried to identify cases fitting the inclusion criteria within the study period. 195 ultrasound examinations met the criteria, but only 179 (92%) had documented outcomes and therefore comprised the study population. All ultrasound exams were performed in the University of North Carolina at Chapel Hill ultrasound unit by registered diagnostic medical sonographers with sub-speciality certification in obstetrics and gynaecology, and under the supervision of perinatologists. Ultrasound exams were performed using an 8-MHz transvaginal ultrasound probe utilising both gray scale and colour or power Doppler imaging to evaluate embryonic cardiac activity. Embryonic viability was confirmed by either a repeat ultrasound examination after 6 weeks of gestation confirming the presence or absence of cardiac activity, or by documentation of the pregnancy outcome. If cardiac activity was present any time after 6 weeks gestation, the pregnancy was considered	**by crown-rump length/mm** **a. In fetuses with cardiac activity seen at repeat ultrasound (number/total (%))** **2.0 - 2.9 mm** Cardiac activity seen: 22/29 (75.9) Cardiac activity not seen: 7/29 (24.1) **3.0 - 3.4 mm** Cardiac activity seen: 21/24 (87.5) Cardiac activity not seen: 3/24 (12.5) (Note: the authors report that the CRL for the 3 fetuses in whom cardiac activity was not seen was 3.0mm in all cases) **3.5 - 3.9 mm** Cardiac activity seen: 13/13 (100) Cardiac activity not seen: 0/13 (0) **4.0 - 4.4 mm** Cardiac activity seen: 21/21 (100)	Data on patients and ultrasounds was collected retrospectively. It has been reported by the authors that there may have been intraobserver or interobserver variability, which, as a result of the study design, they were not able to control for. **Other minor issues** Numbers were small in each group when data was stratified by presence of vaginal bleeding **Other information** For the fetuses with no cardiac activity at 6 weeks, in whom cardiac activity was visible at the first scan, it is not possible to elucidate whether the original scan was interpreted incorrectly, or whether miscarriage occurred in between scans. The authors conclude that the lower limit of crown-rump length for diagnosing a non-viable pregnancy could be set at 3.5 mm, because above this level, there were no viable pregnancies without demonstrated cardiac activity.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
they have no connection to any companies or products mentioned in the paper)	Crown-rump length ≤ 5mm **Exclusion Criteria** Outcome not documented		viable. Indications for ultrasound examination were determined from the ultrasound database. Crown-rump lengths were divided into six groups: 2.0-2.9, 3.0-3.4, 3.5-3.9, 4.0-4.4, 4.5-4.9 and 5.0 mm. The data were also stratified according to the presence or absence of vaginal bleeding.	Cardiac activity not seen: 0/21 (0) **4.5 - 4.9 mm** Cardiac activity seen: 16/16 (100) Cardiac activity not seen: 0/16 (0) **5.0 mm** Cardiac activity seen: 9/9 (100) Cardiac activity not seen: 0/9 (0) **b. In fetuses with no cardiac activity seen at repeat ultrasound (number/total (%))** **2.0 - 2.9 mm** Cardiac activity seen: 3/11 (27.3) Cardiac activity not seen: 8/11 (72.7) **3.0 - 3.4 mm** Cardiac activity seen: 0/19 (0) Cardiac activity not seen: 19/19 (100) **3.5 - 3.9 mm** Cardiac activity seen: 2/8 (25)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Cardiac activity not seen: 6/8 (75) **4.0 - 4.4 mm** Cardiac activity seen: 0/13 (0) Cardiac activity not seen: 13/13 (100) **4.5 - 4.9 mm** Cardiac activity seen: 0/3 (0) Cardiac activity not seen: 3/3 (100) **5.0 mm** Cardiac activity seen: 2/13 (15.4) Cardiac activity not seen: 11/13 (84.6) **Visualisation of cardiac activity by crown-rump length/mm, stratified by presence of vaginal bleeding** **a. In fetuses with cardiac activity seen at repeat ultrasound (number/total (%))** **2.0 - 2.9 mm**	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				With bleeding Cardiac activity seen: 6/8 (75) Cardiac activity not seen: 2/8 (25) **Without bleeding** Cardiac activity seen: 16/21 (76.2) Cardiac activity not seen: 5/21 (23.8) **3.0 - 3.4 mm** **With bleeding** Cardiac activity seen: 5/6 (83.3) Cardiac activity not seen: 1/6 (16.7) **Without bleeding** Cardiac activity seen: 16/18 (88.9) Cardiac activity not seen: 2/18 (11.1) **3.5 - 3.9 mm** **With bleeding** Cardiac activity seen: 1/1 (100) Cardiac activity not seen: 0/1 (0) **Without bleeding** Cardiac activity seen: 12/12 (100) Cardiac activity not seen: 0/12 (0) **4.0 - 4.4 mm** **With bleeding** Cardiac activity seen: 4/4 (100) Cardiac activity not seen: 0/4 (0)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Without bleeding Cardiac activity seen: 17/17 (100) Cardiac activity not seen: 0/17 (0) **4.5 - 4.9 mm** **With bleeding** Cardiac activity seen: 3/3 (100) Cardiac activity not seen: 0/3 (0) **Without bleeding** Cardiac activity seen: 13/13 (100) Cardiac activity not seen: 0/13 (0) **5.0 mm** **With bleeding** Cardiac activity seen: 1/1 (100) Cardiac activity not seen: 0/1 (0) **Without bleeding** Cardiac activity seen: 8/8 (100) Cardiac activity not seen: 0/8 (0) **b. In fetuses with no cardiac activity seen at repeat ultrasound (number/total (%))** Because of the way the data is presented, without knowing more about patterns of vaginal bleeding in each group, it is not possible to stratify by vaginal bleeding in the group of embryos with no visible cardiac activity at 6 weeks.	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Goldstein,S.R., Significance of cardiac activity on endovaginal ultrasound in very early embryos, Obstetrics and Gynecology, 80, 670-672, 1992 **Ref Id** 71150 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To evaluate the significance of the presence or absence of cardiac activity at endovaginal ultrasound in embryos up to 10 mm in length **Study dates** Not reported **Source of funding** Not reported	**Sample size** N=96 **Characteristics** No participants had a history of bleeding **Pregnancy outcome (number/total (%))** Delivery of a healthy newborn: 81/96 (84.4%) Miscarriage: 15/96 (15.6%) **Initial visualisation of cardiac activity (number/total (%))** Cardiac activity present: 74/96 (77.1) Cardiac activity absent: 22/96 (22.9) **Inclusion Criteria** Positive monoclonal antibody pregnancy test Available for follow-up until delivery or completion of a failed pregnancy Discernible embryonic structure of 1-10 mm	**Tests** Endovaginal ultrasound	**Methods** The study population was 96 women, each of whom had a vaginal sonographic examination at the first clinical visit. Ultrasound was done using either an Aloka 633 with a 5-MHz vaginal probe, or a Siemens SL1 with a 5- or 7.5-MHz vaginal probe. The greatest linear measurement of early embryonic size was made along the long axis of the embryo, and rounded to the nearest millimeter. The presence or absence of cardiac activity was determined visually using the highest magnification available. Two investigators, one physician and one nurse, made observations simultaneously. Cardiac activity was deemed absent after at least 3 minutes of scanning time. Women were scanned only once during the study period. Pregnancy failure was documented by either spontaneous miscarriage or analysis of curettage material. No further details are given.	**Results** **Visualisation of cardiac activity by early embryonic size/mm** **a. In pregnancies resulting in delivery (number/total (%))** **1 mm** Cardiac activity seen: 0/6 (0) Cardiac activity not seen: 6/6 (100) **2 mm** Cardiac activity seen: 8/13 (61.5) Cardiac activity not seen: 5/13 (38.5) **3 mm** Cardiac activity seen: 12/15 (80) Cardiac activity not seen: 3/15 (20) **4 mm** Cardiac activity seen: 6/6 (100) Cardiac activity not seen: 0/6 (0) **5 mm** Cardiac activity seen: 6/6 (100)	**Limitations** **Performance of curettage** They report that miscarriage was diagnosed when spontaneous miscarriage occurred, or through analysis of curettage material. However, it is not reported how long they waited before performing curettage in the case of miscarriage, and hence whether women received the gold standard of diagnosis. **Population** None of the participants had a history of vaginal bleeding **Other minor issues:** Study dates are not reported, therefore judging accuracy of scanning equipment is more problematic. **Other information** All cardiac activity that was subsequently visualised was seen by an embryonic size of 4 mm. The authors hypothesise that the absence of a detectable heartbeat in an embryo of 5 mm or larger is strongly suggestive of a non-

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	in size **Exclusion Criteria** Not reported, but in the discussion they state that they only studied women with no antecedent bleeding.			Cardiac activity not seen: 0/6 (0) **6 mm** Cardiac activity seen: 9/9 (100) Cardiac activity not seen: 0/9 (0) **7 mm** Cardiac activity seen: 9/9 (100) Cardiac activity not seen: 0/9 (0) **8 mm** Cardiac activity seen: 5/5 (100) Cardiac activity not seen: 0/5 (0) **9 mm** Cardiac activity seen: 7/7 (100) Cardiac activity not seen: 0/7 (0) **10 mm** Cardiac activity seen: 5/5 (100) Cardiac activity not seen: 0/5 (0) **b. In pregnancies that ended in miscarriage (number/total (%))** **1 mm**	viable pregnancy. For the fetuses with no cardiac activity at subsequent scans, in whom cardiac activity was visible at the first scan, it is not possible to elucidate whether the original scan was interpreted incorrectly, or whether miscarriage had occurred in between scans.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				No miscarriages in this group **2 mm** No miscarriages in this group **3 mm** Cardiac activity seen: 1/2 (50) Cardiac activity not seen: 1/2 (50) **4 mm** Cardiac activity seen: 2/4 (50) Cardiac activity not seen: 2/4 (50) **5 mm** Cardiac activity seen: 1/3 (33.3) Cardiac activity not seen: 2/3 (66.7) **6 mm** Cardiac activity seen: 1/2 (50) Cardiac activity not seen: 1/2 (50) **7 mm** Cardiac activity seen: 1/2 (50)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Cardiac activity not seen: 1/2 (50) **8 mm** No miscarriages in this group **9 mm** Cardiac activity seen: 0/1 (0) Cardiac activity not seen: 1/1 (100) **10 mm** Cardiac activity seen: 1/1 (100) Cardiac activity not seen: 0/0 (0) **Total in miscarriage group** Cardiac activity seen: 7/15 (46.7) Cardiac activity not seen: 8/15 (53.3)	
Full citation Levi,C.S., Lyons,E.A., Zheng,X.H., Lindsay,D.J., Holt,S.C., Endovaginal US: demonstration of cardiac activity in embryos of less than 5.0 mm in crown-rump length, Radiology, 176, 71-74, 1990	**Sample size** N=71 **Characteristics** **Presence of vaginal bleeding** **Present:** 32/71 (45.1%)	**Tests** Endovaginal ultrasound	**Methods** The authors reviewed the records of all patients who presented for diagnostic sonography in the first trimester of pregnancy at the Health Sciences Centre (Winnipeg, Canada) from January 1987 to March 1989. All patients with	**Results** **Initial visualisation of cardiac activity, by outcome (number/total (%))** **Visualised: 46/71 (64.8)** Normal outcome: 35/46 (76.1) Miscarriage: 11/46 (23.9)	**Limitations** **Retrospective study** This data was collected using a retrospective review of patient records. **Diagnosis of miscarriage**

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Ref Id 71485 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort study **Aim of the study** To determine the predictive value of endovaginal ultrasound demonstration of the presence or absence of cardiac activity in early pregnancy. **Study dates** January 1987 to March 1989 **Source of funding** Not reported	(22/32 (68.8%) had a first trimester embryonic death) **Absent:** 39/71 (54.9%) (9/39 (23.1%) had an embryonic death) (Note: 19/71 (26.8%) patients were asymptomatic; none of the patients had undergone IVF) **Inclusion Criteria** Presenting for diagnostic sonography in the first trimester of pregnancy Crown-rump length less than 5.0 mm **Exclusion Criteria** Undergoing elective termination of pregnancy Lost to follow-up		crown-rump length less than 5.0mm were included, regardless of clinical presentation and other sonographic findings. 96 patients fit the inclusion criteria, however 19 were excluded because they underwent elective termination of pregnancy, and 6 were excluded because they were lost to follow-up; therefore the study population comprised 71 patients. All patients underwent endovaginal ultrasound examinations with an ESI 1000 or ESI 2000 real-time scanner, with a 6.5-MHz endovaginal mechanical sector probe. All patients with CRL <5.0mm at initial transvaginal ultrasound exam were followed up until termination of pregnancy (for whatever reason) or, in patients with normal embryos, until the late second trimester. Biometric parameters including mean gestational sac diameter, yolk sac internal diameter, and crown-rump length, were compared with data accumulated from 326 normal first trimester obstetric examinations (Zheng et al., unpublished data) to determine if outcome can be predicted by	**Non-visualised: 25/71 (35.2)** Normal outcome: 5/25 (20) Miscarriage: 20/25 (80) **Visualisation of cardiac activity by crown-rump length/mm** **a. In "normal" (viable into second trimester) embryos (number/total (%))** **0 - 0.9 mm** No pregnancies in this group **1.0 - 1.9 mm** Cardiac activity seen: 0/3 (0) Cardiac activity not seen: 3/3 (100) **2.0 - 2.9 mm** Cardiac activity seen: 12/12 (100) Cardiac activity not seen: 0/12 (0) **3.0 - 3.9 mm** Cardiac activity seen: 11/13 (84.6) Cardiac activity not seen: 2/13 (15.4) (Note: the authors report that for	It is unclear how the diagnosis of miscarriage was judged, and therefore whether women received gold standard diagnosis of multiple ultrasounds. **Other information** For the fetuses that ended in miscarriage, in whom cardiac activity was visible at the first scan, it is not possible to elucidate whether the original scan was interpreted incorrectly, or whether miscarriage had occurred in between the first scan and the later diagnosis of miscarriage. **Study dates** The study dates for this paper are January 1987 to March 1989. This partially overlaps with the study dates of Levi et al. 1988 (November 1986 to June 1987), therefore there may be some overlap of study population. However, the data is reported in different formats in each study, because this paper stratifies by CRL whereas Levi et al. 1988 examine the effect of gestation sac size.

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			comparison of: - yolk sac internal diameter versus mean gestational sac diameter - crown-rump length versus mean gestational sac diameter - yolk sac internal diameter versus crown-rump length Statistical analysis was performed with Fisher's exact test.	one of the two without cardiac activity, the yolk sac diameter was outside the 9%% CI of the mean for normal embryos) **4.0 - 4.9 mm** Cardiac activity seen: 12/12 (100) Cardiac activity not seen: 0/12 (0) **b. In embryos with a subsequent first trimester miscarriage (number/total (%))** **0 - 0.9 mm** No pregnancies in this group **1.0 - 1.9 mm** Cardiac activity seen: 1/1 (100) Cardiac activity not seen: 0/1 (0) **2.0 - 2.9 mm** Cardiac activity seen: 1/9 (11.1) Cardiac activity not seen: 8/9 (88.9) **3.0 - 3.9 mm** Cardiac activity seen: 6/12 (50) Cardiac activity not seen: 6/12	**Vaginal bleeding** Out of the 15 patients with vaginal bleeding and demonstrable cardiac activity, 5/15 subsequently miscarried. In 17 patients with vaginal bleeding and no demonstrable cardiac activity, all 17 ended in miscarriage.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				(50) **4.0 - 4.9 mm** Cardiac activity seen: 3/9 (33.3) Cardiac activity not seen: 6/9 (66.7)	
Full citation de Crespigny,L.C., Early diagnosis of pregnancy failure with transvaginal ultrasound, American Journal of Obstetrics and Gynecology, 159, 408-409, 1988 **Ref Id** 72586 **Country/ies where the study was carried out** Australia **Study type** Prospective cohort study **Aim of the study** To investigate whether the advent of transvaginal ultrasound transducers, with their improved	**Sample size** N=353 **Characteristics** **Clinical indications for ultrasound exam (number of women/total (%))** **Threatened miscarriage:** 172/353 (48.7) **Previous bad obstetric history:** 70/353 (19.8) **Previous infertility:** 43/353 (12.2) **Doubtful dates:** 39/353 (11.0) **Clinical suspicion of ectopic pregnancy:** 29/353 (8.2) **Inclusion Criteria** Ultrasound examination performed within study	**Tests** Transvaginal ultrasound	**Methods** This study includes all patients who had an ultrasound examination during the study period, whose mean gestation sac diameter was 1.0 - 2.0 cm. All women in whom fetal heart movements could not be demonstrated on transabdominal ultrasound were examined with a transvaginal transducer after the bladder was emptied. The vaginal transducer used was the 5-MHz phased array probe of the General Electric 3600 scanner (B mode only). The mean gestation sac diameter was calculated by averaging the maximum diameters taken in three planes at right angles to one another, from the interface of sac wall and chorionic fluid. Because of the improved clarity of transvaginal ultrasound over	**Results** **Visualisation of fetal heart movement, by gestation sac diameter/cm (number/total (%))** **a. 1.0-1.5 cm (n=171)** **Fetal heart seen:** 129/171 (75.4) (Note: the outcome of these pregnancies is not reported) **Fetal heart absent (n=42):** Continuing pregnancy: 10/42 (23.8) Miscarriage: 32/42 (76.2) (Note: all 10 continuing pregnancies had sac diameter of 1.0-1.2 cm; the authors report that foetal life was always demonstrated in an ongoing pregnancy when mean sac diameter was >1.2 cm)	**Limitations** **Population** The women had a transabdominal ultrasound scan, on which fetal heart movements could not be demonstrated. Any women with a sac diameter < 1 cm or > 2 cm were also not included in this study, and their outcomes are unknown. **Criteria for diagnosis of miscarriage** The authors report that uterine curettage was done in pregnancies with gestation sac diameter of 1.0 - 2.0 cm when miscarriage was diagnosed clinically, however they do not state the criteria used for clinical diagnosis of a miscarriage.

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visualisation of early pregnancy, would allow a definitive diagnosis of early pregnancy failure when the mean gestation sac is smaller than is possible to detect with transabdominal equipment. **Study dates** June 1986 to August 1987 **Source of funding** Not reported	period Mean gestation sac diameter of 1.0 - 2.0 cm **Exclusion Criteria** Not reported		transabdominal ultrasound, and previously published reports on the use of transabdominal ultrasound, any patients with a mean gestation sac diameter of > 2 cm in whom fetal heart movements could not be demonstrated was reported as having a pregnancy failure. With transvaginal ultrasound, fetal heart movements could frequently be seen with a gestation sac of < 1 cm diameter. However, it was clear that they could not always be seen in an ongoing pregnancy with such a small diameter, so in such patients, a repeat examination was suggested for the confirmation of fetal life. When the mean gestation sac diameter was between 1.0 and 2.0 cm and no fetal heart movement was demonstrated, a report was issued indicating that a definitive diagnosis could not be made. Uterine curettage was performed if the diagnosis of miscarriage was made clinically, or if repeat ultrasound 7 - 14 days later again failed to show fetal heart movements. The timing of the repeat scan was dependent on the initial size of the gestation sac. Patients were separated into two groups depending on whether the mean gestation sac diameter was 1 - 1.5 cm or	**b. 1.6-2.0 cm (n=182)** **Fetal heart seen:** 164/182 (90.1) (Note: the outcome of these pregnancies is not reported) **Fetal heart absent (n=18):** Continuing pregnancy: 0/18 (0) Miscarriage: 18/18 (100)	**Other information** In this study, fetal life could be demonstrated in all women with an ongoing pregnancy in whom mean sac diameter was > 1.2 cm. However, the authors advocate the use of a broad margin of error before reporting pregnancy failure (e.g. when using high quality transvaginal ultrasound equipment, they recommend only reporting failure in patients with mean sac diameter > 1.5 cm without cardiac activity), and that ultrasonographers should audit their own results before implementing this.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			1.6 - 2.0 cm		
Full citation Bree,R.L., Edwards,M., Bohm-Velez,M., Beyler,S., Roberts,J., Mendelson,E.B., Transvaginal sonography in the evaluation of normal early pregnancy: Correlation with HCG level, American Journal of Roentgenology, 153, 75-79, 1989 **Ref Id** 90998 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To examine correlative data of early pregnancy findings, hCG and gestational age **Study dates** Not reported	**Sample size** N=53 (comprising 75 separate ultrasound exams) **Characteristics** Not reported **Inclusion Criteria** Subsequently proved normal pregnancy **Exclusion Criteria** Not reported	**Tests** Transvaginal ultrasound	**Methods** 75 separate transvaginal examinations were performed on 53 patients with subsequently proved normal early pregnancies, between 32 days after the onset of the last menstrual period and approximately 50 days gestation by clinical estimate. 17 patients were from an IVF program, and were scanned a total of 37 times. The remaining 36 patients were scanned 38 times, therefore all but two patients had a single scan. These patients had various levels of confidence in the accuracy of their menstrual history. Gestational age data were only used from the IVF patients and those who could accurately state the date of their last menstrual period. 35 patients, comprising 54 examinations, had menstrual data considered reliable enough to tabulate. Each patient was scanned with a 7-MHz transvaginal probe (Bruel and Kjaer). The examinations were performed without preparation, with an empty bladder. In the earlier stages of the study, a few patients were scanned with the	**Results** **Visualisation of an embryo with a heartbeat (number/total (%))** **a. By mean gestation sac diameter/mm** **1-5 mm:** **Seen:** 0/16 (0) **Not seen:** 16/16 (100) **6-9 mm:** **Seen:** 4/16 (25) **Not seen:** 12/16 (75) **>9 mm:** **Seen:** 39/39 (100) **Not seen:** 0/39 (0) Note: only 71 examinations are reported because four patients had no sac identified **b. By gestation/days** **<32 days:** **Seen:** 0/4 (0) **Not seen:** 4/4 (100)	**Limitations** **Exclusions** Exclusion criteria, and any patients excluded from the study, are not reported. Similarly, inclusion criteria are not well-defined. **Other minor issues:** - The dates of the study are not reported, therefore it is more problematic to judge the accuracy of the scanning equipment. - The authors report that a few women were scanned using the transabdominal technique early in the study. It is not reported exactly how many participants this was, which data it is, or even if the data was included. **Other information** All participants had a subsequently proved normal early pregnancy.

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Source of funding Not reported			transabdominal technique, however this was abandoned when the advantages of transvaginal scanning were appreciated. Patients were examined for various clinical indications, including suspected abnormal pregnancy, however most of the patients from the fertility clinic were examined to confirm the pregnancy and for the purpose of this study. Transvaginal sonography was performed by a sonographer with a physician supervising. The probe was covered with a condom with acoustic gel placed over the transducer tip. The probe was usually inserted by the patient. In very early gestations, careful scanning in multiple planes was performed in order to identify a small gestation sac. Sac diameters were determined by taking a mean of a measurement of three orthogonal dimensions. In all sacs, the presence of a yolk sac and the presence of an embryo with a heartbeat were sought. At least two observers were asked to confirm the presence of heart activity. 41 out of the 53 patients had an initial or follow-up scan showing an embryo with a	**<u>32-36 days:</u>** **Seen:** 0/13 (0) **Not seen:** 13/13 (100) **<u>37-40 days:</u>** **Seen:** 8/20 (40) **Not seen:** 12/20 (60) **<u>>40 days:</u>** **Seen:** 17/17 (100) **Not seen:** 0/17 (0) Note: only 54 examinations are reported because of unreliable menstrual histories in the other patients	

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			heartbeat. The remaining 12 patients had only single scans in the first trimester, but subsequent scans in the second or third trimester confirmed normal pregnancy. 10 patients had multiple sequential scans performed at 3-day intervals beginning 4 to 6 days after a missed menstrual period. The scanning was discontinued when an embryo with a heartbeat was discovered. hCG levels were obtained within 24 hours of at least one of the sonograms in patients with multiple scans, and within 48 hours (mean 16 +/- 25 hours) of sonograms in patients with single scans.		
Full citation Brown,D.L., Emerson,D.S., Felker,R.E., Cartier,M.S., Smith,W.C., Diagnosis of early embryonic demise by endovaginal sonography, Journal of Ultrasound in Medicine, 9, 631-636, 1990 **Ref Id** 97138 **Country/ies where the study was carried out** USA	**Sample size** N=375 (this is the number of participants - 398 initial and follow-up examinations were performed) **Characteristics** Not reported **Inclusion Criteria** First trimester pregnant patients in whom the	**Tests** Vaginal ultrasound	**Methods** All of the study participants had been referred for evaluation of possible ectopic pregnancy, failed pregnancy or confirmation of early pregnancy. During the study period, 405 sonograms were performed. Follow-up could not be obtained in 7 patients in whom embryonic cardiac activity was absent. In all seven, the gestational sac contained a yolk sac with no observable embryo. Excluding these patients, 398 initial and follow-up scans were performed on 375 patients.	**Results** **<u>Visualisation of cardiac activity by crown-rump length/mm, in normal fetuses (number/total (%))</u>** **<u>0 mm (yolk sac present with no identifiable embryo)</u>** **Cardiac activity present:** 24/82 (29.3) **Cardiac activity absent:** 58/82 (70.7) **<u>1 mm</u>** No embryos with CRL of 1 mm	**Limitations** **<u>Partially retrospective</u>** 259/398 (65.1%) of the scans were evaluated retrospectively. **<u>Follow-up of those in which cardiac activity was seen</u>** The authors did not routinely follow-up those women in whom cardiac activity was initially seen to confirm that the pregnancy was continuing. However, this may not be a clinically significant limitation, because even if they had followed up the women and

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Retrospective cohort study **Aim of the study** To determine the smallest embryonic size at which demise can be confidently diagnosed when cardiac activity is absent by endovaginal ultrasonography. **Study dates** April 1988 to July 1989 **Source of funding** Not reported	gestational sac contained a yolk sac or an embryo with a crown-rump length of 12 mm or less, as determined by vaginal ultrasound **Exclusion Criteria** No follow-up available		Many of the other patients had follow-up scans later in their pregnancies, but 23 were during the time period at which the embryo had a CRL of 12 mm or less. In these 23 patients, the initial scan showed no embryo and absent cardiac activity. Of the 298 sonograms, 259 were evaluated retrospectively and 139 were evaluated prospectively. Generally, the patients were evaluated using vaginal sonography only; transabdominal ultrasound was rarely performed and if it was, it was for reasons unrelated to imaging the embryo and cardiac activity. Sonography was performed with either an Acuson 128 or a Toshiba SSA-90A with a 5-MHz transducer. When present, the embryo was identified as a small, linear, echogenic structure at one edge of the yolk sac. CRL measurements were rounded to the nearest mm. The presence of cardiac activity, seen as a repetitive flickering motion within the embryo or at the edge of the yolk sac, was evaluated at every examination. When it was suspected that maternal vascular pulsations were simulating embryonic cardiac	were identified in this study **2 mm** **Cardiac activity present:** 12/13 (92.3) **Cardiac activity absent:** 1/13 (7.7) **3 mm** **Cardiac activity present:** 31/31 (100) **Cardiac activity absent:** 0/31 (0) **4 mm** **Cardiac activity present:** 28/29 (96.6) **Cardiac activity absent:** 1/29 (3.4) **5mm** **Cardiac activity present:** 32/32 (100) **Cardiac activity absent:** 0/32 (0) **6 mm** **Cardiac activity present:** 33/33 (100)	had found an error, it would be impossible to tell whether the initial scan was incorrect or whether miscarriage had occurred between scans. **Other minor issues:** - Study dates are not reported, which makes judging of the accuracy of the ultrasound equipment more problematic **Other information**

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			activity, the maternal pulse was palpated simultaneously by the person performing the scan. In such cases, embryonic cardiac activity was only considered to be present when the rates were clearly different. Two viewers, one sonographer and one radiologist, evaluated each patient, The determination of absent cardiac activity required the agreement of both viewers after at least 4 minutes of real-time scanning specifically seeking cardiac activity. When cardiac activity was absent, clinical and often sonographic follow-up was done. Confirmation of demise was made in all cases by the demonstration of declining serum hCG levels, in combination with either spontaneous passage of material or a dilatation and curettage with removal of gestational material. Many patients also had a follow-up ultrasound scan, usually at least 1 week after the initial scan.	**Cardiac activity absent:** 0/33 (0) **7 mm** **Cardiac activity present:** 25/25 (100) **Cardiac activity absent:** 0/25 (0) **8 mm** **Cardiac activity present:** 33/33 (100) **Cardiac activity absent:** 0/33 (0) **9 mm** **Cardiac activity present:** 22/22 (100) **Cardiac activity absent:** 0/22 (0) **10 mm** **Cardiac activity present:** 19/19 (100) **Cardiac activity absent:** 0/19 (0) **11 mm** **Cardiac activity present:** 20/20 (100) **Cardiac activity absent:** 0/20 (0) **12 mm**	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Cardiac activity present: 13/13 (100) **Cardiac activity absent:** 0/13 (0) The authors state that, due to their inability to visualise cardiac activity in one 2-mm and one 4-mm embryo that progressed normally, the diagnosis of embryonic demise should not be made based on a single sonogram until the crown-rump length is at least 5 mm. Note: in addition to the scans detailed above, which resulted in normal pregnancies, there were 46 scans with absent cardiac activity which were confirmed as embryonic demise.	
Full citation Rempen,A., Diagnosis of viability in early pregnancy with vaginal sonography, Journal of Ultrasound in Medicine, 9, 711-716, 1990 **Ref Id** 97141 **Country/ies where the study was carried out** Germany	**Sample size** N=363 **Characteristics** Not reported **Inclusion Criteria** Normal, intrauterine, singleton pregnancy Had a detailed vaginal sonogram performed by	**Tests** Transvaginal ultrasound	**Methods** This study was conducted at the University Clinic of Obstetrics and Gynaecology, Wurzburg. Transvaginal ultrasounds were performed using a mechanical sector scanner with a 5-MHz transducer. The urinary bladder was empty, in order to have the uterus and adnexa in the focal zone of the probe. All 363 normal intrauterine singleton pregnancies with a	**Results** **<u>Detection of embryonic heart action (% (number/total))</u>** (Note: total and % were reported in the paper - the number visualised was calculated by the technical team) **<u>a. By menstrual age/weeks</u>** **4 weeks:** 0% (0/4) **5 weeks:** 19% (7/36)	**Limitations** No obvious serious limitations **Other information** The lowest values at which heart motion was detectable are: - **Menstrual age:** 40 days - **Chorionic cavity:** 9.3 mm - **CRL:** 2 mm

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Prospective cohort study **Aim of the study** To investigate the capability of modern vaginal sonography to detect the heart action of an embryo in the first trimester. **Study dates** March 1986 to November 1989 **Source of funding** Not reported	the author between 4 and 13 complete weeks menstrual age **Exclusion Criteria** Pregnancies ending miscarriage Major congenital malformation or chromosomal aberration Termination of pregnancy Lost to follow-up (no information about birth)		detailed vaginal exam performed by the author at 4 - 13 weeks menstrual age were considered for analysis. A precise gestational age based on reliable dates was available for 252 patients. When embryonic heart action was detected on the real-time B-mode image, it was registered with the time-motion display to calculate the heart rate using the electronic caliper and software of the ultrasound machine. The data were accumulated prospectively and documented on a form sheet. Only the first examination of each patient was accepted for analysis. Gestational age is reported in complete days or weeks menstrual age. The mean diameter of the chorionic cavity was calculated by averaging the maximum transverse, longitudinal and anteroposterior diameters, taken from the inner surface of the chorion.	**6 weeks:** 89% (56/63) **7 weeks:** 100% (39/39) **8 weeks:** 100% (34/34) **9-13 weeks:** 100% (68/68) (Note: the authors report that at and beyond a gestational age of 46 days (6 weeks, 4 days), heart motion was always visible) **b. By mean chorionic cavity diameter/mm** **< 5 mm:** 0% (0/28) **5 - 9 mm:** 3% (1/29) **10 - 14 mm:** 77% (33/43) **15 - 19 mm:** 90% (38/42) **20 - 24 mm:** 100% (50/50) **≥ 25 mm:** 100% (162/162) (Note: the authors report that cardiac motion was always visible at and beyond a chorionic cavity size of 18.3 mm) **c. By crown-rump length/mm** **< 5 mm:** 94% (34/36)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				5 - 9 mm: 100% (58/58) **10 - 14 mm:** 100% (41/41) **15 - 19 mm:** 100% (42/42) **20 - 24 mm:** 100% (29/29) **≥ 25 mm:** 100% (86/86) (Note: the authors report that heart motion was always visible at and beyond a CRL of 3 mm)	
Full citation Levi,C.S., Lyons,E.A., Lindsay,D.J., Early diagnosis of nonviable pregnancy with endovaginal US, Radiology, 167, 383-385, 1988 **Ref Id** 97196 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort study **Aim of the study** To diagnose a non-viable pregnancy on the basis of	**Sample size** N=62 (However only 35 of them have the presence/absence of cardiac activity reported and hence are the population of interest for this review question) **Characteristics** Not reported **Inclusion Criteria** Pregnancy less than 10 weeks menstrual age at the time of ultrasound Intrauterine gestation sac identified on either	**Tests** Endovaginal ultrasound	**Methods** Patients were examined with one of two endovaginal scanners: an ESI 1000 or an ESI 2000 (Elscint Inc.). Both had a 6.5-MHz mechanical sector endovaginal probe. 62 consecutive patients satisfying the inclusion criteria were included in this study. Data was accumulated prospectively but analysed retrospectively, with respect to the mean gestation sac diameters greater than which it was always abnormal not to identify a yolk sac or embryo. The mean diameter was determined by averaging three perpendicular diameters of the gestation sac, one of which was the maximum diameter. All measurements were obtained during the examination with	**Results** **Visualisation of cardiac pulsations in gestation sac >=16 mm** **a. In pregnancies with cardiac pulsations visualised on a subsequent scan (number/total (%))** **Cardiac pulsations seen:** 29/29 (100) **Cardiac pulsations not seen:** 0/29 (0) Note: Embryos with cardiac pulsations were identified in gestation sacs as small as 9.5mm. However, endovaginal ultrasound failed to identify an embryo in three gestation sacs between 9.5 and 16mm. The mean diameters of these gestation sacs were 10.1, 13.0	**Limitations** **Retrospective** This is a retrospective study. **Exclusion criteria** Exclusion criteria, and any exclusions from the study, are not reported. **Small sample size** Only 35 women were evaluated for the presence of cardiac activity. **Other minor issues:** - Stratification by gestation sac size is not done, however they do report the threshold size after which cardiac pulsations were seen in all fetuses that

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
gestation sac size and the presence or absence of a yolk sac or embryo as seen with endovaginal ultrasound **Study dates** November 1986 to June 1987 **Source of funding** Not reported	endovaginal or transvesicle ultrasound Both endovaginal and transvesicle ultrasound performed during the same visit **Exclusion Criteria** Not reported		electronic calipers. All patients, except those who opted for elective abortion (n=7), were followed up until at least the middle of the second trimester. The pregnancy was considered normal if a cardiac pulsation was identified on the reference or subsequent ultrasound examination, unless a miscarriage occurred in the first trimester (n=2).	and 15.8mm. Cardiac pulsations and the embryo were subsequently demonstrated in all three cases. **b. In pregnancies with no cardiac pulsations visualised on a subsequent scan (number/total (%))** **Cardiac pulsations seen:** 0/6 (0) **Cardiac pulsations not seen:** 6/6 (100)	had pulsations demonstrated on a later scan. - The use of transvesicle ultrasound is reported in the methods, but no outcomes are reported. However, the authors do state that endovaginal ultrasound consistently added information to the examination that was not available using transvaginal ultrasound. They also report that foetal cardiac activity was often demonstrated with endovaginal ultrasound prior to demonstration with transvesicle ultrasound. **Other information**
Full citation Hassan,R., Sandu,AanaL, Rich,K., Lal,S., Is transvaginal ultrasound a reliable test in the diagnosis of early embryonic demise? Outcomes of embryos less than 6mm in crown-rump length without cardiac activity, International Journal of Gynecology and Obstetrics, #19th FIGO World Congress of Gynecology and Obstetrics Cape Town South Africa. Conference Start, S536-, 2009	**Sample size** N=1174 **Characteristics** Not reported **Inclusion Criteria** All ultrasound examinations with single embryos with CRL ≤ 6mm **Exclusion Criteria** Not reported	**Tests** Transvaginal ultrasound	**Methods** This is a poster presentation and therefore has few methodological details. The data was collected prospectively using a computerised database at an Early Pregnancy Assessment Unit in the University Hospital of Wales, Cardiff. All ultrasound examinations with a single embryo of crown-rump length ≤ 6mm were included, regardless of clinical presentation and other	**Results** **Visualisation of cardiac activity by crown-rump length/mm** **a. In subsequently viable fetuses (number/total (%))** **1.0 - 1.9 mm** Cardiac activity seen: 9/11 (81.8) Cardiac activity not seen: 2/11 (18.2) **2.0 - 2.9 mm** Cardiac activity seen: 157/160	**Limitations** **Lack of methodological details** Generally lacking details about methodology, because it is a poster abstract. The full paper is still in the process of being written. **Exclusions** Exclusion criteria, and any exclusions from the study, are not reported.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 97589 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** To assess the outcomes of embryos with crown-rump length of ≤ 6mm without embryonic cardiac activity on ultrasound scan, and hence to establish whether improvements in sonographic technology would allow detection of embryonic demise at crown-rump length < 6mm. **Study dates** January 2006 to December 2008 **Source of funding** Not reported			sonographic findings. Embryonic viability was determined by a repeat ultrasound scan after one week and further outcomes at the dating scan. Sub-analysis was conducted to evaluate the effect of presenting symptoms on the outcome of embryonic viability.	(98.1) Cardiac activity not seen: 3/160 (1.9) **3.0 - 3.9 mm** Cardiac activity seen: 156/158 (98.7) Cardiac activity not seen: 2/158 (1.3) **4.0 - 4.9 mm** Cardiac activity seen: 221/224 (98.7) Cardiac activity not seen: 3/224 (1.3) **5.0 - 5.9 mm** Cardiac activity seen: 198/200 (99) Cardiac activity not seen: 2/200 (1) **6.0 mm** Cardiac activity seen: 206/206 (100) Cardiac activity not seen: 0/206 (0) Therefore, in total, 12 embryos	**Other information** For pregnancies ending in embryonic demise, in whom cardiac activity was visible at the first scan, it is not possible to elucidate whether the original scan was interpreted incorrectly, or whether miscarriage had occurred in between scans. The poster states that they had 1154 participants; however, all their reporting totals 1174 participants.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				without detectable cardiac activity that had a crown-rump length of ≤ 5mm were subsequently found to be viable. **b. In pregnancies ending in embryonic demise (number/total (%))** **1.0 - 1.9 mm** Cardiac activity seen: 3/4 (75) Cardiac activity not seen: 1/4 (25) **2.0 - 2.9 mm** Cardiac activity seen: 26/38 (68.4) Cardiac activity not seen: 12/38 (31.6) **3.0 - 3.9 mm** Cardiac activity seen: 37/57 (64.9) Cardiac activity not seen: 20/57 (35.1) **4.0 - 4.9 mm** Cardiac activity seen: 13/31 (41.9) Cardiac activity not seen: 18/31	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				(58.1) **5.0 - 5.9 mm** Cardiac activity seen: 26/45 (57.8) Cardiac activity not seen: 19/45 (42.2) **6.0 mm** Cardiac activity seen: 30/40 (75) Cardiac activity not seen: 10/40 (25) **Symptoms in patients with absent cardiac activity, by outcome (n=92)** **a. Viable (number/total (%))** **Pain:** 7/12 (58.3) **Bleeding:** 2/12 (16.7) **Pain and bleeding:** 0/12 (0) **Anxiety:** 2/12 (16.7) **Unknown:** 1/12 **b. Non-viable (number/total (%))** **Pain:** 7/80 (8.8)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Bleeding: 43/80 (53.8) **Pain and bleeding:** 16/80 (20) **Anxiety:** 7/80 (8.8) **Unknown:** 6/80 (7.5) The authors state that the absence of cardiac activity at a crown-rump length of 6 mm had 100% specificity and PPV for embryonic demise. They also report that the presence of vaginal bleeding does not affect this cut-off, but pain and vaginal bleeding together increase the likelihood of embryonic demise.	
Full citation Ferrazzi,E., Garbo,S., Sulpizio,P., Ghisoni,L., Levi,Setti P., Buscaglia,M., Miscarriage diagnosis and gestational age estimation in the early first trimester of pregnancy: transabdominal versus transvaginal sonography, Ultrasound in Obstetrics and Gynecology, 3, 36-41, 1993 **Ref Id** 97652 **Country/ies where the**	**Sample size** N=598 (Note: Not all of these women were evaluated for presence of cardiac activity and therefore do not form part of the population of interest for this review question. The population of interest is 76, which is the total number of scans performed on women to evaluate presence of heart activity; it is unclear whether each woman was scanned once or multiple	**Tests** Transabdominal ultrasound Transvaginal ultrasound	**Methods** 290 patients requiring genetic counselling were examined using transabdominal ultrasound. 308 patients scheduled for early termination of pregnancy were examined using transvaginal ultrasound. The women were scanned by the same personnel in different sessions. The aim of the examinations was to detect early pregnancy failure and to confirm a reliable date of gestation. Convex transducers of 5-MHz were used for transabdominal	**Results** Note: the following % are estimated from bar graphs plotting visualisation rate against gestational age in days **Visualisation of embryo with visible heart activity within the chorionic sac in continuing pregnancies, by gestational age/days (number visualised/total (%))** **Day 31:** **Transabdominal:** 0/2 (0) **Transvaginal:** 1/3 (33.3) **Day 34:**	**Limitations** **Inclusion criteria** Poorly reported. **Population** Women were presenting for genetic counselling or elective termination of pregnancy, therefore are not exactly the population of interest for this review question. **Criteria for "continuing pregnancy"** The data is reported for

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
study was carried out Italy **Study type** Retrospective cohort study **Aim of the study** To study the comparability of transabdominal and transvaginal ultrasound for detecting early pregnancy failure and obtaining a reliable dating of gestational age **Study dates** Not reported **Source of funding** Associazione Italiana per lo Studio delle Malformazioni	times during this process) **Characteristics** 290 patients requiring genetic counselling were examined by transabdominal ultrasound. 32/290 (11.0%) ended in miscarriage. 308 patients scheduled for early termination of pregnancy were examined by transvaginal ultrasound. 26/308 (8.4%) ended in miscarriage. **Inclusion Criteria** Not reported **Exclusion Criteria** Irregular menses Threatened miscarriage		scanning. Microconvex transducers of 5-MHz were used for the transvaginal approach (Hitachi-Ansaldo 560). Patients were asked to empty their bladder before either type of examination. Both ultrasound examinations were performed according to accepted procedures (no further details given, but reference provided). For transabdominal scanning, a gentle pressure on the abdominal wall with the small head of the transducer was sufficient to move any bowel covering the uterus. The aim of each examination was to visualise and measure the chorionic sac and the embryo and its heart activity. A diagnosis of miscarriage was made when: - the heart activity was not detected in a clearly identified embryo >=4mm - the embryonic pole was identified but the secondary yolk sac was not detectable when the chorionic sac had an average diameter >10mm. In doubtful cases, a second examination was performed after 1 week to satisfy these criteria, or to verify that: - the chorionic sac did not grow	**Transabdominal:** 4/6 (66.7) **Transvaginal:** 5/6 (83.3) **Day 35:** **Transabdominal:** 3/5 (60) **Transvaginal:** 5/5 (100) **Day 36:** **Transabdominal:** 3/6 (60) **Transvaginal:** 7/7 (100) **Day 37:** **Transabdominal:** 2/2 (100) **Transvaginal:** NR **Day 38:** **Transabdominal:** NR **Transvaginal:** 3/3 (100) **Day 39:** **Transabdominal:** 7/7 (100) **Transvaginal:** 5/5 (100) **Day 40:** **Transabdominal:** NR **Transvaginal:** 3/3 (100) **Day 41:** **Transabdominal:** 5/5 (100) **Transvaginal:** 4/4 (100) **Day 42:** **Transabdominal:** 3/3 (100) **Transvaginal:** 5/5 (100) Note: it is unclear whether these are scans performed on different women of different gestational ages, or whether women were scanned multiple times during the	women in whom pregnancy was continuing, however the methods and criteria for judging this outcome are not reported. Visualisation rates are reported by gestational age, and it is not reported how this was calculated. **Other minor issues:** **-** The dates of the study are not reported, hence judging the accuracy of the scanning equipment is more problematic. - The ultrasound examinations using different techniques were performed on different sets of women. However, as the purpose of the review question is not to compare different ultrasound techniques, it has not been downgraded. **Other information**

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			as expected Using transabdominal and transvaginal sonography, the following parameters were assessed: - the % visualisation rates of the chorionic sac within the endometrial cavity and the embryo were measured from 28 to 42 days of amenorrhea (analysis was done at 2-day intervals from 28 to 42 days gestation) - the % visualisation rate of the yolk sac was measured from 28 to 77 days of gestation - the yolk sac diameter and crown-rump length were measured in normal pregnancies - the gestational age at the time of a positive diagnosis of missed miscarriage was analysed - the % visualisation rate of the embryo was analysed in miscarriages	study period.	
Full citation Cacciatore,B., Tiitinen,A., Stenman,U.H., Ylostalo,P., Normal early pregnancy: serum hCG levels and vaginal ultrasonography findings, British Journal of Obstetrics and Gynaecology, 97, 899-903,	**Sample size** N=22 (2 had twin/triplet pregnancies and do not form part of the population of interest for this review question; therefore the	**Tests** Vaginal ultrasound	**Methods** The authors studied 22 healthy pregnant women, who conceived while attending their infertility clinic. 12 women had ovulation induced with clomiphene citrate, alone or in combination with hMG. The	**Results** **<u>Point of first detection of fetal heart beat (in the 20 singleton pregnancies)</u>** **<u>a. Gestational age/days</u>** **Mean (SEM):** 41.1 (0.3)	**Limitations** **<u>Exclusions</u>** No exclusion criteria or exclusions from the study are reported. Inclusion criteria are also not well reported.

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1990 **Ref Id** 97687 **Country/ies where the study was carried out** Finland **Study type** Prospective cohort study **Aim of the study** To correlate serum hCG levels with vaginal ultrasound findings in normal early pregnancy. **Study dates** Not reported **Source of funding** Academy of Finland Finnish Social Security Institute	population of interest is 20) **Characteristics** **Method of conception (number of women/total (%))** Ovulation induction with clomiphene citrate: 12/22 (54.5) Conceived without assistance: 10/22 (45.5) **Inclusion Criteria** Healthy pregnant woman Conceived while attending infertility clinic at the hospital **Exclusion Criteria** Not reported		other 10 conceived without assistance. The day of ovulation was assessed by detecting the mid-cycle urinary luteinising hormone (LH) surge in 10 women, or asssumed to occur on the day of hCG administration in 12 women. LH was assayed according to manufacturer's instructions, using an immunochemical test with a sensitivity of 30 iu/l. Gestational age was defined as the number of days after ovulation plus 14 days. Measurements of serum hCG concentration and ultrasound examinations were done every 2-4 days, starting from the first positive pregnancy test and continuing until a living fetus was observed. The ultrasonographer was not aware of the day of ovulation at the time of each scan. 20 women had a singleton pregnancy, 1 had twins and 1 had triplets. All the pregnancies developed normally until delivery. Serum hCG concentrations were assayed in duplicate on the day of the ultrasound, using an immunofluorometric assay calibrated against the	**Range:** 39 - 43 The authors report that vaginal ultrasound can reliably detect fetal echoes with visible heart motion by 43 days gestation. **b. Mean sac diameter/mm** **Mean (SD):** 15.1 (1.4) **Range:** 10 - 18 The authors report that fetal heart motion was always detected when the diameter of the gestation sac exceeded 18mm. (Note: the smallest embryo in which heart motion could be detected had a length of 2mm)	**Small sample size** N=22 **Population** The participants were all scanned as part of an IVF programme. **Other minor issues:** - Study dates are not reported, which makes judging the potential accuracy of the ultrasound equipment more complicated. - Data are not stratified by gestational age or gestation sac diameter. The only outcome that can be reported is the point at which fetal heart motion can be reliably detected. **Other information** The authors report that there was no difference in the rate of embryo development between pregnancies established after natural or treatment cycles. The two incidences of multiple pregnancy were assessed

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			International Reference Preparation. A cut-off level of 10 iu/l was used to indicate pregnancy. Unless analysed the same day, the samples were stored at -20°. Sonography used Aloka and Hitachi vaginal transducers with emission frequencies of 5.0-MHz and 6.5-MHz respectively. The women were placed in the lithotomy position and and a sterile lubricated condom was placed over the head of the vaginal transducer before insertion. The bladder was empty. The presence of a gestation sac was assumed when an intrauterine fluid collection was found which was either eccentrically located within the endometrium or outlined by a hyperechoic trophoblast rim, or both. Efforts were made to identify the double sac sign due to the different echogenicity between chorion and surrounding decidua. The average of measurements in three planes was taken as the diameter of the sac. The point at which fetal heart beat was first detected in the 20 singleton pregnancies is reported.		separately; however details have not been reported here as they are excluded from the population of interest for this review question.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Rowling,S.E., Langer,J.E., Coleman,B.G., Nisenbaum,H.L., Horii,S.C., Arger,P.H., Sonography during early pregnancy: Dependence of threshold and discriminatory values on transvaginal transducer frequency, American Journal of Roentgenology, 172, 983-988, 1999 **Ref Id** 98016 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** To quantify potential differences in visualisation of the gestational sac contents when images obtained with relatively low and high frequency were compared. To determine if a higher frequency transducer could	**Sample size** N=39 (39 patients underwent 42 transvaginal examinations, however only 16 of these were confirmed live intrauterine pregnancies and therefore comprise the main study population of interest for this review question) **Characteristics** **Age/years (range):** 16-40 **Indications for ultrasound (number/total ultrasounds (%))** Exclusion of ectopic pregnancy: 18/42 (42.9) Possible miscarriage/vaginal bleeding: 9/42 (21.4) Assessment of viability: 8/42 (19.0) Pelvic pain: 4/42 (9.5) Establishment of size/menstrual age: 3/42 (7.1) **Inclusion Criteria** Positive urine or serum	**Tests** Transvaginal ultrasound	**Methods** A prospective study using transvaginal ultrasound during early pregnancy was conducted. All examinations were performed with sonographic scanners with a 5-MHz curved transvaginal transducer or a curved 9-5-MHz endocavitary transducer. All patients were initially scanned using the 5-MHz probe, in line with the standard of care at the time of the study. In patients who verbally agreed, immediate re-examination of the intrauterine sac or fluid collection was performed using the 9-5-MHz endocavitary transducer. The second examination was performed by the same technologist and sonologist who performed the first exam. The study population consisted of 39 patients undergoing 42 examinations (37 patients had one examination, one had two examinations and one had three examinations). 41 of the examinations were performed by an experienced technologist and sonologist. An attending radiologist specialising in sonography was present during 20 examinations, and an	**Results** Note: this data has been stratified by the technical team **Visualisation of cardiac activity in live early intrauterine gestations, split by mean sac diameter/mm (number/total (%))** **<5.0 mm** Cardiac activity seen: 0/1 (0) Cardiac activity not seen: 1/1 (100) (Note: 4.6 mm diameter) **5.0 - 5.9 mm** Cardiac activity seen: 0/1 (0) Cardiac activity not seen: 1/1 (100) (Note: 5.0 mm diameter) **6.0 - 6.9 mm** Cardiac activity seen: 0/2 (0) Cardiac activity not seen: 2/2 (100) (Note: 6.0 mm diameter in both	**Limitations** **Small sample size** There were 39 participants in total. n=16 for viable pregnancies, with a maximum of 4 in each stratum. Some strata have only 1 participant. **Population** Only included women who had no fetal cardiac activity visualised on a previous transabdominal scan. **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
be used to definitively diagnose normal or abnormal intrauterine pregnancy at smaller gestational sac sizes, and thus earlier menstrual ages, than when a 5-MHz transducer was used. **Study dates** January 1996 to August 1996 **Source of funding** Not reported	pregnancy test Intrauterine gestational sac or fluid collection that did not appear to contain a live embryo on imaging with a 5-MHz transvaginal transducer **Exclusion Criteria** Diagnosis of extrauterine gestation Embryos measuring 10 mm or larger		abdominal imaging fellow was present during 21 exams. One was performed by a senior radiology resident. During each examination, the ability of the operators to visualise the double decidual reaction, yolk sac, embryo, and cardiac activity with the 5-MHz and 9-5-MHz transducers was recorded. The images were compared objectively for the presence or absence of yolk sac, embryo and heart rate, and then compared subjectively for image clarity, confidence in diagnosis and impact on patient treatment. On the basis of initial and follow-up examinations, the patients were divided into three groups: **Group 1 (n=16):** patients with normal early pregnancies in which embryos with cardiac activity were documented on initial or follow-up sonography (the population of interest for this review question) **Group 2 (n=6):** patients with intrauterine gestational sacs smaller than 13 mm without live embryos, that were probably normal pregnancies but did not	cases) **7.0 - 7.9 mm** Cardiac activity seen: 0/4 (0) Cardiac activity not seen: 4/4 (100) (Note: 7.0 mm in all cases) **8.0 - 8.9 mm** Cardiac activity seen: 1/3 (33.3) (Note: 8.1 mm diameter) Cardiac activity not seen: 2/3 (66.7) (Note: 8.5 mm and 8.6 mm diameters) **9.0 - 9.9 mm** No pregnancies in this group **10.0 - 10.9 mm** No pregnancies in this group **11.0 - 11.9 mm** Cardiac activity seen: 3/4 (75) (Note: 11.0, 11.0, 11.2 mm diameter)	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			have confirmatory ultrasound or pathological follow-up at the authors' institution **Group 3 (n=17):** patients with abnormal gestations, including embryonic demise and anembryonic pregnancy (defined as a gestational sac larger than 13 mm without a yolk sac or embryo) Note: due to the inclusion criteria being absence of a live embryo on the 5-MHz transducer, only the cardiac activity data for 9-5-MHz transducer will be reported here. No cardiac activity was seen using the 5-MHz transducer. Only data for live intrauterine pregnancies will be reported here. No cardiac activity was ever seen in groups 2 or 3.	Cardiac activity not seen: 1/4 (25) (Note: 11.0 mm diameter) **12.0 - 12.9 mm** No pregnancies in this group **13.0 mm** Cardiac activity seen: 1/1 (100) Cardiac activity not seen: 0/1 (0) Note: follow-up to confirm viability was not performed in two of these patients (sac diameters of 11.0 mm and 13.0 mm), however they are classed as viable due to visualisation of cardiac activity on first scan. The authors report that the threshold for detection of an embryo with cardiac activity was 8.1 mm sac diameter using the higher transducer. They also report that a live embryo was not always seen until 13 mm, although this is based on a population of 1. No cardiac activity was ever visualised in the 6 patients with "probable normal intrauterine gestations with unknown outcome" (group 2: sac diameters ranging from 3.4 - 13.0 mm) or in	

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				the group that ended in miscarriage (group 3: sac diameters ranging from 4.7 - 44.0 mm).	
Full citation Abdallah,Y., Daemen,A., Kirk,E., Pexsters,A., Naji,O., Stalder,C., Gould,D., Ahmed,S., Guha,S., Syed,S., Bottomley,C., Timmerman,D., Bourne,T., Limitations of current definitions of miscarriage using mean gestational sac diameter and crown–rump length measurements: a multicenter observational study [EARLY ONLINE VIEW], Ultrasound in Obstetrics & Gynecology, doi: 10.1002/uog.10109, 2011 **Ref Id** 151429 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study**	**Sample size** N = 1060 **Characteristics** **Outcome of pregnancy at 11 - 14 weeks, split by characteristics of embryo and sac (number/total (%))** Viable pregnancy: 473/1060 (44.6) - MSD, no yolk sac, no CRL: 183/473 - MSD, yolk sac, no CRL: 266/473 - CRL: 24/473 Non-viable pregnancy: 587/1060 (55.4) - MSD, no yolk sac, no CRL: 279/587 - MSD, yolk sac, no CRL: 153/587 - CRL: 155/587 No further details are reported regarding the characteristics of the study population.	**Tests** Transvaginal ultrasound	**Methods** This was a multi-centre, prospective observational study. Recruitment was done in three London hospitals during the study period, with additional data used that was collected at another centre during 2006 as part of the development of scoring systems to predict miscarriage. Of the women initially recruited, 112 were excluded due to missing data on viability or measurements. Eventually, 1060 eligible women were recruited. Indications for ultrasound included: lower abdominal pain, vaginal bleeding, poor obstetric history, and estimation of gestational age. Women with an IPUV (see inclusion criteria) were included. In order to establish immediate viability, scans were repeated 7 - 14 days later. The final outcome of the study was viability of the pregnancy at 11 - 14 weeks, at the time of routine nuchal translucency scan. Women were scanned using a Voluson E8, Aloka SSD 5000,	**Results** **Sensitivity* of different CRL thresholds, in the absence of fetal heart activity, for identifying fetuses that are later viable at 11 -14 weeks (% (n), 95% CI)** 3.0 mm: 75.0 (18/24), 95% CI 55.1 - 88.0 3.2 mm: 83.3 (20/24), 95% CI 64.2 - 93.3 3.4 mm: 87.5 (21/24), 95% CI 69.0 - 95.7 3.6 mm: 87.5 (21/24), 95% CI 69.0 - 95.7 3.8 mm: 87.5 (21/24), 95% CI 69.0 - 95.7 4.0 mm: 91.7 (22/24), 95% CI 74.2 - 97.7 4.2 mm: 91.7 (22/24), 95% CI 74.2 - 97.7 4.4 mm: 91.7 (22/24), 95% CI 74.2 - 97.7 4.6 mm: 91.7 (22/24), 95% CI 74.2 - 97.7	**Limitations** Sample size Although the overall study sample size was high, the population for the CRL threshold incorporated the measurements of only 24 women, who were those that had a CRL measurement and were later proved to have a viable pregnancy. Population Demographic characteristics of the study population are not reported; therefore it is unclear how long women waited between their initial scan and the 11 - 14 week scan. Presenting population do not exactly match the guideline's intended population, as an unknown proportion of women are presenting for a scan for reasons other than pain or bleeding. In three out of four centres, women with a MSD of > 20 mm would not have been included. It is not clear what the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
To define the false positive rate for the diagnosis of miscarriage associated with different crown-rump length (CRL) and mean sac diameter (MSD) measurements with or without a yolk sac, in a large study population of patients attending early pregnancies clinics. To define cut-off values for CRL and MSD that, on the basis of a single measurement, can definitively diagnose a miscarriage and so exclude the possibility of an inadvertent termination of pregnancy. **Study dates** 3 centres: September 2010 to March 2011 1 centre: January to October 2006 **Source of funding** One author is supported by the Imperial Health care NHS Trust NIHR Biomedical Research Centre	**Inclusion Criteria** Women classified as having an intrauterine pregnancy of uncertain viability (IPUV) at scan. In three centres, IPUV was defined as: - intrauterine sac of < 20 mm MSD with no obvious yolk sac or embryo - embryo with CRL < 6 mm with no fetal heart activity In one centre, IPUV was defined as: - intrauterine sac of < 30 mm MSD with no obvious yolk sac or embryo - embryo with CRL < 8 mm with no fetal heart activity **Exclusion Criteria** Clinically unstable Subsequently underwent elective abortion (Note: women with missing data on viability, or missing CRL or MSD measurements were also excluded from analysis)		or Samsung Medison Accuvix XG ultrasound machine, with a 6-12-MHz transvaginal transducer. Scans were done in EPAUs by gynaecologists, or nurses with training and experience of ultrasound in early pregnancy. The standard measurements taken were: - measurement of CRL in the sagittal plane - measurement of sac diameter in 3 orthogonal planes - determination of presence of a yolk sac - detection of cardiac activity Demographic variables were also recorded, however the study does not report them. Statistical analysis was performed to calculate the sensitivity, specificity, NPV and PPV for MSD with or without yolk sac from 8 to 30 mm and for CRL from 3 to 8 mm.	4.8 mm: 91.7 (22/24), 95% CI 74.2 - 97.7 5.0 mm: 91.7 (22/24), 95% CI 74.2 - 97.7 5.2 mm: 91.7 (22/24), 95% CI 74.2 - 97.7 5.3 mm: 100 (24/24), 95% CI 86.2 - 100 * Note: this represents the specificity values reported in the paper, as the study is aiming to detect miscarriages, whereas this review is aiming to ensure that all potentially viable fetuses are identified **Sensitivity* of different mean gestational sac diameters in the absence of both a yolk sac and an embryo, for identifying fetuses that are later viable at 11 - 14 weeks (% (n), 95% CI)** 8 mm: 63.9 (117/183), 95% CI 56.8 - 70.5 10 mm: 80.3 (147/183), 95% CI 74.0 - 85.4 12 mm: 88.0 (161/183), 95% CI 82.5 - 91.9 14 mm: 92.9 (170/183), 95% CI 88.2 - 95.8	outcomes for these women are. Criteria for judging viability It is not reported what criteria were used for judging viability at the 11 - 14 week scan. **Other information** The authors state that, because the scans were all carried out using high-quality equipment, and by staff with an interest in the complications of early pregnancy, the quality of the scans was likely to be high. Therefore, the thresholds reported are likely to represent the 'best case scenario.' More false positives for miscarriage are likely to occur where the quality of the scanning equipment is lower and where the scanners are less experienced. The authors also reference Pexsters et al. (2011), which is a study that examines inter- and intra-observer reliability of ultrasound scanning. They state that the limits of agreement mean that an MSD measurement of 20 mm by one examiner may translate to a measurement of anywhere between 16.8 and 24.5 mm for another examiner. Similarly, a

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				16 mm: 95.6 (175/183), 95% CI 91.6 - 97.8 18 mm: 98.9 (181/183), 95% CI 96.1 - 99.7 20 mm: 99.5 (182/183), 95% CI 97.0 - 99.9 21 mm: 100 (183/183), 95% CI 97.9 - 100 * Note: this represents the specificity values reported in the paper, as the study is aiming to detect miscarriages, whereas this review is aiming to ensure that all potentially viable fetuses are identified **Sensitivity* of different mean gestational sac diameters in the presence of a yolk sac but absence of an embryo, for identifying fetuses that are later viable at 11 - 14 weeks (% (n), 95% CI)** 8 mm: 35.7 (95/266), 95% CI 30.2 - 41.6 10 mm: 59.8 (159/266), 95% CI 53.8 - 65.5 12 mm: 77.8 (207/266), 95% CI 72.5 - 82.4 14 mm: 91.7 (244/266) 95% CI	measurement of CRL of 6 mm for one examiner may represent a range of 5.4 - 6.7 mm for someone else.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				87.8 - 94.5 16 mm: 97.4 (259/266) 95% CI 94.7 - 98.7 18 mm: 98.1 (261/266) 95% CI 95.7 - 99.2 20 mm: 99.6 (265/266) 95% CI 97.9 - 99.9 21 mm: 100 (266/266) 95% CI 98.6 - 100 * Note: this represents the specificity values reported in the paper, as the study is aiming to detect miscarriages, whereas this review is aiming to ensure that all potentially viable fetuses are identified	

What is the accuracy of transvaginal ultrasound compared with transabdominal ultrasound for diagnosing ectopic pregnancy?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Schurz,B., Wenzl,R., Eppel,W., Sch&#x00F6,nHJ, Reinold,E., Early detection of ectopic pregnancy by transvaginal ultrasound, Archives of Gynecology and Obstetrics, 248, 25-29, 1990 **Ref Id** 91962 **Country/ies where the study was carried out** Austria **Study type** Nested case-control study **Aim of the study** To estimate the reliability and advantages of transvaginal ultrasound and transabdominal ultrasound compared to clinical signs for detection of early ectopic pregnancy (extra uterine	**Sample size** n = 43 women with suspected EUP **Characteristics** Not reported **Inclusion Criteria** Women with suspected EUP **Exclusion Criteria** Not reported	**Tests** Transvaginal ultrasound (TVU) Transabdominal ultrasound (TAU) Plasma β-hCG level Reference standard: laparoscopy	**Methods** Data for the study were collected from 43 women with suspected EUP, who were referred to the Department of Gynaecology and Obstetrics, University of Vienna. n = 24 women had transabdominal ultrasound (TAU) and n = 19 had transvaginal ultrasound (TVU). Diagnostic laparoscopy was carried out for all women. The first step in the sonographic examination was to look for secondary signs of EUP: no intrauterine gestational sac, fluid in the Douglas pouch, and a thickened endometrium. Then the primary sign of an EUP were searched for: an extra uterine ring echo surrounded by a circular hyperdense wall like structure in the Fallopian tube. In addition, at least one plasma β-hCG level was obtained and clinical findings were recorded. Conservative treatment with prostaglandins or radical surgery was done based on the laparoscopic findings and the β-hCG values. Ultrasound performed at 6 to 10 weeks gestation (not clearly	**Results** **Diagnosis of primary sign of an EUP in women examined by TAU n = 24** n = 6/24 (25%) Clinical finding was positive in n = 14 (58%) of the above group and more significantly informative of EUP than the findings obtained by TAU (p< 0.02) **Diagnosis of primary sign of an EUP in women examined by TVU n = 19** n = 18/19 (94.7%) Clinical findings were positive in only n = 5 (26%) and less significantly informative of EUP than the finding obtained by TVU (p< 0.08) Average gestational age in the TVU group were lower than TAU group (no further details reported in the paper). **Diagnosis of secondary sign of an EUP in women examined by TVU or TAU n = 43** Endometrium < 10 mm n= 22 (55.8%) Endometrium > 10 mm n= 16 (37.2%) Flat endometrium n = 3 (6.9%) Fluid detected in Douglas pouch n = 9 (20.9%) Corpus luteum visualised n = 16 (37.2%) Pseudo gestational sac was found n = 3 (6.9%) (TAU = 4.17%, TVU = 10.53%)	**Limitations** Not clear how women were chosen to have TVU or TAU Not clear when and by whom the sonography examinations were performed Very poorly reported study **Other information** Equipment: For the sonographic examination a Kertz Combison 320 Real-time Scanner was used. Two different transducers were employed: a 3 MHz transabdominal sector scanner for TAU and a 5 (7.5 resp.) MHz panorama 240° vaginal scanner for TVU.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>pregnancy [EUP]).

Study dates

Not reported

Source of funding

Not reported</td><td></td><td></td><td>reported in the paper, assumption made based on the 3 figures that were reported in the paper).

According to the laparoscopic findings and the β-hCG values, either conservative treatment with prostaglandins or radical surgery was performed

<u>Analysis:</u>

For statistical evaluation, Fisher test and Chi-square test were used.</td><td>Vaginal spotting was reported in 83.7% of the women

Transvaginal ultrasound
<table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td></td><td>0</td></tr><tr><td>Predictive Test -ve</td><td></td><td>0</td></tr></table></td><td></td></tr>
<tr><td>Full citation

Shapiro,B.S., Cullen,M., Taylor,K.J., DeCherney,A.H., Transvaginal ultrasonography for the diagnosis of ectopic pregnancy, Fertility and Sterility, 50, 425-429, 1988

Ref Id

91986

Country/ies where the study was carried out

USA

Study type</td><td>Sample size

Total = 25 women with high suspicion of ectopic pregnancy

Characteristics

Not reported

Inclusion Criteria

Pregnant women with suspicion of ectopic pregnancy (pain and vaginal bleeding associated with a positive pregnancy test or by the presence of abnormally raising</td><td>Tests

Transvaginal Ultrasound
Transabdominal Ultrasound
Reference standard = Surgery (the type not specified)</td><td>Methods

n = 25 women with pain and bleeding and a high suspicion of ectopic pregnancy were included in the study. Women were examined by both types of ultrasound (TAU and TVU) on the same day. The transabdominal ultrasound (TAU) was performed and interpreted by a different sonographer blinded to information obtained by transvaginal ultrasound (TVU). Serum hCG titers were drawn on the same day of ultrasound examination and were determined by an immunoradiometric assay and a double antibody technique with the 1st IRP as a reference standard.

The adnexal mass associated with</td><td>Results

<u>Mean size of ectopic gestation</u>

<u>Transabdominal</u>
3.92 ± 0.40 (units not reported)
<u>Transvaginal</u>
3.5 ± 0.57
p = 0.55

The hCG titers at which an ectopic mass was identified ranged from 35 mIU/ml to 45,800 mIU/ml. There was no correlation between the specific hCG titers at the time of the examination and the ability to identify mass by TAU or TVU approach.

<u>Diagnostic accuracy of TVU in diagnosis of ectopic pregnancy (Surgically proven) n = 25</u>
True positive = 20
False positive = 2</td><td>Limitations

Not enough information reported to calculate the diagnostic accuracy of TAU
No information about reference standard provided (surgery)
Gestational age not reported

Other information

<u>Equipment:</u>
The TVU examinations were performed with a model RT 3000 and a 5-mHz vaginal transducer that used real time for the vaginal scans or with an ultrasound machine that</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prospective cohort study **Aim of the study** To compare the ability to identify the adnexal mass associated with ectopic pregnancy between the transvaginal and transabdominal ultrasound approaches in women with high suspicion of an ectopic pregnancy **Study dates** January to October 1987 **Source of funding** Not reported	titers of hCG, or both) **Exclusion Criteria** Not reported		ectopic pregnancy appeared as one of the four presentations that do not differ appreciably from findings described with the abdominal approach: 1. An extra uterine gestational sac containing a fetus with or without fetal heart rate 2. Similar to the 1st except that the sac is empty 3. Modification of the second appearance can be described as a thick echogenic band surrounding a small hypochic core 4. A diffuse echogeneic mass within the tube Analysis: Statistical significance was determined by use of Fisher's exact test, chi-square analysis, or Student's t-test.	True negative = 1 False negative = 2 *Sensitivity = 90% (95% CI 78 to 100) *Specificity = 33% (95% CI 20 to 86) *PPV (Positive Predictive Value) = 90% (95% CI 78 to 100) *NPV (Negative Predictive value) = 33% (95% CI 20 to 86) *LR = 1.36 (95% CI 0.60 to 3.06) *LR- = 0.27 (95% CI 0.05 to 2.17) **Diagnostic accuracy of TAU in diagnosis of ectopic pregnancy (Surgically proven) n = 25** True positive = 11 False negative = 11 *Sensitivity = 50% (95% CI 29 to 70) Not enough information reported to calculate all other diagnosis accuracy measurements * Calculated by NCC **Identification of adnexal mass in women with diagnosis of ectopic pregnancy (Surgically proven)** Transvaginal n = 20/25 (80%) Transabdominal n = 11/25 (44%) p = 0.02 **Identification of adnexal mass in women with ectopic pregnancy (Surgically proven)** Transvaginal n = *20/22 (91%) transabdominal n = *11/22 (50%)	used a 3-mHz or 5-mHz transabdominal probe for the TAU scans.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				p <0.01 **Positive identification of adnexal mass in women with ectopic pregnancy and hCG titers <6500 n = 17** Transabdominal n = 6/17 (35%) Transvaginal n = 15/17 (88%) p <0.01 **Negative identification of adnexal mass in women with ectopic pregnancy and hCG titers <6500 n = 17** Transabdominal n = 11/17 (65%) Transvaginal n = 2/17 (12%) p <0.01 **Positive identification of adnexal mass in women who had ectopic pregnancy and hCG titers <3600 n = 12** Transabdominal n = 6/12 (50%) Transvaginal n = 11/12 (92%) p = 0.037 **Negative identification of adnexal mass in women who had ectopic pregnancy and hCG titers <3600 n = 12** Transabdominal n = 6/12 (50%) Transvaginal n = 1/12 (8%) p = 0.037	

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<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Transvaginal ultrasound
<table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td>20</td><td>2</td></tr><tr><td>Predictive Test -ve</td><td>2</td><td>1</td></tr></table></td><td></td></tr>
<tr><td>Full citation

Thorsen,M.K., Lawson,T.L., Aiman,E.J., Miller,D.P., McAsey,M.E., Erickson,S.J., Quiroz,F., Perret,R.S., Diagnosis of ectopic pregnancy: Endovaginal vs transabdominal sonography, American Journal of Roentgenology, 155, 307-310, 1990

Ref Id

92104

Country/ies where the study was carried out

USA</td><td>Sample size

n = 193 women with suspected ectopic pregnancy

Characteristics

not reported

Inclusion Criteria

All women referred for pelvic sonography with clinical diagnosis of suspected ectopic pregnancy

Exclusion Criteria</td><td>Tests

Transvaginal ultrasound
Transabominal ultrasound
Serum hCG
Reference standard: final clinical diagnosis (surgery, complete abortion, no detectable serum hCG)</td><td>Methods

All women referred for pelvic sonography (with the clinical diagnosis of suspected ectopic pregnancy) underwent both endovaginal and transvaginal sonography. 143/193 had serum hCG test performed within a few hours of sonography. The remaining 50 women had positive urine pregnancy tests performed in the emergency department. The uterine cavity, adnexal regions, and presence or absence of pelvic fluid were evaluated specifically.

All women with documented ectopic pregnancy underwent surgery. Women with incomplete abortions, missed abortions, or blighted ova had dilatation and curettage. All women with normal</td><td>Results

Sonographic findings in suspected pregnancies vs. final clinical diagnosis Total n = 193

<u>Intrauterine pregnancy</u>
Final clinical diagnosis n= 83
Endovaginal n= 83/83 (n = 41 was identified after an indeterminate transabdominal scan)
Trans abdominal n= 34/83

<u>Ectopic pregnancy</u>
Final clinical diagnosis (surgically proved) n= 60

<u>Endovaginal n = 23/60</u>
Sensitivity = 38% (95% CI 26% to 50%)
Specificity = 100% (95% CI 100% to 100%)
Positive predictive value (PPV) = 100%</td><td>Limitations

In most cases the ultrasongrapher was not blinded to the result of the prior ultrasound
Gestational age not reported

Other information

<u>Equipment:</u>
Transabdominal sonography was performed on commercially available real-time sonographic units (general Electric RT/T 3600, RT/T 2800, or Radius systems, Milwaukee, WI) by using 3.5 or 5.0-MHz transducers.</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Nested case-control study **Aim of the study** To compare the diagnostic accuracy of transabdominal and endovaginal sonography in women with suspected ectopic pregnancy and to correlate sonographic findings with serum level of hCG **Study dates** 25 month period (year and date not reported) **Source of funding** Not reported	Not reported		intrauterine pregnancies had normal clinical or sonographic follow up examinations. In women with complete abortions, serial assays showed that serum levels of hCG dropped to zero. In most cases, the transabdominal and endovaginal ultrasounds were performed by the same examiners and interpreted at the same time	(95% CI 100% to 100%) Negative predictive value (NPV) = 78% (95% CI 72% to 84%) LR = infinity -LR = 0.6 (95% CI 0.50 to 0.75%) <u>Transabdominal n= 13*/60</u> Sensitivity = 21% (95% CI 11% to 32%) Specificity = 100% (95% CI 100% to 100%) Positive predictive value (PPV) = 100% (95% CI 100% to 100%) Negative predictive value (NPV) = 73% (95% CI 67% to 80%) LR = infinity -LR = 0.7 (95% CI 0.67 to 0.89) * n= 3 ectopic pregnancy were seen on transabdominal but not in endovaginal (n = 2 had a gestational sac with a viable fetus located above the uterus, n= 1 had a complex mass above the uterus) **<u>Missed abortion blighted ovum</u>** Final clinical diagnosis n = 14 Endovaginal n = 7/14 Transabdominal n = 5/14 **<u>Indeterminate</u>** Final clinical diagnosis n = 36 (n = 28 completed abortion, n = 8 no detectable serum level of hCG) Endovaginal n = 80* Transabdominal n = 141* * Cases of empty uterus and no specific sonographic diagnosis **Transvaginal ultrasound**	Endovaginal sonography was performed by using a 7.5 MHz endovaginal probe (Ausonics, lane Cove, NSW, Australia)

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Transabdominal ultrasound
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</td><td></td></tr>
<tr><td>Full citation

Kivikoski,A.I., Martin,C.M., Smeltzer,J.S., Transabdominal and transvaginal ultrasonography in the diagnosis of ectopic pregnancy: a comparative study.[Erratum appears in Am J Obstet Gynecol</td><td>Sample size

Total = 34 women with suspected EUP
Subgroup of study population:
n = 25 women with tubal pregnancy confirmed operatively

Characteristics</td><td>Tests

Transvaginal and transabdominal ultrasound
Reference Standards = Laparoscopy and surgery (not specified)</td><td>Methods

Data for the study were collected from n = 34 women with pain and bleeding and suspected ectopic pregnancy, who were referred to the Perinatal Laboratory at Barnes Hospital. All women were examined with both transvaginal and transabdominal ultrasound. All women had high index of suspicion for ectopic pregnancy on the basis</td><td colspan="2">Results

<u>Adnexal findings on transabdominal n = 34</u>
True positive = 12
False positive = 0
True negative = 7
False negative = 15
Sensitivity = 44%
Specificity = 100%
NPV = 31%
PPV = 100%</td><td>Limitations

Not clear if the sonographers were blinded to the result of the prior ultrasound.

Other information

Real time scans were performed with an ATL UltraMark 4, with a 3.5 or</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>1990 Dec;163(6 Pt 1):2030], American Journal of Obstetrics and Gynecology, 163, 123-128, 1990

Ref Id

95883

Country/ies where the study was carried out

USA

Study type

Nested case-control study

Aim of the study

To prospectively compare the diagnostic accuracy of transabdominal and transvaginal ultrasoungraphy in a pure population of operatively confirmed cases of ectopic pregnancy

Study dates

1st January 1988 to 4th January 1989

Source of funding</td>
<td>The women were 4 to 12 weeks of amenorrhoea at the time of evaluation (mean = 8.2 weeks)
Mean age (range) = 28.5 (18 - 39)
Mean gravity = 3 (0-9)
Mean parity = 1 (reflecting large number of women with infertility)

Inclusion Criteria

Women with suspected ectopic pregnancy

Exclusion Criteria

Not reported</td>
<td></td>
<td>of a history of previous ectopic pregnancy, prior tubal factor infertility or previous tubal surgery. All women had a positive urine or serum human chorionic gonadotropin (hCG) test result and all lacked an intrauterine gestational sac at the time of sonographic evaluation.

In n = 9/34 cases diagnosis of ectopic pregnancy was excluded basis of the lack of adnexal findings on ultrasound evaluation and at laparoscopy and/or the pathologic demonstration of villi at endometrial curettage. Laparoscopic examination was done in 6/9 cases.

All women were scanned initially with a standard transabdominal technique that included a fully urinary bladder and systematic evaluation of the uterus, adnexal areas, and cul-de-sac. After that, the bladder was emptied and systematic transvaginal ultrasound was performed.

The Adnexal findings were described as

1) Gestational sac containing a fetal pole with or without heart motion
2) An empty sac like structure surrounded by a thick rind of</td>
<td><u>Adnexal findings on transvaginal n= 34</u>
True positive = 19
False positive = 0
True negative = 8
False negative = 7
Sensitivity = 72%
Specificity = 100
NPV = 53%
PPV = 100%

<u>Adnexal findings (mass) on transabdominal vs. transvaginal (n=25 ectopic pregnancy on operated cases)</u>
Transvaginal = 21/25 (84%)
Transabdominal = 17/25 (68%)
p = ns

<u>Gestational sac on transabdominal vs. transvaginal</u>
Transvaginal = 16/25 (64%)
Transabdominal = 8/25 (32%)
p < 0.01
Laparatomy was performed in 24 cases, the tube was unruptured in 86% of the women.

Transvaginal ultrasound

<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>19</td><td>0</td></tr>
</table>
</td>
<td>5.0 MHz abdominal sector transducer and a 5.0 MHz vaginal probe, or a hitachi EUB- 450 with a 3.5 MHz abodminal convex transducer and a 6.5 MHz vaginal probe.</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>Not reported</td><td></td><td></td><td>echoes or 3) a complex or solid mass separate from recognisable ovary.
All 25 women underwent operation for confirmation of the sonographic findings within 24 hours of evaluation.
All ultrasonographic examinations were performed by an experienced sonographer and verified by a physician.</td><td>
<table>
<tr><td>Predictive Test -ve</td><td>7</td><td>8</td></tr>
</table>
Transabdominal ultrasound
<table>
<tr><td></td><td>Reference Test +ve</td><td>Reference Test -ve</td></tr>
<tr><td>Predictive Test +ve</td><td>12</td><td>0</td></tr>
<tr><td>Predictive Test -ve</td><td>15</td><td>7</td></tr>
</table>
</td><td></td></tr>
<tr><td>Full citation

Cacciatore,B., Stenman,U.H., Ylostalo,P., Comparison of abdominal and vaginal sonography in suspected ectopic pregnancy, Obstetrics and Gynecology, 73, 770-774, 1989

Ref Id

96721

Country/ies where the study was carried out</td><td>Sample size

n = 100 women with positive pregnancy tests and clinical suspicion of ectopic pregnancy

Characteristics

Not reported

Inclusion Criteria

Women with a positive pregnancy test and clinical suspicion of ectopic</td><td>Tests

Transabdominal ultrasound
Transvaginal ultrasound
Reference standard = surgery (the type not specified)</td><td>Methods

Vaginal sonography was performed after abdominal scan with an empty bladder. All scans were performed by the same investigator. Hard copy images of both scans were examined separately by an independent reviewer in each case, to reduce the bias error.
Based on the sonographic findings at the first examination, women were assigned to one of the following groups:

Group A: A living intrauterine fetus or yolk sac was seen; women received normal care

Group B: An intrauterine double</td><td>Results

<u>Comparison of Vaginal and Abdominal Sonography Accuracy (Ectopic pregnancies n = 34)</u>

<u>Adnexal mass</u>
Abdominal n = 31 (80%)
Vaginal n = 35 (90%)
p = ns

<u>Ectopic fetus</u>
Abdominal n = 0 (0)
Vaginal n = 8 (21%)
p < 0.05

<u>Ectopic sac</u>
Abdominal n = 17 (44%)
Vaginal n = 27 (69%)
p < 0.05</td><td>Limitations

Not clear how women were recruited
Both travsvaginal and transabdominal scans were performed by the same ultrasonographer
Study period not reported

Other information

<u>Equipment:</u>

Sector scanners (Aloka SSD 710, 280 LS, and 360) with 3.0-, 3.5- and 5.0-MHz transducers for abdominal sonography</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Finland **Study type** Prospective cohort study **Aim of the study** To evaluate accuracy of vaginal and abdominal sonography in cases of suspected ectopic pregnancy **Study dates** Not reported **Source of funding** Supported by a grant from Academy of Finland	pregnancy **Exclusion Criteria** Not reported		sac or an eccentric ring, or both, were seen. Intrauterine pregnancy was considered probable, and quantitative assay and ultrasound scan were performed 1 week later. Group C: The uterus was empty or central ring was seen, but no adnexal mass or cul-de-sac fluid was found. Ectopic pregnancy was considered possible, and hCG assay and ultrasound scan for every second day were scheduled. Laparoscopy was performed if an intrauterine gestational sac was not detected by abdominal sonography at the serum hCG level of less than 1800 IU/L. An increase in the hCG level less than 66% within 2 days was also considered abnormal. Group D: The uterus was empty or a central ring was seen, and adnexal mass or cul-de-sac fluid was found. Ectopic pregnancy was considered probable and laparoscopy was performed. Group E: A viable extra uterine fetus was detected and laparotomy was performed. The intrauterine pregnancies were classified as normal if the scan revealed a viable intrauterine fetus and abnormal if a miscarriage was diagnosed histologically after curettage. Ectopic pregnancy was confirmed by histologic examination of tissue	<u>Unruptured ectopic n = 34</u> Abdominal n = 17 (50%) Vaginal n = 28 (82%) p < 0.05 <u>Hemoperitoneum n = 13</u> Abdominal n = 6 (46%) Vaginal n = 10 (77%) p = nc** **<u>Comparison of Vaginal and Abdominal Sonography Accuracy (Intrauterine pregnancies n = 61 [n=35 developed normally; n= 26 ended in spontaneous miscarriage])</u>** <u>Gestational sac</u> Abdominal n = 54 (89%) Vaginal n = 56 (92%) p = ns* <u>Yolk sac or viable fetus</u> Abdominal n = 0 (0%) Vaginal n = 30 (49%) p < 0.001 *ns = not significant **nc = not calculated In intrauterine pregnancy, gestational sacs were detected in two cases at 31 and 32 days from the last menstruation (no gestational ages at the time of ultrasound were reported for the rest of population)	Three kinds of vaginal transducers (KretzTechnik, General Electric, and Aloka) and a frequency of 5.0-MHz were used throughout the study

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			samples obtained by surgery. Analysis The difference in proportion was tested by the McNemar test.		

What is the diagnostic accuracy of two or more hCG measurements for determining an ectopic pregnancy in women with pain and bleeding and pregnancy of unknown location?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Thorburn,J., Bryman,I., Hahlin,M., Lindblom,B., Differential diagnosis of early human pregnancies: impact of different diagnostic measures, Gynecologic and Obstetric Investigation, 33, 216-220, 1992 **Ref Id** 70502 **Country/ies where the study was carried out** Sweden **Study type** Prospective cohort study **Aim of the study** To evaluate the	**Sample size** N=261 **Characteristics** **Final diagnosis (number of women/total (%))** EP: 90/261 (34.5) Normal IUP: 82/261 (31.4) Miscarriage: 40/261 (15.3) Pathologic pregnancy with unclear location: 49/261 (18.8) **Presenting symptoms** **a. Pain/bleeding (%)** EP: 88 Normal IUP: 61	**Tests** hCG score (calculated by plotting the initial hCG against the absolute slope of the hCG) **Test positive:** abnormal hCG score **Test negative:** normal hCG score	**Methods** 261 outpatients were included. The women presented because of bleeding or pain, and/or suspected pregnancy in the presence of previously known risk factors for EP. Only stable women with a positive pregnancy test were included. For each patient, a risk score for EP was calculated and used in a risk model. The model's variables were: previous EP, IUCD in situ, history of infertility, and previous abdominal surgery. Vaginal ultrasound was performed, and if an intrauterine gestation sac was identified and there were no pathological symptoms, the patient was excluded. The ultrasound criterion for EP was restricted to a sac with foetal echoes outside the uterine cavity. Cases with indirect proofs, such as an adnexal mass or cul-de-sac fluid were classified as gestations of unclear location. A serum sample was drawn for hCG and progesterone analysis, and women returned within 24-72 hours to allow calculation of an hCG “score.” [The hCG score is a	**Results** **Proportion of women with abnormal hCG score (number/total (%))** EP: 73/90 (81) IUP: 13/82 (16) Miscarriage: 34/40 (86) PUL: 49/49 (100) **Diagnostic accuracy of an abnormal hCG score for diagnosing ectopic pregnancy (95% CI)** **Sensitivity:** 81.1 (73.0 to 89.2) **Specificity:** 43.9 (36.4 to 51.3) **PPV:** 43.2 (35.7 to 50.7) **NPV:** 81.5 (73.6 to 89.5) **LR+:** 1.44 (1.22 to 1.71) **LR-:** 0.43 (0.27 to 0.68)	**Limitations** **Population** Not all the participants presented with pain and bleeding; women were also included who had risk determinants for ectopic pregnancy. **Blinding** It is not reported whether the clinicians performing the reference tests were blinded to the results of the index test. **hCG score** The paper does not define hCG score, but instead refers the reader to an alternative paper by the same authors (Lindblom et al. 1989). Similarly, the paper does not define what a "pathologic hCG score" is, however in Lindblom et al. 1989

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>usefulness of different diagnostic measures (clinical findings, hCG assays and sonography) in arriving at a correct final diagnosis in very early pregnancies.

Study dates

December 1988 to December 1989

Source of funding

Swedish Medical Research Council

Merchant Hjalmar Svensson's Foundation, Goteborg</td>
<td>Miscarriage: 85

Pathologic pregnancy with unclear location: 98

b. Normal pelvic status (%)

EP: 69

Normal IUP: 90

Miscarriage: 87

Pathologic pregnancy with unclear location: 90

c. Risk score for EP points (mean)

EP: 2.52

Normal IUP: 1.47

Miscarriage: 1.18

Pathologic pregnancy with unclear location: 0.94

(Note: <1.75: no increased risk for EP; 1.75-3.33: 10% increased risk for EP; 3.34-5.94: 20% increased risk for EP; >5.94: 100% for EP in</td>
<td></td>
<td>data point found by plotting the initial hCG against the absolute slope of the hCG (absolute slope: 2nd hCG - 1st hCG / interval between measurements)]. If the preliminary diagnosis was still unclear, patients returned for a 2nd ultrasound. In 8% of patients, the final diagnosis was established at the first visit by combined use of clinical symptoms/findings, risk score value, one ultrasound and a single hCG and progesterone value. In 42% of cases the hCG score (therefore using two blood samples) had to be added to this to make a diagnosis. In 49% of cases, the hCG score and a 2nd ultrasound had to be considered.

A preliminary diagnosis was set for each patients within 4 days after consultation and one of the following measures was selected or performed:
- Surgery (laparoscopy or dilation and curettage)
- Active expectation
- Referral to a maternal health care unit

The clinical course or histopathological examination after a dilation and curettage necessitated a second intervention in 40 cases.</td>
<td>Pathologic vs. normal hCG score
<table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td>73</td><td>96</td></tr><tr><td>Predictive Test -ve</td><td>17</td><td>75</td></tr></table></td>
<td>they distinguished IUP and EP by drawing a line to separate the clusters, and they appear to have used the same threshold again.

<u>Ultrasound criteria</u>

It is unclear that the inclusion/exclusion criteria for this paper correctly restrict the study population to exactly what other papers have considered a PUL. Only cases with a sac with foetal echoes outside the uterine cavity were classed as EP; cases with indirect proofs such as adnexal masses and cul-de-sac fluid were classed as PUL. There was a visible sac on first ultrasound examination in 1% of the women finally diagnosed with EP, 79% finally diagnosed with IUP, 62% finally diagnosed with miscarriage, and 8% finally diagnosed with pathological pregnancy of unclear location. Not everyone received an intervention</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	case of pregnancy) **d. hCG/IU/l (mean)** EP: 2774 Normal IUP: 11288 Miscarriage: 7666 Pathologic pregnancy with unclear location: 477 **e. Progesterone/nmol/l (mean)** EP: 23.7 Normal IUP: 48.7 Miscarriage: 25.5 Pathologic pregnancy with unclear location: 13.6 **Gestational age/days (mean)** At time of preliminary diagnosis: 43 At time when first treatment		**Classification of final outcome** **EP/miscarriage:** The final diagnosis of EP or miscarriage was based on the histopathological examination of surgical specimens. **Normal IUP:** The diagnosis of a normal IUP was based on further development of the pregnancy, including routine ultrasound in the 16-17th gestational week. **PUL:** Cases with low and declining hCG levels or no clear histopathological diagnosis and/or negative findings at laparoscopy or dilation and curettage were classified as pathological pregnancies of unknown location (PUL). After surgery, cases of EP or miscarriage were followed with consecutive hCG analyses until non-pregnant levels were obtained (<20IU/l).		as a result of an hCG score, because 8% of women were diagnosed at first visit without a second hCG being needed. However, the hCG scores for the whole population are known, irrespective of ultrasound findings, and therefore a 2x2 can be created. **Pathologic PUL** The location of these pregnancies is not reported, therefore some could have been ectopic pregnancies. However, they had low and declining hCG levels, and did not receive further intervention. **Other information** This paper has one author in common with Hahlin et al. 1991 and was conducted in the same location. The study period for this paper is contained within the study period of Hahlin et al. 1991,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	was selected/performed: 47 **Inclusion Criteria** Stable clinical condition Positive urinary pregnancy test Bleeding or pain, and/or suspected pregnancy in the presence of previously known risk determinants for ectopic pregnancy **Exclusion Criteria** Intrauterine gestational sac was clearly identified on scan and no pathological symptoms				therefore some of the women may appear in both papers. This is less likely for the viable IUP, as Hahlin et al. had fewer included cases of viable IUP despite a study period that was twice as long, however it is possible for the EP, considering the rarity of the event. Calculations of diagnostic accuracy were performed by the technical team. **First treatment measure in relation to final diagnosis (number of women)** **Active expectation (n=78)** PUL: 32 IUP: 23 Miscarriage: 12 EP: 11 **Curettage (n=54)** Miscarriage: 25 PUL: 15 EP: 14 **Laparoscopy (n=55)** EP: 49

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Miscarriage: 3 PUL: 2 IUP:1 **Laparotomy (n=16)** EP: 16 **Discharged to maternal health care (n=58)** IUP: 58 It is unclear that they waited sufficient time before doing curettage. Out of the 54 women who had curettage as their primary intervention, only 25 had a miscarriage (15 had negative findings and 14 had an EP). Therefore, they may have inadvertently terminated viable IUPs. However, this does not affect the diagnosis of EP. **Progesterone** Progesterone was measured (see characteristics), and the authors report that a single serum progesterone value is

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					useful for separating normal IUP and pathological pregnancies (p<0.001) but not for distinguishing EP from miscarriages. No further details are given.
Full citation Hahlin,M., Sjoblom,P., Lindblom,B., Combined use of progesterone and human chorionic gonadotropin determinations for differential diagnosis of very early pregnancy, Fertility and Sterility, 55, 492-496, 1991 **Ref Id** 72394 **Country/ies where the study was carried out** Sweden **Study type**	**Sample size** N=307 **Characteristics** **<u>Final diagnosis (number of women/total (%))</u>** EP: 159/307 (51.8) Viable IUP: 73/307 (23.8) Miscarriage: 75/307 (24.4) Note: presenting symptoms are not reported **Inclusion Criteria** Positive urine hCG test Clinical suspicion of EP (based on symptoms or the	**Tests** hCG score (calculated by plotting the initial hCG value against the rate of change of the serum level of hCG) **Positive test:** pathologic / abnormal hCG score (falling below the curve that separates normal IUP and EP) **Negative test:** normal hCG score (falling above the curve that separates normal IUP and EP)	**Methods** During the study period, two blood samples with an interval of 1-6 days (mean 2.2, SD 1.21) were obtained from patients meeting the inclusion criteria. In addition to the 307 patients eventually included, there were 18 patients whose final diagnosis was unknown because no chorionic villi or trophoblast cells were found intrauterinely or extrauterinely, despite temporarily elevated serum hCG levels in the range of 100-850 IU/l. Another 22 patients were excluded because their serum hCG declined rapidly below 50 IU/l without therapeutic measures. Finally, in 9 patients, it was not possible to wait for a second serum sample due to the patient's clinical condition. Blood samples were obtained from one of the antecubital veins and centrifuged. The serum was stored at -20 degrees Celsius until	**Results** **<u>Proportion of women with a pathological hCG score (number/total (%))</u>** EP: 141/159 (88.7) Miscarriage: 74/75 (98.7) Viable IUP: 4/73 (5.5) **<u>Diagnostic accuracy of a pathological hCG score for diagnosing EP (95% CI)</u>** Sensitivity: 88.7 (83.8 to 93.6) Specificity: 47.3 (39.3 to 55.3) PPV: 64.4 (58.0 to 70.7) NPV: 79.6 (71.1 to 88.0) LR+: 1.68 (1.43 to 1.98)	**Limitations** **<u>Population</u>** An unknown proportion of patients were analysed due to the suspicion of EP based on risk factors. Therefore, not all of the women in this study presented with pain and bleeding. The study also only included women with hCG of 100-4000 IU/l. **<u>Blinding</u>** It is not reported whether the clinicians performing the reference tests were blinded to the results of the index test.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Prospective cohort study

Aim of the study

To evaluate the diagnostic potential of the combined application of progesterone and an increase in hCG in differentiating viable intrauterine pregnancies from pathological pregnancies

Study dates

January 1987 to April 1989

Source of funding

Swedish Medical Research Council

Goteborg Medical Society, Goteborg</td>
<td>presence of risk factors)

Initial serum hCG between 100 and 4000 IU/l (the lower limit was set to reduce the number of cases in which it was impossible to establish a definite diagnosis; the upper limit was set to exclude cases in which endovaginal sonography has high diagnostic accuracy)

Clinical examination, including vaginal sonography, failed to give clear diagnosis

Exclusion Criteria

Ovarian stimulation

Unknown final diagnosis

Rapid decline in hCG to below 50 IU/l without intervention

Aggravated clinical condition which prevented second serum sample being taken</td>
<td></td>
<td>analysed. Serum progesterone and hCG were determined using time-resolved fluoroimmunoassay.

The hCG score was calculated by plotting the initial hCG value against the rate of change in serum hCG levels. In a previous study, it was shown that a line with the equation $y = 12.31x^{0.46}$ discriminated normal IUP and EP, where y is the absolute daily change and x is the initial hCG value. A patient with an hCG score falling below the curve is designated as having an "abnormal" hCG score, whereas a patient with an hCG score above the curve has a "normal" hCG score. For daily use, copies of the curve on graph paper were prepated, and the data point of each patient was plotted to see where it fell in relation to the curve. Diagnostic accuracy of the test could then be calculated.

<u>Classification of final outcome</u>

Viable IUP: The criteria was normal foetal development including heart activity in the 8th-10th gestational week, evaluated using vaginal sonography

EP: Diagnosed based on laparoscopy, and confirmation of</td>
<td>LR-: 0.24 (0.15 to 0.38)

Pathologic vs. normal hCG score
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>141</td><td>78</td></tr>
<tr><td>Predictive Test -ve</td><td>18</td><td>70</td></tr>
</table>
</td>
<td>Other information

Calculations of diagnostic accuracy were performed by the technical team.

This paper's study period overlaps with that of Thorburn et al. 1992 and was conducted in the same hospital. Therefore some women may appear in both papers, particularly the women eventually diagnosed with EP, as it is a rare event.

Progesterone is also assayed in this study, however it is not relevant to this review question and will be reported elsewhere.

The interval between two consecutive measurements ranged from 1 to 6 days, however the mean was 2.2 days and the hCG score is calculated using a slope which accounts for different time intervals.</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			extrauterine trophoblast by histopathological examination **Miscarriage:** Diagnosis was based on histological confirmation of the presence of chorionic villi in curettage material		
Full citation Condous,G., Okaro,E., Khalid,A., Timmerman,D., Lu,C., Zhou,Y., Van,HuffelS, Bourne,T., The use of a new logistic regression model for predicting the outcome of pregnancies of unknown location, Human Reproduction, #19, -1910, 2004 **Ref Id** 91114 **Country/ies where the study was carried out** UK **Study type** Prospective cohort	**Sample size** N=196 (This is the test set, on whom the model was tested prospectively, and on whom diagnostic accuracy measures were calculated. The original data set was 199 women, but 3 were excluded. A further 186 women comprised the training set, on whom the model was developed) **Characteristics** **<u>Final Diagnosis (number of women/total (%))</u>** **Training set:** EP: 20/189 (10.6) IUP: 63/189 (33.3) Failing PUL: 102/189 (54.0)	**Tests** Model M1 (incorporates serum hCG ratio)	**Methods** **<u>Data collection</u>** All women were seen in one single Early Pregnancy Unit (St George's Hospital, London). When pregnancies were classified as PUL (see inclusion criteria), peripheral blood was taken. All scans were reviewed and followed up by the same primary investigator. The study group consisted of 388 consecutive women with pregnancies of unknown location. The first 189 women (data collected between June 2001 and February 2002) were used as the training set. Statistical analysis and building of the logistic regression models were based on this data set. The next 199 women (recruited March 2002 to December 2002) were taken as the test set, to prospectively evaluate the performance of the models.	**Results** **<u>Model M1</u>** This model uses hCG ratio only, and allows calculation of the predicted probability of an EP, using equations involving natural logs and hCG ratio: Probability of EP = $(e^{5.79 - 4.21hCG\ ratio}) / (1 + e^{5.79 - 4.21hCG\ ratio} + e^{9.92 - 7.66hCG\ ratio})$ **<u>Area under ROC curve of M1 for diagnosing ectopic pregnancy (95% CI)</u>** **Training set**: 0.839 (0.728 to 0.950) **Test Set:** 0.885 (0.760 to 1) **<u>Diagnostic accuracy of M1 for diagnosis of EP (using Test Set)</u>** **a. when using probability threshold of 0.21 for distinguishing EP from non-EP (95% CI)** Sensitivity: 83.3 (62.3 to 100)	**Limitations** **<u>Population</u>** Some of the women presented for ultrasound without pain and bleeding, i.e. due to poor obstetric history or to determine gestational age **<u>Blinding</u>** It is not reported whether the clinicians performing the reference tests were blinded to the results of the index test. **<u>Generalisability</u>** The model was designed and tested on a specific inner city London population, therefore may not be generalisable.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
study **Aim of the study** To generate and evaluate new logistic regression models, based on demographic and hormonal parameters, to predict the outcome of pregnancies of unknown location (PUL). **Study dates** June 2001 to December 2002 **Source of funding** Katholieke Universiteit Leuven, Belgium Belgian Programme on Interuniversity Poles of Attraction Concerted Action Project MEFISTO-666 of the Flemish Community	Persisting PUL: 4/189 (2.1) **Test set:** EP: 12/199 (6.0) IUP: 75/199 (37.7) Failing PUL: 109/199 (54.8) Persisting PUL: 3/199 (1.5) **Indications for the ultrasound scan** - lower abdominal pain, with or without vaginal bleeding - poor obstetric history - to determine gestational age **Presenting symptoms (number of women/total (%))** **Training set:** not reported		The following data was collected: serum hCG and serum progesterone (at presentation and 48 hours), demographics (age and gestation), and ultrasound features (endometrial thickness, the character of its midline echo and the presence/absence of free fluid in the pouch of Douglas). Women were followed up until an outcome diagnosis was established: failing PUL, IUP or EP. **Classification of final outcome** **Persistent PUL:** 4 women in the training set and 3 women in the test set had serum hCG levels that plateaued, and no pregnancy was seen at any time. These women were classified as having persistent PUL, and were treated with methotrexate and excluded from the analysis. They were not used for model development or validation, because the outcome is unknown and the numbers were so few. **Failing PUL:** If initial serum progesterone level was <20nmol/l, the women were classified as having a failing PUL. Spontaneous resolution of the pregnancy was defined as a decrease in the serum hCG level to <5IU/l with the disappearance of symptoms. The location of the failing PULs	Specificity: 88.0 (83.4 to 92.7) PPV: 31.3 (15.2 to 47.3) NPV: 98.8 (97.1 to 100) LR+: 6.97 (4.37 to 11.11) LR-: 0.19 (0.05 to 0.67) **b. when using cost values of 1, 1, and 4 for failing PUL, IUP and EP (95 % CI)** Sensitivity: 83.3 (62.3 to 100) Specificity: 86.4 (81.5 to 91.4) PPV: 28.6 (13.6 to 43.5) NPV: 98.8 (97.1 to 100) LR+: 6.13 (3.94 to 9.56) LR-: 0.19 (0.05 to 0.68) **c. when using cost values of 1, 1, and 5 for failing PUL, IUP and EP (95% CI)** Sensitivity: 91.7 (76.0 to 100) Specificity: 84.2 (79.0 to 89.5)	**Location of failing PULs** The location of the failing PULs is not reported, therefore some of them could have been ectopic pregnancies. However, they spontaneously resolved without intervention, therefore this may not be a clinically important limitation. The study has not been downgraded in GRADE for this reason. **Other information** **M2 and M3** These models both incorporate progesterone measurements, and therefore are not reported here **Calculations** Likelihood ratios and all 95% confidence intervals were calculated by the technical team

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>One author (C. Lu) is supported by a KU Leuven PhD scholarship</td>
<td>Test set:

Lower abdominal pain: 136/196 (69.4)

Vaginal bleeding with clots: 62/196 (31.6)

Vaginal bleeding without clots: 68/196 (34.7)

Inclusion Criteria

No sign of either an intrauterine or extrauterine pregnancy or retained products of conception, when examined with transvaginal ultrasound (TVS)

Positive pregnancy test (hCG>5IU/l)

Exclusion Criteria

Visualisation of any evidence of an intrauterine sac

Identification of an adnexal</td>
<td></td>
<td>remained unknown. Serum hCG levels were repeated within 7 days to confirm the diagnosis.

IUP: If the serum rise was >66% over a 48 hour period, the women were classified as having an IUP and were rescanned 2 weeks later to confirm diagnosis.

Women who didn't fall into either category were reviewed every 48 hours until a diagnosis was made by ultrasonography.

EP: The diagnosis of an EP was based on positive visualisation of an adnexal mass. Ultrasonographic diagnosis of an EP was based on the following grey-scale appearances:

- an inhomogeneous or inconglomerate mass adjacent to the ovary and moving separate to this (designated the "blob" sign)

- a mass with a hyperechoic ring around the gestational sac, referred to as the "bagel" sign

- a gestational sac with a foetal pole with or without cardiac activity

The diagnosis of an EP was confirmed at laparoscopy, with</td>
<td>PPV: 27.5 (13.7 to 41.3)

NPV: 99.4 (98.1 to 100)

LR+: 5.82 (4.00 to 8.46)

LR-: 0.10 (0.02 to 0.65)

Model M1 (using probability cut-off)
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>10</td><td>22</td></tr>
<tr><td>Predictive Test -ve</td><td>2</td><td>162</td></tr>
</table>
Model M1 (using costs 1, 1, 4)
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>10</td><td>25</td></tr>
<tr><td>Predictive</td><td>2</td><td>159</td></tr>
</table>
</td>
<td><u>Gestational age</u>

These models do not have to be used at the same gestational period, provided that serum hCG levels are <10,000 IU/l, because below this point the rate of the change in hCG is linear.</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>mass through to be an EP

Presence of heterogenous, irregular tissues within the uterus thought to be an incomplete miscarriage

Women who were clinically unstable or demonstrated the presence of haemoperitoneum on ultrasound scan

Women with persistent PUL were excluded from the testing of the models</td>
<td></td>
<td>histological confirmation of chorionic villi in the fallopian tube. If an EP was not visualised, but there was a high index of suspicion based on symptomatology, clinical findings and suboptimal rises of serial serum hCG levels, a laparoscopy was performed with or without an evacuation of the uterus.

<u>Data analysis</u>

The data were pre-processed prior to further analysis. Some variables were created by transformation of the original variables:

- hCG ratio: Refers to the ratio of two hCG levels, i.e. serum hCG at 48 hours / serum hCG at 0 hours

- progesterone average: The mean of the two progesterone levels in an interval of 48 hours was calculated. Because it was shown that the distribution of progesterone levels was extremely dispersed, the average progesterone levels were also transformed logarithmically.

Univariate and multivariate analysis was performed retrospectively on the training data, in order to highlight the most significant variables for model</td>
<td>
<table>
<tr><td>Test -ve</td><td></td><td></td></tr>
</table>
Model M1 (using costs 1, 1, 5)
<table>
<tr><td></td><td>Reference Test +ve</td><td>Reference Test -ve</td></tr>
<tr><td>Predictive Test +ve</td><td>11</td><td>29</td></tr>
<tr><td>Predictive Test -ve</td><td>1</td><td>155</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			development. Non-parametric Wilcoxon rank sum tests were used to compare group means for categorical data (they were non-normally distributed), and Fisher's exact tests were used to check the association of categorical variables. A p-value of <0.05 was considered statistically significant. **Model building** Baseline multi-categorical models were constructed to investigate the relationship between variables and the outcome of PULs. In the models, each outcome category is paired with baseline category, i.e. IUP leads to two equations, revealing the contrasts of the EP versus IUP group, and the failing pregnancy versus IUP group. **Performance measure and classification rules** Predictions can be made for the models by using thresholds/cut-offs on the output probability of the model. However, the choice of the threshold influences accuracy, may vary between institutions, and depends on the trade-off between sensitivity and false-positive rate. In order to elucidate the predictive power of the models for each outcome category, the authors first		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			considered binary classification problems, i.e. using the predictive probability for type of PUL to distinguish from all other PULs. The authors constructed receiver operating characteristic (ROC) curves. The area under the curve (AUC) can be interpreted as the probability of the test correctly distinguishing abnormal patients from normal ones. The performance of the models was also evaluated in terms of sensitivity, specificity, PPV and NPV. Cases had to be classified in to one of three initial categories, and were done so according to rules: - if the predicted probability for a PUL to be an EP was over a threshold, it was classed as an EP, otherwise it was classed as a non-EP - for PULs classed as non-EP, if the predicted probability for a PUL to be failing was greater than a threshold, it was classed as a failing pregnancy, otherwise it was classified as an IUP The probability thresholds were identified by minimising the square root of [$(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$], in order to try and maximise both sensitivity and		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			specificity. The model also incorporates the cost of misclassifying different classes. The cost for one category of PUL is assumed to be constant, regardless of which class it is mistakenly assigned to. The predicted class incorporates both the initial probability from the model, and the cost of misclassification, creating a weighted probability. The class predicted by the model is the one with the highest weighted probability. (note: the "optimal" costs for misclassification were chosen according to training performance) **Model validation** The models were first validated on the training set by the use of ROC analysis for three binary classification problems. They also used the bootstrap technique to obtain nearly unbiased estimates of the predictive ability of the models. 100 random samples of the same size as the initial set of data were drawn with replacement from the initial data set. The logistic models were fitted on each bootstrap sample, and performance was measured on the bootstrap samples and the original sample.		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			The models were validated further on an independent data with 196 PULs (excluding the 3 persistent PULs). **<u>Reporting of diagnostic accuracy</u>** They report sensitivity, specificity, PPV and NPV for Model 1 only, as it was the best performing model. However, they report its performance when using different rules: - Performance when probability threshold is set to be 0.21 for distinguishing EP from non-EP, and 0.72 for distinguishing failing PULs from IUPs among the non-EP - Performance based on weighted probabilities. They set the costs for misclassifying a failing PUL as 1, an IUP as 1, and an EP as either 4 or 5.		
Full citation Condous,G., Van,CalsterB, Kirk,E., Haider,Z., Timmerman,D., Van,HuffelS, Bourne,T.,	**Sample size** N=173 (Note: there were an additional 201 women that constituted the training data	**Tests** Model M4 [incorporates the log(hCG average), the hCG ratio and	**Methods** All women attending St George's Hospital during the study period were examined by transvaginal ultrasound (TVS) for PUL. Those meeting the inclusion criteria in	**Results** **<u>Model M4</u>** The model generates an equation for the probability of an EP:	**Limitations** **<u>Population</u>** Some of the women presented for ultrasound without pain and

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prediction of ectopic pregnancy in women with a pregnancy of unknown location, Ultrasound in Obstetrics and Gynecology, 29, 680-687, 2007 **Ref Id** 91118 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** To improve on the performance of the previously published model M1 for the detection of developing ectopic pregnancies in women with pregnancies of unknown location. **Study dates**	set, however only accuracy when tested prospectively on the test set is reported here. The test set comprised of 175 women, but 2 were excluded for having a persisting PUL) **Characteristics** Indications for sonography were: - lower abdominal pain with/without vaginal bleeding - poor obstetric history - determination of gestational age **Final diagnosis (number of women/total (%))** **a. Training set** Failing PUL: 109/201 (54.2) IUP: 76/201 (37.8) EP: 12/201 (6.0)	the quadratic effect of the hCG ratio] Model M1 [incorporates hCG ratio]	whom pregnancy could not be located had peripheral blood taken at presentation to measure hCG and progesterone. These tests were done again 48 hours later. 376 women had a PUL. The first 201 women (data collected March to November 2002) were the training set, used for development of the model. The next 175 women with a PUL (collected November 2002 to July 2003) were the test set, used to assess the model prospectively. All women were managed expectantly until a final diagnosis was made, i.e. the location of the pregnancy was established on TVS, or the hCG declined, indicating that the pregnancy had failed and resolved spontaneously. **Follow-up and classification of final outcome** The follow-up protocol was as follows: **IUP:** if serum hCG rise over the 48 hour period was >66%, women were initially classified as having an early IUP, and were rescanned 2 weeks later. Diagnosis was confirmed at follow-up scan by the presence of an intrauterine sac,	Probability of an ectopic = $e^{z2} / (1 + e^{z1} + e^{z2})$ where z1 = 5.88 - (1.18 x loghCG average) - (5.56 x hCGratioC) + (2.05 x hCG ratioC^2) and z2 = 0.39 - (0.06 x loghCG average) - (0.26 x hCGratioC) - (3.93 x hCG ratioC^2) **Diagnostic accuracy (on test set) for diagnosing ectopic pregnancy (95% CI)** **a. M4** AUC: 0.900 (0.812 to 0.988) Sensitivity: 80.0 (59.8 to 100) Specificity: 88.6 (83.7 to 93.6) PPV: 40.0 (22.5 to 57.5) NPV: 97.9 (95.6 to 100) LR+: 7.02 (4.25 to 11.61) LR-: 0.23 (0.08 to 0.62) **b. M1**	bleeding - indications for ultrasound included poor obstetric history and determination of gestational age. **Gold standard** Not all women with ectopic pregnancies had their diagnosis confirmed with a laparoscopy - some were managed conservatively (numbers not reported) **Blinding** It is not reported whether the clinicians performing the reference test were blinded to the results of the index test. **Generalisability** The model was developed on an inner-city London hospital population, and the authors reported that general applicability of the model has yet to be established. They state that prospective, multi-

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>March 4th 2002
to July 17th 2003

Source of funding

Research Council of K.U.Leuven

Flemish Government

Research communities (ICCoS and ANMMM)

Belgian Federal Government

IUAP V-22

EU</td>
<td>Persisting PUL: 4/201 (2.0)

b. Test set

Failing PUL: 94/175 (53.7)

IUP: 64/175 (36.6)

EP: 15/175 (8.6)

Persisting PUL: 2/175 (1.1)

Inclusion Criteria

Women with a PUL, defined as: no evidence of either an intra- or extra-uterine pregnancy or retained products of conception

Positive pregnancy test

Exclusion Criteria

Clinically unstable

Acute abdomen

Blood in the pouch of Douglas, according to the ultrasound images at the time of initial scan

Persistent PULs were</td>
<td></td>
<td>surrounded by a brightly echoic ring situated eccentrically within the endometrial cavity. The women were scanned a further 2 weeks later to confirm viability.

Failing PUL: if initial progesterone was <20nmol/l, women were initially classified as having a failing PUL. Spontaneous resolution was defined as a decrease in hCG to <5U/l with disappearance of symptoms. The location of the PUL remained unknown. In these women, serum hCG was repeated within 7 days to confirm diagnosis

EP: women who didn't fall in to either category were reviewed every 48 hours with serum hCG testing and/or ultrasound until a diagnosis was made. If an EP was not visualised on TVS but there was a high index of suspicion (based on symptoms, clinical findings and sub-optimal rises in hCG), a laparoscopy was performed, with or without evacuation of the uterus.

The gold standard for diagnosis of ectopic pregnancy (histological confirmation of villi in the tube) was not applied to all women in this study, because some women with ultrasound diagnosis of EP were managed conservatively.</td>
<td>AUC: 0.842 (0.722 to 0.962)

Sensitivity: 73.3 (51.0 to 95.7)

Specificity: 87.3 (82.2 to 92.5)

PPV: 35.5 (18.6 to 52.3)

NPV: 97.2 (94.5 to 99.9)

LR+: 5.79 (3.48 to 9.66)

LR-: 0.31 (0.13 to 0.71)

Note: The authors report that M4 is a promising model, due to the higher AUC, however to be proved clinically superior to the simpler model M1 (incorporating hCG ratio only), it would need to be tested on a large number of women.

Model M1 (using costs 1, 1, 4)
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>11</td><td>20</td></tr>
<tr><td>Predictive Test -ve</td><td>4</td><td>138</td></tr>
</table>
</td>
<td>centre studies are needed.

<u>Outcome of failing PULs</u>

The location of the failing PULs is never determined, therefore some could have been ectopic. However, if these are the ectopics that resolve spontaneously and do not require intervention, this may not be a clinically significant limitation and it has not been downgraded in GRADE for this reason.

Other information

This is not the same study group used for the development of model 1.

95% CI were calculated by the technical team.

The authors state that the models do not have to be used at the same gestational age, provided serum hCG levels are <10000 U/l.</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>excluded from the analysis</td>
<td></td>
<td>An ultrasound diagnosis of EP was based on one of the following findings:

- an inhomogenous mass seen in the adnexal region adjacent to the ovary and moving separate to this (the "blob" sign)

- a mass with a hyperechoic ring around the gestational sac, referred to as the "bagel" sign

- a gestational sac with a fetal pole with or without cardiac activity seen in the adnexal region

Persisting PUL: There were 4 women in the training set and 2 in the test set whose serum hCG plateaued and in whom no pregnancy was seen during TVS at any time. These were classified as having a persisting PUL, and may represent women with a persistent intrauterine trophoblast or a missed EP on ultrasound. They were treated with methotrexate and excluded because final outcome was unknown.

<u>Data analysis</u>

Data were pre-processd prior to further analysis:</td>
<td>Model M4 - UK population only
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>12</td><td>18</td></tr>
<tr><td>Predictive Test -ve</td><td>3</td><td>140</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			Serum hCG levels were analysed using the hCG average (mean of two serum hCG levels over a 48 hour interval) and the hCG ratio (serum hCG at 48 hours / serum hCG at 0 hours) Serum progesterone was also analysed as an average and a ratio. The averages of both hCG and progesterone (but not ratios) were log transformed due to skewed distribution. A centred version of the hCG ratio (hCGratio - hCG average) known as hCGratioC was used to suppress the correlation between the hCG ratio and it's square. The authors state that centering is common practice because high correlation causes instability in parameter estimates. **Model building** Multicategorical logistic regression was conducted. Model M4 was created. To determine the predictive power of the model, they first considered binary classification problems, i.e. distinguishing one class of PUL from all others. ROC analysis was done, generating AUC estimates.		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			M4 was also evaluated using sensitivity, specificity, PPV and NPV. Cases were classified using weighted predicted probabilities, with the highest weighted probability becoming the predicted outcome. Optimal weights were chosen subjectively using the training data, and changed to obtain balanced sensitivity and specificity. Withoutthis weighting, sensitivity and specificity for EP could be unbalanced, as it is a less common outcome. The optimal weights for misclassification were selected as 1 for a failing PUL, 1 for an IUP and 4 for an EP. The performance of M4 was also compared to the performance of model M1 on this test set (M1 incorporates hCG ratio only; for full details of M1, see Condous et al. 2004). They report that they use the version of model M1 incorporating weighted predicted probabilities that proved optimal when the model was developed, which elsewhere in the paper they state to be 1, 1 and 4.		
Full citation Dart,R.G., Mitterando,J., Dart,L.M., Rate of change of serial beta-human chorionic	**Sample size** N=307 **Characteristics** **<u>Final diagnosis (number</u>**	**Tests** Serial serum hCG **Test positive:** decline in hCG levels, or rise that is	**Methods** This study was a retrospective review of a cohort of emergency department patients who fit the inclusion criteria. A total of 729 women had indeterminate ultrasounds over the study period,	**Results** **<u>Final diagnosis, split by pattern of hCG (n)</u>** Decline > 50% - EP: 2 - Normal IUP: 0	**Limitations** **<u>Retrospective</u>** This was a retrospective study

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
gonadotropin values as a predictor of ectopic pregnancy in patients with indeterminate transvaginal ultrasound findings, Annals of Emergency Medicine, 34, 703-710, 1999 **Ref Id** 91155 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To determine the predictive value of the rate of change of serial beta-human chorionic gonadotropin values in patients with symptoms suggestive of ectopic pregnancy,	**of women/total (%))** EP: 33/307 (10.7) Normal IUP: 53/307 (17.3) Abnormal IUP: 221/307 (72.0) **Interval between hCG measurements/days (number of women/total (%))** 1: 41/307 (13.4) 2: 180/307 (58.6) 3: 48/307 (15.6) 4: 23/307 (7.5) 5: 6/307 (2.0) 6: 5/307 (1.6) 7: 4/307 (1.3) **Inclusion Criteria** Abdominal pain or vaginal	<66% over 48 hours **Test negative:** rise in hCG levels >66% over 48 hours	of which 108 were lost to follow-up before the exclusion of an ectopic prenancy. 331 of these patients had 2 hCG assays performed within 7 days of each other and before intervention, however 24 were lost to follow-up and therefore excluded. This left 307 patients who were enrolled. Quantitive hCG results were assayed using a Stratus hCG Fluorometric Immunoassay, standardised to the WHO Third International Standard. Patients were divided in to 4 groups based on the rate of increase or decrease shown by hCG. These rates were determined a priori from the results of other studies: - Patients with >66% increase in hCG over 48 hours - Patients whose hCG increased but by a rate <66% over 48 hours - Patients with hCG that decreased by <50% over 48 hours - Patients with hCG that decreased >50% over 48 hours For patients in whom the follow-up interval was only 24 hours but who had increasing hCG values, the cut-off was determined by	- Abnormal IUP: 107 Decline < 50% - EP: 8 - Normal IUP: 0 - Abnormal IUP: 75 Rise < 66% - EP: 17 - Normal IUP: 13 - Abnormal IUP: 33 Rise > 66% - EP: 6 - Normal IUP: 40 - Abnormal IUP: 6 **Diagnostic accuracy of serum hCG (rise <66% or decline) for diagnosing ectopic pregnancy (95% CI)** Sensitivity: 81.8 (68.7 to 95.0) Specificity: 16.8 (12.4 to 21.2) PPV: 10.6 (6.8 to 14.4) NPV: 88.5 (79.8 to 97.2) LR+: 0.98 (0.83 to 1.16) LR-: 1.08 (0.50 to 2.34)	**Gold standard** Some women were managed with methotrexate, and therefore did not receive the gold standard of laparoscopy to verify the diagnosis of ectopic pregnancy. **Other information** Calculations of diagnostic accuracy were performed by the technical team. **Blinding** Blinding was done, because the study investigator who calculated the rate of hCG change and classified women into groups was otherwise blinded to clinical information. **Interval between hCG measurements** Only 59% of patients had an interval of exactly 2 days between

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>who have indeterminate transvaginal ultrasound findings, and to determine whether the predictive value was enhanced depending on whether the endometrial cavity was empty at ultrasound examination.

Study dates

August 1st 1991 to August 1st 1998

Source of funding

Not stated</td>
<td>bleeding

Positive pregnancy test

Ultrasound examination performed during their emergency department (ED) visit which was classed as indeterminate

Second hCG performed within 7 days of ED visit, and the test was obtained before the performance of dilation and evacuation procedure, laparoscopy or methotrexate therapy.

Exclusion Criteria

Lost to follow-up before final diagnosis was determined

Time interval between hCG assays was >7days</td>
<td></td>
<td>multiplying 1.29 x initial hCG value. The factor 1.29 is the square root of 1.66, therefore an increase of 1.29 per day would equal an increase of 1.66 over 48 hours. In patients with follow-up after 24 hours with decreasing hCG levels, the cut-off was determined by multiplying 0.71 x initial hCG value.

Patients in whom follow-up was greater than 48 hours were handled as follows: those with an even number of days follow-up had a predicted increase/decrease calculated every 48 hours, and the value was adjusted every 48 hours until actual follow-up date was reached. An odd day was calculated in the same fashion, except a multiple of 1.29 was used to account for the odd day.

In cases where hCG assays were obtained on more than 2 visits, the emergency department assay and the one done 48 hours later were used if available. Otherwise, the assay with the closest temporal relationship to the emergency department assay was used. Calculations of rate of change and assignment to the four groups was performed by a study investigator who was otherwise blinded to any clinical information.</td>
<td>Decline or rise in hCG <66%
<table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td>27</td><td>228</td></tr><tr><td>Predictive Test -ve</td><td>6</td><td>46</td></tr></table></td>
<td>their hCG measurements. In the remaining patients, the hCG change over 2 days was calculated using the equations described in the methods section.

<u>Endometrial cavity (number of women/total (%))</u>

a. Normal IUP
Empty: 19/53 (35.8)
Not empty: 34/53 (64.2)

b. Abnormal IUP
Empty: 96/221 (43.4)
Not empty: 125/221 (56.6)

c. EP
Empty: 29/33 (87.9)
Not empty: 4/33 (12.1)</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			Changes to emergency department protocol during study period All women of childbearing age presenting to the ED with abdominal pain and/or vaginal bleeding have a qualitative pregnancy test. All women with positive results then have a quantitative serum test. August 1991 - December 1994: during daytime hours, all symptomatic patients underwent transabdominal scanning unless they had a normal IUP documented at a previous visit or they had an open cervical os, or a uterine size greater than 12 weeks by pelvic exam. The transabdominal scan was followed by a transvaginal examination if an IUP was not identified. During evenings or nights, ultrasound scanning was limited to those with hCG>1000mIU/mL January 1995 - end of study: 24-hour-a-day in house ultrasound coverage became available and ultrasound was performed irrespective of hCG value August 1991 - January 1996: all patients without evidence of an IUP by ultrasound were admitted		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			for further evaluation January 1996 - end of study: the decision to admit or discharge patients without evidence of an IUP was left to the discretion of the treating clinician **<u>Identification of cases</u>** Cases were identified in one of three ways: August 1991 - August 1992: patients were identified from a prior prospective study of consecutive ED patients with abdominal pain or vaginal bleeding September 1992 - December 1994: patients were identified by a search of the institution's computerised radiology database. The authors identified all women who had pelvic ultrasound examinations ordered from the ED to assess the status of a first trimester pregnancy. From these, ultrasounds that met the study criteria were identified, and the patients' medical records were reviewed to confirm eligibility January 1995 - August 1998: patients were prospectively identified by daily tracking of all ED patients with positive hCG results.		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			Confirmation of eligibility was based on ultrasound report and ED record. Clinical data was primarily obtained from medical records. Laboratory, pathology and ultrasound results were available in a computerised database. Data elements were abstracted using standardised data collection forms, by people who had received at least 4 hours of training under the supervision of the principal investigator. Final diagnosis was made using predefined criteria. All decisions about eligibility, exclusion and final diagnosis were made before calculation of the rate of change of hCG. **Classification of final outcome** **Normal IUP:** pregnancy was carried to delivery, or at a later date there was demonstration of a normal IUP with a foetal heartbeat by ultrasound **Abnormal IUP:** **-** hCG>3000 mIU/ml in association with an empty uterus, decreasing hCG, or a progesterone value <5.0 ng/ml, before dilation and evacuation and evidence of chorionic villi in pathology specimen		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			- no villi in the dilation and evacuation specimen but with hCG values that decrease to zero without further intervention - hCG values that decrease to zero without intervention **Ectopic pregnancy:** - extrauterine pregnancy visualised at laparoscopy - in patients managed medically with methotrexate, no chorionic villi after dilation and evacuation, and either increasing or abnormally decreasing hCG values or EP visualised at ultrasound **<u>Ultrasound criteria</u>** An ultrasound was considered indeterminate if it was neither diagnostic of an IUP (did not contain an intrauterine yolk sac or foetal pole), nor diagnostic or suggestive of an EP (no extrauterine adnexal mass or saclike structure, no more than a small amount of fluid visualised in the cul-de-sac). Indeterminate ultrasounds were divided into two groups: those with an empty endometrial cavity and those in whom the cavity was not empty. "Not empty" was characterised by findings such as small anechoic fluid collections		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			without a well-defined echogenic bordere, the presence of echogenic material in the absence of a sac-like structure, and well-defined but empty sac-like structures. Ultrasound characterisation was determined by a review of the official ultrasound report, before and separate from the determination of the patient's final diagnosis. The ultrasound exams were performed by ultrasound technicians under the direct supervision of either a radiology attending physician or resident. All supervising radiology attending physicians had specific expertise in pelvic ultrasonography. In cases supervised by a resident, the hard copy was reviewed by an attending before the final report. Frequency of EP were calculated for each of the four groups based on the rate of increase or decrease of hCG, and these frequencies were compared using logistic regression. For the secondary analysis, women were subdivided on whether the endometrial cavity was empty or not empty, to assess whether the addition of ultrasound findings affected results.		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Daus,K., Mundy,D., Graves,W., Slade,B.A., Ectopic pregnancy. What to do during the 20-day window, Journal of Reproductive Medicine, 34, 162-166, 1989 **Ref Id** 91158 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To determine if normal intrauterine pregnancies could be differentiated from abnormal pregnancies by serial quantitation of serum hCG levels.	**Sample size** N=357 **Characteristics** **Final diagnosis (number of women/total (%))** EP: 47/357 (13.2) Normal IUP: 62/357 (17.4) Abnormal IUP: 64/357 (17.9) Undiagnosed: 184/357 (51.5) **Inclusion Criteria** Suspicion of EP Stable condition on clinical examination Culdocentesis results not diagnostic of haemoperitoneum Serial quantitative hCG values ranging from 5 to 10,000 mIU/ml or until	**Tests** Serial serum hCG **Positive test:** Abnormally rising (rise of less than 63%) or falling hCG levels **Negative test:** Normal, rising hCG levels (rise of >63%)	**Methods** During the study period, 375 (the technical team believe this to be a typo on the part of the paper and it should be 357) patients were suspected of having eccyesis and met the criteria for inclusion (see inclusion criteria). Data was collected using a retrospective chart review. hCG levels were measured using the Stratus hCG Fluorometric Enzyme Immunoassay, which detects intact hCG using a 2-site monoclonal antibody sandwich technique. This assay is sensitive to 5mIU of hCG per millilitre and is calibrated against the first International Reference Standard Preparation. All assays were performed according to the manufacturer's instructions by the Clinical Laboratory of Grady Memorial Hospital. 357 patients were followed for suspected eccyesis. Patients with documented IUP were used as controls. All patients in this group had three or more quantitative hCG values. If serial values were greater than 10 days apart they were excluded. Patients in the remaining groups (miscarriage, EP, abnormal pregnancy) were included if two or more hCG	**Results** **Final diagnosis, split by pattern of hCG** Decline - EP: 27 - Normal IUP: 0 - Abnormal IUP: 48 - PUL: 170 Rise < 63% - EP: 17 - Normal IUP: 8 - Abnormal IUP: 13 - PUL: 14 Rise > 63% - EP: 3 - Normal IUP: 54 - Abnormal IUP: 3 - PUL: 0 **Diagnostic accuracy for serial serum hCG (decline or rise <63%) for diagnosing ectopic pregnancy** Sensitivity: 93.6 (86.6 to 100) Specificity: 18.4 (14.1 to 22.7) PPV: 14.8 (10.8 to 18.9) NPV: 95.0 (89.5 to 100)	**Limitations** **Retrospective** This study is retrospective. **Blinding** It is unclear that the authors were blinded to the final diagnosis when interpreting hCG results. **Ultrasound** The authors discuss the inaccuracy of ultrasound before 28 days in their introduction, a time during which ectopic pregnancy may remain undiagnosed. However, their methods do not report ultrasound results or criteria, therefore the participants may not have true PULs. **Final outcome** 184/357 (51.5%) patients were classed as "undiagnosed" for their final diagnosis. They were clinically

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Study dates

January 1st 1986 to January 1st 1987

Source of funding

Not stated</td>
<td>resolution of the problem

Final outcome determined to be one of the following:
- Normal IUP
- Spontaneous miscarriage or blighted ovum with tissue confirmation obtained from dilation and curettage
- Ectopic pregnancy requiring surgery and confirmed by tissue diagnosis
- Abnormal pregnancy not requiring surgery

Exclusion Criteria

Consecutive serial hCG values more than ten days apart</td>
<td></td>
<td>values were known prior to resolution of the problem. Slopes of hCG change were then calculated for each patient. If only 2 values were known, the slope was computed from the line connecting the two values. If more values were obtained, linear regression was used to calculate the slope.

After determining slopes for each patient, the mean and standard deviation for patients with positive slopes in the four groups was calculated. The analysis was only performed for positive slopes because no patients having a negative slope showed evidence of a normal IUP or therefore presented a diagnostic problem.

The authors used 0.016 as the lower limit of a normal increase in hCG (this correlated with a rise of 63% in 48 hours). This value was derived using one standard deviation from the normal IUP group mean slope. Using this threshold, women were classified as having normally rising levels, abnormally rising levels or falling levels.

<u>Classification of final outcome</u>

Normal IUP: criteria not</td>
<td>LR+: 1.15 (1.05 to 1.26)

LR-: 0.35 (0.11 to 1.06)

Decline or rise in hCG
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>44</td><td>253</td></tr>
<tr><td>Predictive Test -ve</td><td>3</td><td>57</td></tr>
</table>
</td>
<td>stable, and never received a surgical intervention. The location of the pregnancy was never determined and no diagnosis was made. Some of these pregnancies could have been ectopic, however if they did not require intervention, then this may not be a clinically significant limitation. For this reason, the study has not been downgraded in GRADE.

Other information

Calculations of diagnostic accuracy were performed by the technical team.

<u>Interval between serum hCG measurements</u>

Women were only excluded for having an interval longer than 10 days. However, they did evaluate women according to a slope of 0.016, corresponding to an increase of 63% over</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			reported **Spontaneous miscarriage or blighted ovum:** tissue confirmation obtained from dilation and curettage **Ectopic pregnancy:** confirmed by tissue diagnosis after surgery **Abnormal pregnancy:** not requiring surgery (e.g. persisting PUL without final diagnosis)		48 hours. **Definition of "suspicion of ectopic pregnancy" as an inclusion criterion** This is not defined in the methods, however the paper starts by discussing that suspicion of EP arises when a pregnant woman is clinically stable but complains of mild to moderate abdominal pain. Therefore the technical team assumed that they used the same criteria for inclusion.
Full citation Mol,B.W.J., Hajenius,P.J., Engelsbel,S., Ankum,W.M., van,derVeenF, Hemrika,D.J., Bossuyt,P.M.M., Serum human chorionic gonadotropin measurement in the diagnosis of ectopic	**Sample size** n=195 Note: 354 women are included in the study, but only 195 had repeated evaluation (i.e. a second hCG), and therefore they are the population of interest to this review question.	**Tests** Serial serum hCG concentration **Test positive:** rise <50% or any decline in hCG **Test negative:** rise >50% in hCG	**Methods** Consecutive patients presenting with suspected EP (see inclusion criteria) in two large teaching hospitals in Amsterdam were included. Transvaginal sonography was performed by one of the study investigators or, during shifts, by the resident on call. The intrauterine cavity was scanned, and an IUP diagnosed when a IU gestational sac was visualised. When an IU gestational sac could	**Results** **Final diagnosis, split by pattern of hCG (n)** Decline > 50% - EP: 0 - Viable IUP: 0 - Non-viable pregnancy: 63 Decline < 50% - EP: 11 - Viable IUP: 0 - Non-viable pregnancy: 57	**Limitations** **Population** The women are a sub-set of the population of interest, who have hCG <1500 with an indeterminate ultrasound. Women with hCG>1500 with an indeterminate ultrasound have already

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
pregnancy when transvaginal sonography is inconclusive, Fertility and Sterility, 70, 972-981, 1998 **Ref Id** 91712 **Country/ies where the study was carried out** the Netherlands **Study type** Prospective cohort study **Aim of the study** To assess the accuracy of initial and repeated serum hCG measurements in the diagnosis of ectopic pregnancy in whom transvaginal sonography is inconclusive and to evaluate whether patient characteristics influence the accuracy of serum	**Characteristics** **<u>Final diagnosis (number of women/total (%))</u>** **a. in women who a second hCG was used for diagnosis (population of interest for this review question)** EP: 38/195 (19.5) Viable IUP: 15/195 (7.7) Non-viable IUP: 16/195 (8.2) Chemical pregnancy: 126/195 (64.6) **b. in whole study population** EP: 129/354 (36.4) Viable IUP: 67/354 (18.9) Non-viable IUP: 23/354 (6.5)		not be visualised, both adnexal regions were scanned for the presence of an ectopic gestational sac, an ectopic mass or fluid in the pouch of Douglas. An ectopic gestational sac was defined as the presence of a yolk sac, a fetal pole, or fetal cardiac activity. When an ectopic gestational sac was visualised, an EP was diagnosed. 824 women presented with a suspected EP, but 470 were excluded from analysis. Reasons for exclusion were that the pregnancy resulted from IVF (n=26), the patient presented with symptoms suggesting complete miscarriage (n=10), the ultrasound was diagnostic (n=407), haemodynamic instability (n=23) and missing data (n=4). This left 354 included patients, however only 195 of them had a second evaluation before diagnosis, and hence comprise the population of interest to this review question. After sonography was done, serum hCG concentration was determined using the Microparticle Enzyme Immunoassay. An EP was diagnosed in women with hCG concentration >1500 IU/l in patients in whom ultrasound failed to show an intrauterine or ectopic gestational sac. An exception was made for women presenting with a	Rise < 50% - EP: 15 - Viable IUP: 1 - Non-viable pregnancy: 18 Rise > 50% - EP: 12 - Viable IUP: 14 - Non-viable pregnancy: 4 **<u>Diagnostic accuracy of % difference in hCG between 0 and 2 days (decline or rise <50%) for diagnosing ectopic pregnancy</u>** AUC: 0.83 (0.73 to 0.93) Sensitivity: 68.4 (53.6 to 83.2) Specificity:11.5 (6.5 to 16.5) PPV: 15.8 (10.2 to 21.3) NPV: 60.0 (42.5 to 77.5) LR+: 0.77 (0.62 to 0.97) LR-: 2.75 (1.45 to 5.22) **Decline or rise in hCG**	left the pathway. Not all women presented with pain and bleeding. **<u>Blinding</u>** It is not reported whether the clinicians performing the reference test were blinded to the results of the index test. **<u>Final diagnosis</u>** Over 60% of the women that compose the population of interest (who had re-evaluation at 2 days) were finally diagnosed with a chemical pregnancy, and the location is not reported so some could have been ectopic. However, as these pregnancies resolved without intervention, this may not be a clinically significant limitation and for this reason, the study has not been downgraded in GRADE. **<u>Verification bias</u>** This is reported by the

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>hCG measurements

Study dates

September 1993 to April 1996

Source of funding

Dutch Health Insurance Council, Amstelveen</td>
<td>Chemical pregnancy: 135/354 (38.1)

<u>Presenting symptoms (number of women/total (%))</u>

Abdominal pain: 223/354 (63.0)

Vaginal bleeding: 228/354 (64.4)

At least one risk indicator for EP: 134/354 (37.9)

(note: the presenting characteristics for the women who required a second hCG are not reported separately)

Inclusion Criteria

Positive urine pregnancy test

Patients with suspected EP, who had one or more of the following criteria:
- clinical symptoms (abdominal pain and/or vaginal bleeding)</td>
<td></td>
<td>clinical picture suggestive of complete miscarriage, who were managed expectantly and excluded from the study.

If there was no gestational sac on ultrasound, but serum hCG was <1500 IU/l, the patients were re-evaluated 2 days later as outpatients. A diagnosis of viable IUP or EP was made if pregnancy was detected within or outside the uterine cavity, respectively. If US was repeatedly inconclusive, further management depended on hCG concentrations:
- serum hCG concentrations of >1000 IU/l obtained 2-4 days after the start of the diagnostic process were assumed conclusive for EP
- when three consecutive serum hCG were <1000 IU/l and US were repeatedly negative, the diagnosis of a non-viable pregnancy was made
- if a plateauing serum hCG pattern emerged (a rise in two consecutive measurements or no decline in three consecutive measurements) then an EP was diagnosed

<u>Patients in whom hCG was used to diagnose (population of interest for this review)</u>

Two hundred and eighty five patients underwent re-</td>
<td>
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>26</td><td>139</td></tr>
<tr><td>Predictive Test -ve</td><td>12</td><td>18</td></tr>
</table>
</td>
<td>authors as a limitation. Confirmative laparoscopy weas performed when serum hCG concentrations were initially >1500 IU/l, or was >1000 IU/l at repeated measurement, or plateaued after three consecutive measurements. Therefore, these women are more likely to have a detected EP, whereas women with lower hCG concentrations were diagnosed as chemical pregnancies with declining serum hCG and managed expectantly. However, this is likely to have mostly affected women who do not form part of the population of interest for this review (i.e the women with hCG >1500).

Other information

Calculations of diagnostic accuracy were performed by the technical team.

<u>Sonographic findings</u></td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	- presence of one or more risk indicators for EP (previous EP, known tubal pathology detected on hysterosalpingography and/or laparoscopy, previous tubal surgery, PID, diethylstilbestrol exposure in utero, and sterilisation/contraceptive device in situ at conception) - routine sonography, performed after a gestational age of 6 weeks, that failed to show an intrauterine gestational sac - microscopic absence of chorionic villi after dilation and curettage **Exclusion Criteria** Haemodynamic instability Excluded from analysis: - pregnancy resulting from IVF - presenting with symptoms suggesting complete miscarriage - US was diagnostic (i.e. visualisation of an intra- or extra-uterine gestational sac) - missing data		evaluation two days after the start of the diagnostic process. Of these, transvaginal ultrasound led to a diagnosis in 63 patients (11 EP, 52 viable IUP). In the remaining 195, serum hCG was used to diagnose patients. (note: these numbers do not add up - it is likely to be a typo, and that 258 women underwent re-evaluation; otherwise they have lost patients) 136 patients underwent a second re-evaluation 4 days after the start of the process. Repeated ultrasound led to a diagnosis in 41 patients (17 EP, 24 IUP). In the remaining 95 patients, the serum hCG concentration was used to make a diagnosis. It is not reported whether % difference after 4 days is comparing the 4 day measurement to the first or the second hCG measurement. Therefore, diagnostic accuracy of the first hCG ratio is reported below. **<u>Classification of final outcome</u>** **EP:** verified by laparoscopy **IUP/miscarriage:** verified by repeated ultrasound at a gestational age of 12 weeks, or by histopathologic evaluation in case of a miscarriage. When hCG		The authors recommend that in patients in whom ultrasound does not reveal a clear diagnosis, the presence of sonographic abnormalities should be taken into account when interpreting hCG levels.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			declined, it was measured repeatedly until it declined below detection threshold (not reported, but there is a reference) The final diagnostic categories were: EP, viable IUP, and non-viable pregnancy (inclues non-viable IUP and chemical pregnancies that resolved without treatment) **Analysis** Analysis was limited to women in who ultrasound findings were inconclusive (i.e. gestational sac could not be visualised anywhere). Patients who conceived after IVF were also excluded because the transfer of multiple embryos could influence the cut-off levels for positive tests. Women with missing data were excluded. An ROC curce was constructed, and the AUC calculated, for diagnosis of EP. The authors also evaluated the diagnostic accuracy of serum hCG in association with patient characteristis. Subgroups were defined based on presence/absence of abdominal pain, vaginal bleeding, and an ectopic mass and/or fluid in the		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			pouch of Douglas. A p-value <0.05 was considered significant. For patients with serum concentrations of <1500 IU/l, the hCG concentrations obtained 2 days and 4 days after the start were compared with the final diagnosis. Diagnostic accuracy of these repeated serum hCG concentrations for diagnosing EP was evaluated using ROC curves of absolute serum concentration, absolute difference and % difference. (Note: Only the diagnostic accuracy of % difference in hCG will be reported here, as this was chosen by the GDG as the test of interest. % difference also had the highest AUC)		
Full citation Stewart,B.K., Nazar-Stewart,V., Toivola,B., Biochemical discrimination of pathologic pregnancy from early, normal intrauterine gestation in	**Sample size** N=77 **Characteristics** **<u>Final diagnosis (number</u>**	**Tests** Serial serum hCG tests **Test positive:** rate of change of log hCG < threshold or declining **Test negative:** rate	**Methods** Women with symptoms suggestive of EP were identified through two sources: - A computer search of pathology records identified women with a diagnosis of EP seen at the University of Washington Medical Centre (UWMC) or Harborview	**Results** **<u>Diagnostic accuracy of rate of change of log hCG (decline or rise < threshold) for diagnosing EP</u>** **a. Using a cut-off 0.11** Sensitivity: 89.7 (81.8 to 97.5)	**Limitations** **<u>Retrospective</u>** Participants were identified through a retrospective review of patients. **<u>Blinding</u>**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>symptomatic patients, American Journal of Clinical Pathology, 103, 386-390, 1995

Ref Id

92050

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study

To examine the utility of using the rate of change of hCG level and the progesterone concentration to distinguish ectopic from normal intrauterine pregnancies.

Study dates

January 1989 to</td>
<td><u>of women/total (%))</u>

a. Among all women

EP: 37/77 (48.1)

Normal IU gestation: 21/77 (27.3)

Inevitable miscarriage: 19/77 (24.7)

b. Among the pairs of hCG used for analysis

EP: 58/117 (49.6)

Normal IU gestation: 20/117 (17.1)

Inevitable miscarriage: 39/117 (33.3)

(Note: this is not reported in the paper, but was established by the technical team from the graph. The outcomes for 3 pairs are missing.)

Inclusion Criteria

Symptoms suggestive of ectopic pregnancy</td>
<td>of change of log hCG > threshold</td>
<td>Medical Centre (HMC) from January 1989 to February 1192

- Patients for whom an EP screen had been ordered at either of the above facilities. These patients were either being followed at a fertility clinic or had presented acutely to the emergency room with little or no prenatal care.

All women had symptoms suggestive of EP. Their charts were reviewed to ascertain the outcome of the pregnancy, ultrasound findings, pathologic findings, whether any progesterone/hCG was administered and the time of any surgical intervention.

99 patients were identified through the sources, but 22 were excluded: 7 were not pregnant, 8 had no quantitative hCG done before surgery, 3 had no follow-up available, 1 only had outside lab values available, 1 was terminated before outcome was clear, 1 had ruptured corpus luteum and 1 developed gestational trophoblastic disease.

<u>Classification of final outcome</u>

Patients were classified according</td>
<td>Specificity: 37.3 (25.0 to 49.6)

PPV: 58.4 (48.2 to 68.7)

NPV: 78.6 (63.4 to 93.8)

LR+: 1.43 (1.15 to 1.77)

LR-: 0.28 (0.12 to 0.63)

b. Using a cut-off of 0.14

Sensitivity: 98.3 (94.9 to 100)

Specificity: 22.0 (11.5 to 32.6)

PPV: 55.3 (45.7 to 64.9)

NPV: 92.9 (79.4 to 100)

LR+: 1.26 (1.10 to 1.45)

LR-: 0.08 (0.01 to 0.58)

Rate of change of log hCG
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive</td><td>52</td><td>37</td></tr>
</table>
</td>
<td>It is not reported whether authors were blinded to final diagnosis when interpreting hCG.

<u>Missing data</u>

36 women had multiple hCGs, but they had variables numbers of measurements taken and it is very poorly reported. The prevalence of EP, normal IUP and miscarriage among the 120 pairs of hCG used for analysis is not reported. This had to be estimated by the technical team using the graphical representation in the paper. However, only 117 out of 120 values could be accounted for.

<u>Inclusion criteria</u>

The "symptoms suggestive of EP" are not defined further. It is also not reported whether women had an ultrasound prior to biochemical tests, and</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>February 1992

Source of funding

Not stated</td>
<td>Exclusion Criteria

Not directly reported as "criteria", but they excluded women for the following reasons:

- not pregnant

- hCG not done before surgical intervention

- no follow-up

- outside lab used for tests

- termination before outcome is clear

- ruptured corpus luteum

- diagnosis of gestational trophoblastic disease</td>
<td></td>
<td>to pregnancy outcome:

Normal intrauterine gestation: Patients had either a documented full term pregnancy, or a clinical impression of a normal viable foetus based on TVS showing an intrauterine fetal sac with a fetal heart rate.

Ectopic pregnancy: Based on operative findings and pathology reports

Inevitable miscarriage: Based on a clinical impression of spontaneous or inevitable miscarriage, based on findings such as TVS showing non-viable foetus, documented passage of products of conception, falling hCG levels and low progesterone levels.

<u>Tests performed</u>

Only values measured at the Endocrinology Laboratory in the Department of Laboratory Medicine of UWMC were used. No tests done following surgical intervention were included.

Quantitative serum hCG was measured using a chemiluminometric sandwich immunoassay specific for the beta</td>
<td>
<table>
<tr><td>Test +ve</td><td></td><td></td></tr>
<tr><td>Predictive Test -ve</td><td>6</td><td>22</td></tr>
</table>

Rate of change of log hCG
<table>
<tr><td></td><td>Reference Test +ve</td><td>Reference Test -ve</td></tr>
<tr><td>Predictive Test +ve</td><td>57</td><td>46</td></tr>
<tr><td>Predictive Test -ve</td><td>1</td><td>13</td></tr>
</table>
</td>
<td>hence whether the participants are women with true PUL.

Other information

Measures of diagnostic accuracy were calculated by the technical team using the sensitivity and specificity reported in the papers, combined with the number of each final outcome.

The authors report that the thresholds were chosen for their own institution, and that it would be wise for other institutions to determine their own thresholds. They also only included hCG assays done at one specific lab.

<u>Interval between hCG measurements</u>

The second hCG test could be up to 7 days after the first, however the slope was calculated</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			subunit of hCG. Quantitative serum progesterone was measured with a competitive binding radioimmunoassay. The rate of change of hCG was calculated using the formula: s = 1 / t[log (C2/C1)] where s is the slope, t is the time in days, C1 is the initial concentration and C2 is the concentration at the second time point which could be 2-7 days later. More than one pair of hCG values from overlapping time periods for the same patient were allowed. For example, if hCG concentrations were done on days 1, 4 and 7, then three time intervals were used: days 1 to 4, days 1 to 7 and days 4 to 7. A total of 120 pairs of hCG values were obtained when overlapping time periods are allowed. If only the initial pair for each patient is considered, there are 36 pairs (some only had 1 hCG value). The mean slopes and standard deviations of the rate of the change of log hCG were not statistically significantly different for the EP group when all hCG values were considered and when only the initial pair of hCG values for each patient were considered. **Analysis**		**Progesterone** Progesterone was also measured in this paper, but results of diagnostic accuracy of progesterone are not relevant to this review question and have not been reported here.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			ROC curves of cut-off values for progesterone and the s value for rate of change of hCG were calculated. Sensitivity and specificity were calculated as normal, however they are reported for the incorrect comparisons in the paper, therefore the measures below were calculated by the technical team.		
Full citation Barnhart,K.T., Sammel,M.D., Appleby,D., Rausch,M., Molinaro,T., Van Calster,B., Kirk,E., Condous,G., Van Huffel,S., Timmerman,D., Bourne,T., Does a prediction model for pregnancy of unknown location developed in the UK validate on a US population?, Human Reproduction, 25, 2434-2440, 2010 **Ref Id** 96675 **Country/ies where the study was carried out**	**Sample size** N=1038 (UK: n=431 US: n=607, however adjusted US: n=544) **Characteristics** **<u>Final diagnosis (number of women/total (%))</u>** **a. UK cohort (n=431)** Failing PUL: 228/431 (52.9) IUP: 177/ 431 (41.1) EP: 26/431 (6.0) **b. US cohort (n=607)**	**Tests** Model M4 (see Condous et al. 2007)	**Methods** <u>US POPULATION</u> The University of Pennsylvania maintains a database of all women in the first trimester of pregnancy (positive pregnancy test or history of missed period) who present with pain and/or bleeding. Data is directly entered by clinical staff caring for patients. Women were followed in this database until they were definitively diagnosed with an EP, an IUP or a miscarriage. Where appropriate, missing data and/or questionable values were double-checked against electronic records and charts for validation. This data was collected retrospectively. <u>Classification of final outcome in US population</u> Spontaneous miscarriage: Confirmed either by the	**Results** **<u>Diagnostic accuracy of Model M4 for diagnosing EP (95% CI)</u>** **a. UK Cohort** AUC: 0.904 (0.789 to 0.960) Sensitivity: 80.8 (65.6 to 95.9) Specificity: 88.9 (85.8 to 92.0) PPV: 31.8 (20.6 to 43.1) NPV: 98.6 (97.4 to 99.8) LR+: 7.27 (5.21 to 10.14) LR-: 0.22 (0.10 to 0.48)	**Limitations** **<u>Retrospective</u>** The USA population was evaluated retrospectively. It is not directly reported for the UK population, however it appears to be retrospective as well. **<u>Blinding</u>** It is not reported whether the authors were blinded. **<u>Gold standard</u>** Some women were treated medically for an EP, therefore their diagnosis was not confirmed with the gold standard of laparoscopy

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
USA and UK **Study type** Retrospective cohort study **Aim of the study** To assess the utility of model M4 to predict the outcome for a woman with PUL in a USA population **Study dates** February 1st 2003 to September 30th 2007 **Source of funding** NIH Research Council KUL Research Foundation - Flanders Belgian Federal Science Policy Office	Spontaneous miscarriage: 351/607 (57.8) IUP: 157/607 (25.9) EP: 96/607 (15.8) **c. Adjusted US cohort (n=544)** Spontaneous miscarriage/failing PUL: 302/544 (55.5) IUP: 138/544 (25.4) EP: 104/544 (19.1) **Baseline characteristics (median (IQR))** **a. hCG ratio** **UK cohort** Spontaneous miscarriage/failing PUL: 0.41 (0.35) IUP: 2.25 (0.53) EP: 1.16 (0.27)		histopathology of products of conception on suction dilation and curettage, or by the spontaneous decline of hCG levels to <5IU/l. The data was also used to class women by type of miscarriage. Ongoing IUP: Confirmed by observing ongoing progression of the pregnancy by ultrasound with visualisation of an intrauterine yolk sac, or foetal pole EP: Confirmed by either the presence of chorionic villi in the fallopian tube, by visualising an extrauterine gestational sac (with yolk sac or embryonic cardiac activity) with ultrasonography for those treated medically, or by a rise or plateau in hCG level after dilation and evacuation (and no evidence of chorionic villi in the endometrial curettage sample.) Women were stratified based on diagnostic criteria: diagnosed at surgery, diagnosed with ultrasound or non-visualised (hCG rise after uterine evacuation). UK POPULATION The US data was compared to a UK data set collected July 2003 to October 2004, from the same	**b. US cohort** AUC: 0.807 (0.757 to 0.849) Sensitivity: 49.0 (39.0 to 59.0) Specificity: 87.4 (84.5 to 90.3) PPV: 42.3 (33.2 to 51.5) NPV: 90.1 (87.4 to 92.7) (note: the NPV reported in the paper is 90.0, however, this is incorrect, likely due to a rounding error) LR+: 3.89 (2.86 to 5.28) LR-: 0.58 (0.48 to 0.71) **c. Adjusted US cohort** AUC: 0.831 (0.783 to 0.869) Sensitivity: 54.8 (45.2 to 64.4) Specificity: 87.7 (84.7 to 90.8) PPV: 51.4 (42.1 to 60.7) NPV: 89.2 (86.2 to 92.1)	**Differences in populations** Not all women in the UK presented with pain and bleeding, there were various indications for a scan. The authors note that women in the UK present later in the natural history of an IUP, having a greater gestational age (34 vs. 29 days) but with a similar median hCG level. US women with a miscarriage also present later but have an average hCG almost 3 times higher than women in the UK. Women with an EP in the USA have an almost identical gestational age, but a lower average hCG. There was also a difference in the prevalence of EP (16% in the USA, 6% in the UK), which could be a result of either a higher prevalence in the USA, or more EP picked up at first ultrasound in the UK and hence not included in the PUL population.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>US cohort

Spontaneous miscarriage/failing PUL: 0.42 (0.49)

IUP: 2.58 (0.99)

EP: 1.15 (0.75)

Adjusted US population

Spontaneous miscarriage/failing PUL: 0.42 (0.47)

IUP: 2.69 (1.01)

EP: 1.23 (0.67)

<u>b. Gestational age (days)</u>

UK cohort

Spontaneous miscarriage/failing PUL: 44 (14)

IUP: 29 (5)

EP: 39 (7)

US cohort</td>
<td></td>
<td>setting where the model was developed. Women presenting to the EPU at St George's Hospital, London with a positive pregnancy test underwent transvaginal ultrasound, indicated due to lower abdominal pain, vaginal bleeding, maternal anxiety or confirmation of gestational age. They were classified as a PUL if there was no evidence of an IUP or EUP. This population is partially represented in four other papers: Condous et al. 2006; Gevaert et al. 2006; Bignardi et al. 2008; Van Calster et al. 2009.

All women were managed expectantly until a final diagnosis was made, i.e. until the location of the pregnancy was established using transvaginal ultrasound or serum hCG declined to undetectable levels. The outcome groups were: failing PUL, IUP or EP.

<u>Classification of final outcome in UK population</u>

IUP: If serum hCG rose >66% over a 48 hour period, women were initially classified as having an early IUP and were rescanned 2 weeks later. Diagnosis was confirmed by the presence of an intrauterine sac surrounded by a brightly echoic ring, situated</td>
<td>LR+: 4.47 (3.29 to 6.06)

LR-: 0.52 (0.46 to 0.64)

NOTE: the UK population and the adjusted US population have been used for analysis and the GRADE table, as they are the best match to the population for which the model was designed.

Model M4 - UK population only

<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>21</td><td>45</td></tr>
<tr><td>Predictive Test -ve</td><td>5</td><td>360</td></tr>
</table>

Model M4 - USA adjusted population only

<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive</td><td>57</td><td>54</td></tr>
</table>
</td>
<td><u>Generalisability of UK results</u>

In the UK, the model was tested in the same location and population on which it was designed, therefore the results of the UK analysis may not be generalisable.

<u>Failing PUL</u>

Location is never determined, therefore they could be EP. However, if these pregnancies resolve without intervention, this may not be a clinically significant limitation, and it has not been downgraded in GRADE for this reason.

Other information

Calculations of 95% CI and likelihood ratios were performed by the technical team.

<u>Definition of outcomes</u>

The definition of a PUL</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	Spontaneous miscarriage/failing PUL: 47.0 (21.0) IUP: 34.0 (11.0) EP: 39.0 (11.0) **Adjusted US cohort** Spontaneous miscarriage/failing PUL: 45.0 (16.0) IUP: 34.0 (8.0) EP: 39.0 (12.0) Note: the authors report that there were differences in estimated gestational age at presentation between the UK and US patients **Inclusion Criteria** **UK cohort:** - positive pregnancy test - PUL after ultrasound **US cohort:**		eccentrically within the endometrial cavity Failing PUL: Spontaneous resolution of the pregnancy was defined as a decrease in the serum hCG levels to <5IU/l. The location of these pregnancies remained unknown. Women who did not fall into either of the above categories were reviewed every 48 hours with serum hCG testing and/or sonography until a diagnosis was made. EP: A diagnosis was made using ultrasound if a mass was seen in the adnexa with echogenicity consistent with an EP: this included an inhomogeneous mass or empty gestational sac, as well as those with a sac containing a yolk sac or foetal pole. If an EP was not visualised but there was high index of suspicion based on symptoms, clinical findings and suboptimal hCG rises, a laparoscopy was performed with or without evacuation of the uterus. Note: some women with an ultrasound diagnosis of EP were treated medically, therefore not everyone received the gold standard of	**Test +ve** | | | **Predictive Test -ve** | 47 | 386	differs in the UK and the USA, therefore adjustments had to be made to try and make the data compatible, however this only modestly improved the model's performance. The authors also note that despite the adjustments, there were still significant differences.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	- first trimester of pregnancy (positive pregnancy test or history of missed period) - presenting with pain and bleeding To fit with the UK population, analysis was also restricted to: - women ultimately diagnosed with miscarriage, IUP or EP - women whose diagnosis not definitive at presentation - women who had two hCG tests ~48 hours apart **Exclusion Criteria** Not reported		laparoscopy. (proportion not reported) <u>Model application</u> The UK and US populations had slightly different inclusion criteria and terminology. Therefore, the authors also performed analyses using an adjusted US population whose inclusion criteria and definition of outcome more closely matched the UK population. The adjusted US population was created according to the following criteria: Reclassification of outcomes: Condous et al. 2007 defined IUP to include all women with an intrauterine gestation, regardless of viability. Therefore, 11 women from the USA population with an empty sac (anembryonic gestation), missed miscarriage or incomplete miscarriage were reclassified to the outcome of IUP. However, these women were subsequently excluded when the analysis was limited to include only women who received a non-diagnostic ultrasound at presentation, removing cases where there was suspicion for EP or IUP based on non-definitive		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			ultrasound criteria (156 women) or when the population was limited to women with an initial hCG below 10000 IU/l (10 women). Interval of hCG test: The authors broadened their criteria to allow women who had second hCG readings at 1 or 3 days (54 and 52 women respectively) after initial presentation. For these women, a "2 day hCG" was interpolated by assuming a linear change in hCG over time. The "adjusted US population" consisted of 544 women: 302 spontaneous miscarriage/failing PUL, 138 IUP and 104 EP <u>Data analysis</u> The performance of the model M4 was assessed by calculating the area under the ROC curve. The predicted outcome was generated for each patient using probabilities (as described in Condous et al. 2007) and then diagnostic accuracy measures were calculated for each outcome.		
Full citation Morse,C.B., Sammel,M.D.,	**Sample size**	**Tests** Serial hCG	**Methods** The study was done at 3 sites, all	**Results** **<u>Model performance for predicting</u>**	**Limitations** 167/1180 of patients

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Shaunik,A., Ien-Taylor,L., Oberfoell,N.L., Takacs,P., Chung,K., Barnhart,K.T., Performance of human chorionic gonadotropin curves in women at risk for ectopic pregnancy: Exceptions to the rules, Fertility and Sterility, 97, 101-106, 2012 **Ref Id** 156595 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To compare observed hCG curves to expected curves in a diverse set of patients with symptomatic early	N = 1005 **Characteristics** **Final diagnosis (n/total)** Ectopic pregnancy: 179/1005 IUP: 259/1005 Miscarriage: 567/1005 **Initial hCG level (n/total)** Ectopic pregnancy - 0-500: 82/179 - 501-2000: 70/179 - 2001-4000: 12/179 - > 4000: 15/179 IUP - 0-500: 117/259 - 501-2000: 89/259 - 2001-400: 39/259 - > 4000: 14/259 Miscarriage - 0-500: 235/567 - 501-2000: 146/567 - 2001-400: 79/567 - > 4000: 107/567 **Inclusion Criteria** Pain and/or bleeding in the first trimester of pregnancy	measurements Test positive: hCG change between an upper threshold (various) and a lower threshold of 36-47% (depending on initial value) Test negative: other patterns of hCG change	US universities. Data was collected using a centralised computerised database, and patients were entered in to it when the first presented with pain and/or bleeding in the first trimester. Patients were diagnosed with one of the following: - Ectopic pregnancy: included visualised and non-visualised ectopic pregnancies and treated persistent PULs - Miscarriage: included spontaneously resolved PUL (resolution of serum hCG, two decreasing hCGs with the final level below 25 MIU/ml, or three declining levels with the final level below 500 mIU/ml) - Resolved persistent PUL - Histologic IUP hCG concentration measurements were done at the clinical laboratory of each centre. Model based classification Prediction rules did not impact care because they were applied retrospectively. The timing and frequency of serial hCG values was decided by the treating clinician. The trend of values was determined to be increasing or decreasing. For those with an initial increase,	**EP, split by expected 2-day increase for an IUP (% (95% CI)** **a. 35% increase in hCG** Sensitivity: 83.2 (77.7 to 88.8) Specificity: 70.8 (67.7 to 73.9) PPV: 38.2 (33.4 to 43.0) NPV: 95.1 (93.4 to 96.8) Accuracy: 73.0 (70.3 to 75.8) **b. 53% increase in hCG** Sensitivity: 91.1 (86.8 to 95.3) Specificity: 66.6 (63.4 to 69.8) PPV: 37.1 (32.6 to 41.7) NPV: 97.2 (95.8 to 98.5) Accuracy: 70.9 (68.1 to 73.8) **c. 71% increase in hCG** Sensitivity: 92.2 (88.2 to 96.2) Specificity: 62.8 (59.5 to 66.1) PPV: 35.0 (30.6 to 39.3) NPV: 97.4 (96.0 to 98.7) Accuracy: 68.1 (65.2 to 70.9) Note: all of these use the 90% CI bounds for expected 2-day decrease for a miscarriage, corresponding to a decline of 36%-47% (depending on level)	who met the inclusion criteria were lost to follow-up Unclear whether anyone was blinded 65% of women presented with bleeding and 66% presented with pain. Therefore, it is unclear whether all of the participants of the study presented with pain and bleeding Those diagnosed with ectopic pregnancy included visualised and non-visualised EPs; therefore, not all of them were verified with the gold standard **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
pregnancy and a PUL **Study dates** October 2007 to June 2009 **Source of funding** Some of the authors are supported by grants: R01-HD036455, K24HD060687, and the Doris Duke Clinical Research Fellowship	No signs of an intrauterine or extrauterine gestation on TVS at presentation At least 2 hCG values at least 1 day apart Documented date of eventual definitive diagnosis **Exclusion Criteria** Diagnosed at presentation Never received a definitive diagnosis hCG level or more than 10000 MIU/ml		the rate was calculated and compared with the minimum expected gradient for an IUP. For patients whose hCG was initially declining, the decrease was compared with the decreased expected. If the change observed was between the minimum decrease and the minimum increase, the patient was classified as a suspected EP by the model. If the observed hCG level was increasing or decreasing more than the threshold the process of classification was repeated based on the comparison of the next hCG with the previous one value. If later values the slope failed to increase or decrease as expected, or the slope switched directions, the woman was classified as a suspected EP. If the change did not deviate from 'normal' then diagnosis was made based on ultrasound findings, clinical symptoms, or resolution of hCG from serum. <u>Analysis</u> Confidence interval bounds representing the expected increase based on 95%, 99% and 99.9% CI for the slope of increasing IUPs were used. Lower		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			limits represent an expected increase of 71%, 53% and 35% respectively, over 2 days. The expected decline for 90% and 95% CI was calculated based on decreasing miscarriage curves. The decrease expected was based on the value at presentation. The use of three hCG values was explored using patients with an initial increase. Sensitivity, specificity, PPV and NPV were calculated for each combination of bounds. The outcomes were IUP, miscarriage and EP. Disease positive was defined as the presence of one, and disease negative was the combination of the other two.		

What is the diagnostic accuracy of two or more hCG measurements plus progesterone for determining an ectopic pregnancy in women with pain and bleeding and pregnancy of unknown location?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Hahlin,M., Sjoblom,P., Lindblom,B., Combined use of progesterone and human chorionic gonadotropin determinations for differential diagnosis of very early pregnancy, Fertility and Sterility, 55, 492-496, 1991 **Ref Id** 72394 **Country/ies where the study was carried out** Sweden **Study type** Prospective cohort study **Aim of the study** To evaluate the diagnostic potential of the combined application of progesterone and an increase in hCG in differentiating viable intrauterine pregnancies from	**Sample size** N=307 **Characteristics** **Final diagnosis (number of women/total (%))** EP: 159/307 (51.8) Viable IUP: 73/307 (23.8) Miscarriage: 75/307 (24.4) Note: presenting symptoms are not reported **Inclusion Criteria** Positive urine hCG test Clinical suspicion of ectopic pregnancy (based on symptoms or the presence of risk factors)	**Tests** hCG score (calculated by plotting the initial hCG value against the rate of change of the serum level of hCG) Progesterone concentration **Positive test:** abnormal hCG score (falling below the curve that separates normal IUP and EP) AND progesterone concentration <30 nmol/l **Negative test:** any other pattern of hCG and progesterone	**Methods** During the study period, two blood samples with an interval of 1-6 days (mean 2.2, SD 1.21) were obtained from patients meeting the inclusion criteria. In addition to the 307 patients eventually included, there were 18 patients whose final diagnosis was unknown because no chorionic villi or trophoblast cells were found intrauterinely or extrauterinely, despite temporarily elevated serum hCG levels in the range of 100-850 IU/l. Another 22 patients were excluded because their serum hCG declined rapidly below 50 IU/l without therapeutic measures. Finally, in 9 patients, it was not possible to wait for a second serum sample due to the patient's clinical condition. Blood samples were obtained from one of the antecubital veins and centrifuged. The serum was stored at -20 degrees Celsius until analysed. Serum progesterone and hCG were determined using time-resolved fluoroimmunoassay.	**Results** **Proportion of women with abnormal hCG score and progesterone <30 nmol/l** Ectopic pregnancy: 114/159 (71.7) Miscarriage: 61/75 (81.3) Viable IUP: 0/73 (0) **Diagnostic accuracy of an abnormal hCG score in conjunction with a progesterone <30 nmol/l for diagnosing ectopic pregnancy (95% CI)** Sensitivity: 71.7 (64.7 to 78.7) Specificity: 58.8 (50.9 to 66.7) PPV: 65.1 (58.1 to 72.2) NPV: 65.9 (57.8 to 74.0) LR+: 1.74 (1.40 to 2.16) LR-: 0.48 (0.36 to 0.64) Note: The combination of an abnormal hCG and a low progesterone was the best test for diagnosing ectopic pregnancy. The other combinations do	**Limitations** **Population** An unknown proportion of patients were analysed due to the suspicion of ectopic pregnancy based on risk factors. Therefore, not all of the women in this study presented with pain and bleeding, and may be outside the population of interest for this review question. This study only included women with hCG 100-4000 IU/l. **Blinding** It is not reported whether the clinicians performing the reference tests were blinded to the results of the index test. **Progesterone** It is not reported whether the progesterone concentration from the first or second serum

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>pathological pregnancies

Study dates

January 1987 to April 1989

Source of funding

Swedish Medical Research Council

Goteborg Medical Society, Goteborg</td>
<td>Initial serum hCG between 100 and 4000 IU/l (the lower limit was set to reduce the number of cases in which it was impossible to establish a definite diagnosis; the upper limit was set to exclude cases in which endovaginal sonography has high diagnostic accuracy)

Clinical examination, including vaginal sonography, failed to give clear diagnosis

Exclusion Criteria

Ovarian stimulation

Unknown final diagnosis

Rapid decline in hCG to below 50 IU/l without intervention

Aggravated clinical condition which prevented second serum sample being taken</td>
<td></td>
<td>The hCG score was calculated by plotting the initial hCG value against the rate of change in serum hCG levels. In a previous study, it was shown that a line with the equation $y = 12.31x^{0.46}$ discriminated normal IUP and EP, where y is the absolute daily change and x is the initial hCG value. A patient with an hCG score falling below the curve is designated as having an "abnormal" hCG score, whereas a patient with an hCG score above the curve has a "normal" hCG score. For daily use, copies of the curve on graph paper were prepated, and the data point of each patient is plotted to see where it falls in relation to the curve.

A single serum progesterone measurement was judged against a threshold of 30 nmol/l, which has previously been suggested as a threshold for distinguishing normal and pathologic pregnancies.

The validity of the tests was evaluated separately (reported in review question 2) and when used in combination (reported here).

<u>Classification of final</u></td>
<td>not perform as well:

- abnormal hCG score and progesterone >30 nmol/l:
Sensitivity: 17.0%
Specificity: 88.5%
PPV: 61.4%
NPV: 49.8%

- normal hCG score and progesterone <30 nmol/l
Sensitivity: 3.8%
Specificity: 99.3%
PPV: 85.7%
NPV: 49.0%

- normal hCG score and progesterone >30 nmol/l
Sensitivity: 7.5%
Specificity: 50%
PPV: 14.8%
NPV: 31.9%

Abnormal hCG score plus progesterone
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>114</td><td>61</td></tr>
<tr><td>Predictive Test -ve</td><td>45</td><td>87</td></tr>
</table>
</td>
<td>sample was used to judge against the threshold of 30 nmol/l

Other information

Calculations of diagnostic accuracy were performed by the technical team.

This paper's study period overlaps with that of Thorburn et al. 1992 and was conducted in the same hospital. Therefore some women may appear in both papers, particularly the women eventually diagnosed with ectopic pregnancy, as it is a rare event.

<u>Interval between measurements</u>

The interval between two consecutive measurements ranged from 1 to 6 days, however the mean was 2.2 days and the hCG score is calculated using a slope which accounts for different time intervals.</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			<u>outcome</u> **Ectopic pregnancy:** Diagnosed based on laparoscopy, and confirmation of extrauterine trophoblast by histopathological examination **Viable intrauterine pregnancy:** The criteria was normal foetal development including heart activity in the 8th-10th gestational week, evaluated using vaginal sonography **Miscarriage:** Diagnosis was based on histological confirmation of the presence of chorionic villi in curettage material		
Full citation Condous,G., Okaro,E., Khalid,A., Timmerman,D., Lu,C., Zhou,Y., Van,HuffelS, Bourne,T., The use of a new logistic regression model for predicting the outcome of pregnancies of unknown location, Human Reproduction, #19, -1910, 2004 **Ref Id**	**Sample size** N=195 (This is the test set, on whom the model was tested prospectively, and on whom diagnostic accuracy measures were calculated. The original data set was 199 women, but 3 were excluded because they were persistent PULs, and 1 had no progesterone	**Tests** Model 3 (incorporates variables: hCG ratio, log progesterone average and age)	**Methods** **<u>Data collection</u>** All women were seen in one single Early Pregnancy Unit (St George's Hospital, London). When pregnancies were classified as PUL (see inclusion criteria), peripheral blood was taken. All scans were reviewed and followed up by the same primary investigator. The study group consisted of	**Results** **<u>Model M3</u>** This model uses hCG ratio, log progestereone average and age, and allows calculation of the predicted probability of an ectopic pregnancy. Probability of an EP = $(e^{12.31 - 4.73hCGratio - 2.31logprogaverage + 0.09age}) / (1 + e^{12.31 - 4.73hCG\ ratio - 2.31logprogaverage + 0.09age} + e^{14.68 - 7.65hCGratio - 3.63logprogaverage + 0.24age})$	**Limitations** **<u>Population</u>** Some of the women presented for ultrasound without pain and bleeding, i.e. due to poor obstetric history or to determine gestational age **<u>Blinding</u>** It is not reported whether the clinicians performing

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
91114 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** To generate and evaluate new logistic regression models based on demographic and hormonal parameters to predict the outcome of pregnancies of unknown location (PUL). **Study dates** June 2001 to December 2002 **Source of funding** Katholieke Universiteit Leuven, Belgium Belgian Programme on Interuniversity Poles of Attraction Concerted Action Project MEFISTO-666 of the	measurement taken. A further 186 women were the training set, on whom the model was developed) **Characteristics** **Final Diagnosis (number of women/total (%))** **Training set:** EP: 20/189 (10.6) IUP: 63/189 (33.3) Failing PUL: 102/189 (54.0) Persisting PUL: 4/189 (2.1) **Test set:** EP: 12/199 (6.0) IUP: 75/199 (37.7) Failing PUL: 109/199 (54.8) Persisting PUL: 3/199		388 consecutive women with PUL. The first 189 women (data collected between June 2001 and February 2002) were used as the training set. Statistical analysis and building of the logistic regression models were based on this data set. The next 199 women (recruited March 2002 to December 2002) were taken as the test set, to prospectively evaluate the performance of the models. The following data was collected: serum hCG and serum progesterone (at presentation and 48 hours), demographics (age and gestation), and ultrasound features (endometrial thickness, the character of its midline echo and the presence/absence of free fluid in the pouch of Douglas). Women were followed up until an outcome diagnosis was established: failing PUL, intrauterine pregnancy or ectopic pregnancy **Classification of final outcome** **Persistent PUL:** 4 women in the training set and 3 in the test set had serum hCG levels that plateaued, and no	**AUC of model M3 for diagnosis of EP** Training set: 0.920 (0.836 to 1.00) Test set: 0.836 (0.693 to 0.979) Model M1 (using hCG ratio only) had an AUC of 0.885 (0.760 to 1.00) for diagnosis of EP and was the better performing model on the test set. Therefore the authors chose to perform further diagnostic accuracy analysis on this model only. Sensitivity, specificity and other measures of diagnostic accuracy are not reported for model M3	the reference tests were blinded to the results of the index test. **Generalisability** The model was designed and tested on a specific inner city London population, therefore may not be generalisable. **Reporting of diagnostic accuracy** Because model M3 (incorporating serial hCG and progesterone) was not the best performing model, reporting of diagnostic accuracy was limited. **Location of failing PULs** The location of these failing PULs is never reported, therefore they could have been ectopic pregnancies. However, they were spontaneously resolving without intervention, therefore this may not be a clinically important limitation. For this

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Flemish Community One author (C. Lu) is supported by a KU Leuven PhD scholarship	(1.5) (Note: The 3 persisting PULs were excluded and 1 women with no progesterone measurement was not included in the analysis) **Indications for the ultrasound scan** - lower abdominal pain, with or without vaginal bleeding - poor obstetric history - to determine gestational age **Presenting symptoms (number of women/total (%))** **Training set:** not reported **Test set:** Lower abdominal pain:		pregnancy was seen at any time. These women were classified as having persistent PUL, and were treated with methotrexate and excluded from the analysis. They were not used for model development or validation, because the outcome is unknown and the numbers were so few. **Failing PUL:** If initial serum progesterone level was <20nmol/l, the women were classified as having a failing PUL. Spontaneous resolution of the pregnancy was defined as a decrease in the serum hCG level to <5IU/l with the disappearance of symptoms. The location of the failing PULs remained unknown. Serum hCG levels were repeated within 7 days to confirm the diagnosis. **Intrauterine pregnancy:** If the serum rise was >66% over a 48 hour period, the women were classified as having an IUP and were rescanned 2 weeks later to confirm diagnosis. Women who didn't fall into either category were reviewed every 48 hours until a diagnosis was made by		reason, it has not been downgraded in GRADE. **Other information** **M1 and M2** This paper also describes the performance of other models, which are not reported here. Model M1 incorporates hCG ratio only and hence is reported in review questions 2b and 2c. Model M3 only incorporates a single progesterone measurement and hence is not relevant to any of the review questions. **Gestational age** These models do not have to be used at the same gestational period, provided that serum hCG levels are <10,000 IU/l, because below this point the rate of the change in hCG is linear. **Bias correction** They also report a bias

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	136/196 (69.4) Vaginal bleeding with clots: 62/196 (31.6) Vaginal bleeding without clots: 68/196 (34.7) **Inclusion Criteria** No sign of either an intrauterine or extrauterine pregnancy or retained products of conception, when examined with transvaginal ultrasound (TVS) Positive pregnancy test (hCG>5IU/l) **Exclusion Criteria** Visualisation of any evidence of an intrauterine sac Identification of an adnexal mass thought to be an ectopic pregnancy Presence of heterogenous, irregular tissues within the uterus		ultrasonography. **Ectopic pregnancy:** The diagnosis of an ectopic pregnancy was based on positive visualisation of an adnexal mass. Ultrasonographic diagnosis of an ectopic pregnancy was based on the following grey-scale appearances: - an inhomogeneous or inconglomerate mass adjacent to the ovary and moving separate to this (designated the "blob" sign) - a mass with a hyperechoic ring around the gestational sac, referred to as the "bagel" sign - a gestational sac with a foetal pole with or without cardiac activity The diagnosis of an ectopic pregnancy was confirmed at laparoscopy, with histological confirmation of chorionic villi in the fallopian tube. If an ectopic pregnancy was not visualised, but there was a high index of suspicion based on symptomatology, clinical findings and suboptimal rises of serial serum hCG levels, a		corrected AUC in the study, which has a slightly different performance (AUC: 0.834 for model 3 diagnosing EP). This was generated using the bootstrap validation. However, the bias correction did not affect the ranking of the models, and the paper reports the results without the bootstrap as it's main results, therefore this has been reported here.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	thought to be an incomplete miscarriage Women who were clinically unstable or demonstrated the presence of haemoperitoneum on ultrasound scan Women with persistent PUL were excluded from the testing of the models		laparoscopy was performed with or without an evacuation of the uterus. **Data analysis** The data were pre-processed prior to further analysis. Some variables were created by transformation of the original variables: - **hCG ratio:** refers to the ratio of two hCG levels, i.e. serum hCG at 48 hours / serum hCG at 0 hours **- progesterone average:** The mean of the two progesterone levels in an interval of 48 hours was calculated. Because it was shown that the distribution of progesterone levels was extremely dispersed, the average progesterone levels were also transformed logarithmically. Univariate and multivariate analysis was performed retrospectively on the training data, in order to highlight the most significant variables for model development. Non-parametric Wilcoxon rank sum tests were used to compare group means for categorical data (they were non normally		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			distributed), and Fisher's exact tests were used to check the association of categorical variables. A p-value of <0.05 was considered statistically significant. **Model building** Baseline multi-categorical models were constructed to investigate the relationship between variables and the outcome of PULs. In the models, each outcome category is paired with baseline category, i.e. IUP leads to two equations, revealing the contrasts of the EP versus IUP group, and the failing pregnancy versus IUP group. **Performance measure and classification rules** Predictions can be made for the models by using thresholds/cut-offs on the output probability of the model. However, the choice of the threshold influences accuracy, may vary between institutions, and depends on the trade-off between sensitivity and false-positive rate. In order to elucidate the predictive power of the models for each		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			outcome category, they first considered binary classification problems, i.e. using the predictive probability for one class of PUL to distinguish from all other PULs. They constructed receiver operating characteristic (ROC) curves. The area under the curve (AUC) can be interpreted as the probability of the test correctly distinguishing abnormal patients from normal ones. The performance of the models was also evaluated in terms of sensitivity, specificity, PPV and NPV. Cases had to be classified in to one of three initial categories, and was done so according to rules: - if the predicted probability for a PUL to be an EP was over a threshold, it was classed as an EP, otherwise it was classed as a non-EP - for PULs classed as non-EP, if the predicted probability for a PUL to be failing was greater than a threshold, it was classed as a failing pregnancy, otherwise it was classified as an IUP The probability thresholds were identified by minimising the		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			square root of [(1 - sensitivity)^2 + (1 - specificity)^2], in order to try and maximise both sensitivity and specificity. **Model validation** The models were first validated on the training set by the use of ROC analysis for three binary classification problems. They also used the bootstrap technique in order to obtain nearly unbiased estimates of the predictive ability of the models. A total of 100 random samples of the same size as the initial data set were drawn with replacement from the initial data set. The logistic models were fitted on each bootstrap sample, and performance was measured on the bootstrap samples and the original sample. The models were validated further on an independent data with 195 PULs (excluding the 3 persistent PULs and 1 participant without a progesterone measurement). **Reporting of diagnostic accuracy** After comparing AUC, it was judged that model M1 was the		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			best performing model. Therefore, the authors report sensitivity, specificity, PPV and NPV for Model 1 only. Model M3 had a lower AUC and hence was not evaluated further. Only the area under the curve can be reported for model M3, as it is not possible to create a 2x2 table.		
Full citation Gevaert,O., De,SmetF, Kirk,E., Van,CalsterB, Bourne,T., Van,HuffelS, Moreau,Y., Timmerman,D., De,MoorB, Condous,G., Predicting the outcome of pregnancies of unknown location: Bayesian networks with expert prior information compared to logistic regression, Human Reproduction, 21, 1824-1831, 2006 **Ref Id** 91316 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study	**Sample size** N=257 (A total of 856 women were included. 257 comprised the validation set, on whom the model was tested. The model-building set consisted of 599 women) **Characteristics** **Final diagnosis (number of women/total (%))** Failing PUL: 460/856 (53.7) IUP: 330/856 (38.6) EP: 66/856 (7.7) Note: the model	**Tests** **Model PPM** (incorporates hCG ratio, level of progesterone at 48 hours and number of gestation days) **Model SPPM** (specific incorporated variables are not described)	**Methods** 1003 consecutive women presented with a PUL. 58 were lost to follow-up, 129 were excluded because of incomplete data, and 18 were excluded because they were persisting PULs. Therefore, 856 women were included. **Data collection** Data were collected prospectively from consecutive women presenting with a PUL at St George's Hospital London during the study period. Women underwent transvaginal ultrasound using a 5-MHz probe, and blood was taken to measure the levels of serum hCG and progesterone at both 0 and 48 hours. Other data were also collected, leading to ten variables in the data set:	**Results** Note: the following all refer to the performance of the models on the validation data set only **Diagnostic accuracy of models** **a. SPPM (using threshold of 0.06)** AUC: 0.86 Sensitivity: 77% Specificity: 80% LR+: 3.9 LR-: 0.29 **b. PPM (using threshold of 0.13)** AUC: 0.88	**Limitations** **Population** Not all women presented with pain and/or bleeding **Blinding** It is not reported whether blinding occurred. **Gold standard** "...diagnosis was subsequently confirmed at laparoscopy...in those women who underwent surgery." Therefore, not all women had their diagnosis verified with the gold standard. **Generalisability** Model was designed and tested on a specific inner

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study To evaluate the use of discrete-valued Bayesian networks in combination with different forms of prior information when predicting the outcome of pregnancies of unknown location **Study dates** June 2001 to October 2004 **Source of funding** Institute for the Promotion of Innovation through Science and Technology in Flanders (IWTVlaanderen) Research council KUL: GOA AMBioRICS, CoE EF/05/007 SymBioSys, IDO (Genetic networks) Several PhD/postdoc and fellow grants The Flemish Government: FWO: PhD/postdoc grants, G.0407.02 (support vector machines), G.0413.03 (inference in bioi), G.0388.03 (microarrays for clinical	building set had 44 EP (7.3%), whereas the validation set had 22 EP (8.6%) **Characteristics of the women in the validation Set, divided by diagnosis** **a. Pain (number of women/total (%))** Non-EP: 116/235 (49) EP: 7/22 (32) **b. Any bleeding (number of women/total (%))** Non-EP: 135/235 (57) EP: 13/22 (60) **c. Free fluid (number of women/total (%))** Non-EP: 37/235 (16) EP: 2/22 (9) **d. Disrupted midline echo (number of**		- age - endometrial thickness (mm) - gestation days (days) - hCG ratio (hCG 48 h/hCG 0 h) - progesterone 0h (nmol/l) - progesterone 48h (nmol/l) - bleeding: no/yes without clots/yes with clots - free fluid: no/yes - midline echo: intact/disrupted - pain: no/yes The continuous variables were discretised according to intervals specified by an expert in early pregnancy, who based the intervals on past experience and chose thresholds empirically known to reflect clinical states. The intervals were chosen to balance keeping as much information as possible while limiting the number of intervals to reduce the number of parameters. **Classification of final outcome** Women were followed up until a final diagnosis could be established: **Failing PUL:** confirmed when there were persistent negative sonographic findings in the	Sensitivity: 77% Specificity: 83% LR+: 4.5 LR-: 0.28 The authors state that the PPM model had a higher AUC and better specificity, and therefore has the potential to be used in a clinical setting. However, although they report that PPM performed better overall, they also report that SPPM had an advantage at high specificity levels. At high specificity (>98%), SPPM maintains a sensitivity of >40%. Note: These diagnostic accuracy measures were reported in the paper. It was not possible for the technical team to create a 2x2 table to verify these calculations and calculate 95% CI. Due to a lack of information about the variables incorporated into SPPM, only PPM is reported in the GRADE table.	city population, and therefore may not be generalisable. **Statistical reporting** Confidence intervals around diagnostic acccuracy measures are not reported and cannot be calculated. **Complexity of models** If one variable had missing data, more information (e.g. clinical data like bleeding and pain, ultrasound findings or progesterone at 0 hours) will be needed to predict probability of ectopic pregnancy. If this occurs, the authors report that the Bayesian networks could become more costly and time-consuming to use, and would be more prone to variation in performance if they relied on subjective variables (e.g. pain) and sonographers skills. **Other information** **Supplementary**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
use), G.0229.03 (ontologies in bioi), G.0241.04 (Functional Genomics), G.0499.04 (Statistics), G.0232.05 (Cardiovascular), G.0318.05 (subfunctionalization), G.05503.06 (VitamineD) and research communities (ICCoS,ANMMM and MLDM); IWT: PhD grants, GBOU-McKnow (Knowledge management algorithms), GBOU-SQUAD (quorum sensing), GBOU-ANA (biosensors), TAD-BioScope, Silicos; Belgian Federal Science Policy Office: IUAP P5/22 (Dynamical Systems and Control: Computation, Identification and Modelling, 2002–2006); EU-RTD: FP5-CAGE (Compendium of Arabidopsis Gene Expression); ERNSI: European Research Network on System Identification; Biopattern (FP6-2002-IST 508803); eTUMOUR (FP6-2002-LIFESCIHEALTH	**women/total (%))** Non-EP: 30/235 (13) EP: 4/22 (18) **e. Age/years (mean (minimum-maximum))** Non-EP: 30 (15-49) EP: 30 (22-39) **f. Endometrial thickness/mm (mean (minimum-maximum))** Non-EP: 11 (2-31) EP: 11 (3.8-22) **g. Gestation/days (mean (minimum-maximum))** Non-EP: 43 (10-93) EP: 42 (19-93) **h. hCG ratio [48h/0h]/U/l (mean (minimum-maximum))** Non-EP: 1.2 (0.08-4.2)		presence of falling serum hCG levels ultimately reaching <5U/l **Intrauterine pregnancy:** confirmed sonographically during follow-up with the presence of a gestational sac eccentrically placed within the endometrial cavity **Ectopic pregnancy:** Diagnosis was based on the positive visualisation of an adnexal mass. Ultrasound diagnosis was based on the following grey-scale appearances: an inhomogenous mass adjacent to the ovary and moving separate to this ("blob sign"), or a mass with a hyper-echoic ring around the gestational sac ("bagel sign"), or a gestational sac with a fetal pole with or without cardiac activity. The diagnosis was confirmed at laproscopy with histological confirmation of chorionic villi in the Fallopian tube in women who had surgery. Note: if an ectopic pregnancy was not visualised but there was a high index of suspicion based on symptoms, clinical findings, and suboptimal rises of serial serum hCG, a laparoscopy was performed with or without		**<u>information</u>** This paper is accompanied by supplementary information on a website, where it is possible to input in gestational age, progesterone at 48 hours and hCG ratio. The website generates a probability of ectopic pregnancy, which can then be compared to the threshold of 0.13 using PPM. Presumably, the authors are imagining that this could be distributed to doctors more widely for use in clinical practice. **<u>Patterns in the model</u>** The authors report the following from the model PPM, with regards to biochemical variables: - when hCG ratio<0.8, the probability of an ectopic pregnancy rises with rising levels of progesterone at 48 hours - when hCG ratio>1.66, the probability of an

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
503094) and FP6-MC-EST Bioptrain.	EP: 1.3 (0.34-2.4) **i. Progesterone 0h/nmol/l (median (minimum-maximum))** Non-EP: 10 (1-191) EP: 3 (4-89) **j. Progesterone 48h/nmol/l (median (minimum-maximum))** Non-EP: 6 (1-250) EP: 22 (5-84) **Inclusion Criteria** Presenting with a pregnancy of unknown location **Exclusion Criteria** Diagnosed with a persistent pregnancy of unknown location Incomplete data		evacuation of the uterus. **<u>Model building</u>** The data was randomly split into the "model-building data set" (n=599) and the "validation data set" (n=257). Splitting was done in a stratified manner to ensure that the proportion of ectopic pregnancies in each set was about equal. The model used Bayesian networks to detect the EPs in the PUL population. The authors evaluated models using different combinations of prior information, to create the ROC curve with the highest AUC. Two models (SPPM and PPM) had equal AUC when run on the model-building set, and were therefore tested on the validation data set. Using the model-building set, the authors selected an operating point on the ROC curve that would maximise the sum of the sensitivity and specificity. In the PPM, the probability threshold is 0.13, and in the SPPM the probability threshold is 0.06 . The probability predicted by the model is considered an EP if it is greater than the threshold, and a non-		ectopic pregnancy drops with rising levels of progesterone at 48 hours - when 0.8<hCG ratio<1.66, the relationship is more complex: the probability of ectopic pregnancy has a local maximum when progesterone at 48 hours is 10-40 nmol/l, but there is a higher probability when progesterone is above 80 nmol/l. The authors also state that the number of gestation days has a large influence. When this variable is <35, then the probability of an ectopic pregnancy is much higher when the hCG ratio is below 0.8 and the progesterone levels at 48 hours are high, compared to the case when the number of gestation days is above 35.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			ectopic below this threshold. The two models were tested on the validation data set, and the AUC was calculated to represent the performance of the model on unseen data. **Included variables** Analysis of the PPM model showed that if the hCG ratio, the level of progesterone at 48 hours and the number of gestation days is known, the other variables will have no influence on outcome. The authors focus on PPM in their results and discussion, as it is considered to be the better performing model. The specific variables in the SPPM model are not described in detail.		

What is the diagnostic accuracy of two or more hCG measurements for determining a viable intrauterine pregnancy in women with pain and bleeding and pregnancy of unknown location?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Hahlin,M., Sjoblom,P., Lindblom,B., Combined use of progesterone and human chorionic gonadotropin determinations for differential diagnosis of very early pregnancy, Fertility and Sterility, 55, 492-496, 1991 **Ref Id** 72394 **Country/ies where the study was carried out** Sweden **Study type** Prospective cohort study **Aim of the study** To evaluate the diagnostic potential of the combined application of progesterone and an increase in hCG in differentiating viable	**Sample size** N=307 **Characteristics** **Final diagnosis (number of women/total (%))** Viable IUP: 73/307 (23.8) EP: 159/307 (51.8) Miscarriage: 75/307 (24.4) Note: presenting symptoms are not reported **Inclusion Criteria** Positive urine hCG test Clinical suspicion of EP (based on symptoms or the presence of risk factors) Initial serum hCG between 100 and 4000 IU/l (the lower limit was set to reduce the number of cases in which it was impossible to establish a definite diagnosis; the upper	**Tests** hCG score (calculated by plotting the initial hCG value against the rate of change of the serum level of hCG) **Positive test:** normal hCG score (falling above the curve that separates normal IUP and EP) **Negative test:** abnormal hCG score (falling below the curve that separates normal IUP and EP)	**Methods** During the study period, two blood samples with an interval of 1-6 days (mean 2.2, SD 1.21) were obtained from patients meeting the inclusion criteria. In addition to the 307 patients eventually included, there were 18 patients whose final diagnosis was unknown because no chorionic villi or trophoblast cells were found intrauterinely or extrauterinely, despite temporarily elevated serum hCG levels in the range of 100-850 IU/l. Another 22 patients were excluded because their serum hCG declined rapidly below 50 IU/l without therapeutic measures. Finally, in 9 patients, it was not possible to wait for a second serum sample due to the patient's clinical condition. Blood samples were obtained from one of the antecubital veins and centrifuged. The serum was stored at -20 degrees celsius until analysed. Serum progesterone and hCG were determined using time-resolved fluoroimmunoassay.	**Results** **Proportion of women with a normal hCG score (number/total (%))** Viable IUP: 69/73 (94.5) EP: 18/159 (11.3) Miscarriage: 1/75 (1.3) **Diagnostic accuracy of a normal hCG score for diagnosing viable intrauterine pregnancy (95% CI)** Sensitivity: 94.5 (89.3 to 99.7) Specificity: 91.9 (88.4 to 95.4) PPV: 78.4 (69.8 to 87.0) NPV: 98.2 (96.4 to 100) LR+: 11.64 (7.54 to 17.98) LR-: 0.06 (0.02 to 0.15)	**Limitations** **Population** An unknown proportion of patients were analysed due to the suspicion of EP based on risk factors. Therefore, not all of the women in this study presented with pain and bleeding. This study also only included women with hCG of 100-400 IU/l. **Blinding** It is not reported whether the clinicians performing the reference tests were blinded to the results of the index test. **Gold standard** It is unclear how long they waited before intervening in the case of a diagnosed miscarriage, i.e. whether all women received the

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>intrauterine pregnancies from pathological pregnancies

Study dates

January 1987 to April 1989

Source of funding

Swedish Medical Research Council

Goteborg Medical Society, Goteborg</td>
<td>limit was set to exclude cases in which endovaginal sonography has high diagnostic accuracy)

Clinical examination, including vaginal sonography, failed to give clear diagnosis

Exclusion Criteria

Ovarian stimulation

Unknown final diagnosis

Rapid decline in hCG to below 50 IU/l without intervention

Aggravated clinical condition which prevented second serum sample being taken</td>
<td></td>
<td>The hCG score was calculated by plotting the initial hCG value against the rate of change in serum hCG levels. In a previous study, it was shown that a line with the equation $y = 12.31x^{0.46}$ discriminated normal IUP and EP, where y is the absolute daily change and x is the initial hCG value. A patient with an hCG score falling below the curve is designated as having an "abnormal" hCG score, whereas a patient with an hCG score above the curve has a "normal" hCG score. For daily use, copies of the curve on graph paper were prepated, and the data point of each patient was plotted to see where it fell in relation to the curve. Diagnostic accuracy of the test could then be calculated.

<u>Classification of final outcome</u>

Viable intrauterine pregnancy: The criteria was normal foetal development including heart activity in the 8th-10th gestational week, evaluated using vaginal sonography

Ectopic pregnancy: Diagnosed based on laparoscopy, and confirmation of extrauterine trophoblast by</td>
<td>Normal hCG score
<table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td>69</td><td>19</td></tr><tr><td>Predictive Test -ve</td><td>4</td><td>215</td></tr></table></td>
<td>gold standard of multiple ultrasounds. It is possible that viable IUP could have been inadvertently terminated if clinicians intervened incorrectly or too early.

Other information

Calculations of diagnostic accuracy were performed by the technical team.

This paper's study period overlaps with that of Thorburn et al. 1992 and was conducted in the same hospital. Therefore some women may appear in both papers, particularly the women eventually diagnosed with EP, as it is a rare event.

Progesterone is also assayed in this study, however it is not relevant to this review question and will be reported elsewhere.

<u>Interval between hCG measurements</u>

The interval between</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			histopathological examination **Miscarriage:** Diagnosis was based on histological confirmation of the presence of chorionic villi in curettage material		two consecutive measurements ranged from 1 to 6 days, however the mean was 2.2 days and the hCG score is calculated using a slope which accounts for different time intervals
Full citation Dart,R.G., Mitterando,J., Dart,L.M., Rate of change of serial beta-human chorionic gonadotropin values as a predictor of ectopic pregnancy in patients with indeterminate transvaginal ultrasound findings, Annals of Emergency Medicine, 34, 703-710, 1999 **Ref Id** 91155 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study	**Sample size** **N=307** **Characteristics** **Final diagnosis (number of women/total (%))** Normal IUP: 53/307 (17.3) EP: 33/307 (10.7) Abnormal IUP: 221/307 (72.0) **Interval between hCG measurements/days (number of women/total (%))** 1: 41/307 (13.4) 2: 180/307 (58.6) 3: 48/307 (15.6)	**Tests** Serial serum hCG **Test positive:** rise in hCG levels >66% over 48 hours **Test negative:** decline in hCG levels, or rise that is <66% over 48 hours	**Methods** This study was a retrospective review of a cohort of emergency department patients who fit the inclusion criteria. A total of 729 women had indeterminate ultrasounds over the study period, of which 108 were lost to follow-up before the exclusion of an ectopic pregnancy. 331 of these patients had 2 hCG assays performed within 7 days of each other and before intervention, however 24 were lost to follow-up and were therefore excluded. This left 307 patients who were enrolled. Quantitative hCG results were assayed using a Stratus hCG Fluorometric Immunoassay, standardised to the WHO Third International Standard. Patients were divided in to 4 groups based on the rate of increase or decrease shown by hCG. These rates were determined a priori	**Results** **Final diagnosis, split by pattern of hCG (n)** Rise > 66% - Normal IUP: 40 - EP: 6 - Abnormal IUP: 6 Rise < 66% - Normal IUP: 13 - EP: 17 - Abnormal IUP: 33 Decline < 50% - Normal IUP: 0 - EP: 8 - Abnormal IUP: 75 Decline > 50% - Normal IUP: 0 - EP: 2 - Abnormal IUP: 107	**Limitations** **Retrospective** This is a retrospective study **Gold standard** Unclear how long they waited before intervening in the case of a diagnosis of miscarriage - it is possible that not all women received the gold standard verification of diagnosis. **Other information** Calculations of diagnostic accuracy were performed by the technical team. **Blinding**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Aim of the study

To determine the predictive value of the rate of change of serial beta-human chorionic gonadotropin values in patients with symptoms suggestive of ectopic pregnancy who have indeterminate transvaginal ultrasound findings, and to determine whether the predictive value was enhanced depending on whether the endometrial cavity was empty at ultrasound examination.

Study dates

August 1st 1991 to August 1st 1998

Source of funding

Not stated</td>
<td>4: 23/307 (7.5)

5: 6/307 (2.0)

6: 5/307 (1.6)

7: 4/307 (1.3)

Inclusion Criteria

Abdominal pain or vaginal bleeding

Positive pregnancy test

Ultrasound examination performed during their emergency department (ED) visit which was classed as an indeterminate ultrasound

Second hCG performed within 7 days of ED visit, and the test was obtained before the performance of dilation and evacuation procedure, laparoscopy or methotrexate therapy

Exclusion Criteria

Lost to follow-up before final diagnosis was determined</td>
<td></td>
<td>from the results of other studies:

- Patients with >66% increase in hCG over 48 hours

- Patients whose hCG increased but by a rate <66% over 48 hours

- Patients with hCG that decreased by <50% over 48 hours

- Patients with hCG that decreased >50% over 48 hours

For patients in whom the follow-up interval was only 24 hours but who had increasing hCG values, the cut-off was determined by multiplying 1.29 x initial hCG value. The factor 1.29 is the square root of 1.66, therefore an increase of 1.29 per day would equal an increase of 1.66 over 48 hours. In patients with follow-up after 24 hours with decreasing hCG levels, the cut-off was determined by multiplying 0.71 x initial hCG value.

Patients in whom follow-up was greater than 48 hours were handled as follows: those with an even number of days follow-up had a predicted increase/decrease calculated</td>
<td><u>Diagnostic accuracy of >66% rise in hCG for diagnosing viable intrauterine pregnancy</u>

Sensitivity: 75.5 (63.9 to 87.1)

Specificity: 95.3 (92.7 to 97.9)

PPV: 76.9 (65.5 to 88.4)

NPV: 94.9 (92.2 to 97.6)

LR+: 15.97 (9.01 to 28.34)

LR-: 0.26 (0.16 to 0.41)

Rise >66%
<table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td>40</td><td>12</td></tr><tr><td>Predictive Test -ve</td><td>13</td><td>242</td></tr></table></td>
<td>Blinding <u>was</u> done - calculations of rate of hCG change and classification into categories was done by a study investigator otherwise blinded to clinical information.

<u>Interval between hCG measurements</u>

Only 59% of patients had an interval of exactly 2 days between their hCG measurements. In the remaining patients, the hCG change over 2 days was calculated using the equations described in the methods section.

<u>Endometrial cavity (number of women/total (%))</u>

a. Normal IUP
Empty: 19/53 (35.8)
Not empty: 34/53 (64.2)

b. Abnormal IUP
Empty: 96/221 (43.4)
Not empty: 125/221 (56.6)

c. Ectopic pregnancy</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	Time interval between hCG assays was >7days		every 48 hours, and the value was adjusted every 48 hours until actual follow-up date was reached. An odd day was calculated in the same fashion, except a multiple of 1.29 was used to account for the odd day. In cases where hCG assays were obtained on more than 2 visits, the emergency department assay and the one done 48 hours later were used if available. Otherwise, the assay with the closest temporal relationship to the emergency department assay was used. Calculations of rate of change and assignment to the four groups was performed by a study investigator who was otherwise blinded to any clinical information. **Changes to emergency department protocol during study period** All women of childbearing age presenting to the ED with abdominal pain and/or vaginal bleeding have a qualitative pregnancy test. All women with positive results then have a quantitative serum test. August 1991 - December 1994: during daytime hours, all		Empty: 29/33 (87.9) Not empty: 4/33 (12.1)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			symptomatic patients underwent transabdominal scanning unless they had a normal IUP documented at a previous visit or they had an open cervical os, or a uterine size greater than 12 weeks by pelvic exam. The transabdominal scan was followed by a transvaginal examination if an IUP was not identified. During evenings or nights, ultrasound scanning was limited to those with hCG>1000mIU/mL January 1995 – end of study: 24-hour-a-day in house ultrasound coverage became available and ultrasound was performed irrespective of hCG value August 1991 - January 1996: all patients without evidence of an IUP by ultrasound were admitted for further evaluation January 1996 - end of study: the decision to admit or discharge patients without evidence of an IUP was left to the discretion of the treating clinician **Identification of cases** Cases were identified in one of		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			three ways: August 1991 - August 1992: patients were identified from a prior prospective study of consecutive ED patients with abdominal pain or vaginal bleeding September 1992 - December 1994: patients were identified by a search of our institution's computerised radiology database. The authors identified all women who had pelvic ultrasound examinations ordered from the ED to assess the status of a first trimester pregnancy. From these, ultrasounds that met the study criteria were identified, and the patients' medical records were reviewed to confirm eligibility January 1995 - August 1998: patients were prospectively identified by daily tracking of all ED patients with positive hCG results. Confirmation of eligibility was based on ultrasound report and ED record. Clinical data was primarily obtained from medical records. Laboratory, pathology and ultrasound results were available in a computerised		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			database. Data elements were abstracted using standardised data collection forms, by people who had received at least 4 hours of training under the supervision of the principal investigator. Final diagnosis was made using predefined criteria. All decisions about eligibility, exclusion and final diagnosis were made before calculation of the rate of change of hCG. **Classification of final outcome** **Normal IUP:** pregnancy was carried to delivery, or at a later date there was demonstration of a normal IUP with a foetal heartbeat by ultrasound **Abnormal IUP:** **-** hCG>3000 mIU/ml in association with an empty uterus, decreasing hCG, or a progesterone value <5.0ng/ml, before dilation and evacuation and evidence of chorionic villi in pathology specimen - no villi in the dilation and evacuation specimen but with hCG values that decreased to zero without further intervention - hCG values that decrease to zero without intervention		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			Ectopic pregnancy: - extrauterine pregnancy visualised at laparoscopy - in patients managed medically with methotrexate, no chorionic villi after dilation and evacuation, and either increasing or abnormally decreasing hCG values or EP visualised at ultrasound **<u>Ultrasound criteria</u>** An ultrasound was considered indeterminate if it was neither diagnostic of an IUP (did not contain an intrauterine yolk sac or foetal pole), nor diagnostic or suggestive of an EP (no extrauterine adnexal mass or sac-like structure, no more than a small amount of fluid visualised in the cul-de-sac). Indeterminate ultrasounds were divided into two groups: those with an empty endometrial cavity and those in whom the cavity was not empty. "Not empty" was characterised by findings such as small anechoic fluid collections without a well-defined echogenic border, the presence of echogenic material in the absence of a sac-like structure, and well-defined but empty sac-like structures.		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			Ultrasound characterisation was determined by a review of the official ultrasound report, before and separate from the determination of the patient's final diagnosis. The ultrasound exams were performed by ultrasound technicians under the direct supervision of either a radiology attending physician or resident. All supervising radiology attending physicians had specific expertise in pelvic ultrasonography. In cases supervised by a resident, the hard copy was reviewed by an attending before the final report. Frequency of EP was calculated for each of the four groups based on the rate of increase or decrease of hCG, and these frequencies were compared using logistic regression. For the secondary analysis, women were subdivided on whether the endometrial cavity was empty or not empty, to assess whether the addition of ultrasound findings affected results.		
Full citation Daus,K., Mundy,D., Graves,W., Slade,B.A., Ectopic pregnancy. What to do during the 20-day window, Journal of Reproductive	**Sample size** N=357 **Characteristics** **<u>Final diagnosis (number of</u>**	**Tests** Serial serum hCG **Positive test:** Normal, rising	**Methods** During the study period, 375 (the technical team believe this to be a typo on the part of the paper and it should be 357) patients were suspected of having eccyesis and met the	**Results** **<u>Final diagnosis, split by hCG pattern (n)</u>** Rise > 63% - Normal IUP: 54 - Abnormal IUP: 3	**Limitations** **<u>Retrospective</u>** This study is retrospective.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Medicine, 34, 162-166, 1989

Ref Id

91158

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study

To determine if normal intrauterine pregnancies could be differentiated from abnormal pregnancies by serial quantitation of serum hCG levels.

Study dates

January 1st 1986 to January 1st 1987

Source of funding

Not stated</td>
<td><u>women/total (%))</u>

Normal IUP: 62/357 (17.4)

Abnormal IUP: 64/357 (17.9)

EP: 47/357 (13.2)

Undiagnosed: 184/357 (51.5)

Inclusion Criteria

Suspicion of EP

Stable condition on clinical examination

Culdocentesis results not diagnostic of haemoperitoneum

Serial quantitative hCG values ranging from 5 to 10,000 mIU/ml or until resolution of the problem

Final outcome determined to be one of the following:
- Normal IUP
- Spontaneous miscarriage or blighted ovum with tissue confirmation obtained from dilation and curettage
- Ectopic pregnancy requiring surgery and</td>
<td>hCG levels (defined as a rise of 63% or greater)

Negative test: Abnormally rising (rise less than 63%) or falling hCG levels</td>
<td>criteria for inclusion (see inclusion criteria). Data was collected using a retrospective chart review.

hCG levels were measured using the Stratus hCG Fluorometric Enzyme Immunoassay, which detects intact hCG using a 2-site monoclonal antibody sandwich technique. This assay is sensitive to 5mIU of hCG per millilitre and is calibrated against the first International Reference Standard Preparation. All assays were performed according to the manufacturer's instructions by the Clinical Laboratory of Grady Memorial Hospital.

357 patients were followed for suspected eccyesis. Patients with documented IUP were used as controls. All patients in this group had three or more quantitative hCG values. If serial values were greater than 10 days apart they were excluded. Patients in the remaining groups (miscarriage, EP, abnormal pregnancy) were included if two or more hCG values were known prior to resolution of the problem. Slopes of hCG change were then calculated for each patient. If only 2 values were known, the</td>
<td>- EP: 3
- PUL: 0

Rise < 63%
- Normal IUP: 8
- Abnormal IUP: 13
- EP: 17
- PUL: 14

Decline
- Normal IUP: 0
- Abnormal IUP: 48
- EP: 27
- PUL: 170

<u>Diagnostic accuracy of hCG rise >63% for diagnosing viable IUP</u>

Sensitivity: 87.1 (78.8 to 95.4)

Specificity: 98.0 (96.4 to 99.6)

PPV: 90.0 (82.4 to 97.6)

NPV: 97.3 (95.5 to 99.2)

LR+: 42.82 (19.28 to 95.09)

LR-: 0.13 (0.07 to 0.25)

Rise >63%
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
</table>
</td>
<td><u>Blinding</u>

It is unclear that the authors were blinded to the final diagnosis when interpreting hCG results.

<u>Gold standard</u>

All women with a miscarriage had a dilation and curettage and products of conception confirmed by pathology reports, however it is not reported how long the clinicians waited before intervening. Therefore, it is possible that not all women had their miscarriages diagnosed using the gold standard of repeat ultrasounds, and hence mistakes could have occurred. Criteria for judging a normal intrauterine pregnancy are not described.

<u>Ultrasound</u>

The authors discuss the inaccuracy of ultrasound before 28 days in their introduction, a time during which ectopic</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	confirmed by tissue diagnosis - Abnormal pregnancy not requiring surgery **Exclusion Criteria** Consecutive serial hCG values more than ten days apart		slope was computed from the line connecting the two values. If more values were obtained, linear regression was used to calculate the slope. After determining slopes for each patient, the mean and SD for only patients with positive slopes in the four groups was calculated. The analysis was only performed for positive slopes because no patients having a negative slope showed evidence of a normal IUP or therefore presented a diagnostic problem. The authors used 0.016 as the lower limit of a normal increase in hCG (this correlated with a rise of 63% in 48 hours). This value was derived using one standard deviation from the normal IUP group mean slope. Using this threshold, women were classified as having normally rising levels, abnormally rising levels or falling levels. **Classification of final outcome** **Normal IUP:** criteria not reported **Spontaneous miscarriage or**	**Predictive Test +ve** 54 6 **Predictive Test -ve** 8 289	pregnancy may remain undiagnosed. However, their methods do not report ultrasound results or criteria, therefore the participants may not have true PULs. **Final outcome** Over half the women remain undiagnosed at the end of the study period, however they did not require intervention and therefore this may not be a clinically significant limitation. For this reason, it has not been downgraded in GRADE. **Other information** Calculations of diagnostic accuracy were performed by the technical team. **Interval between serum hCG measurements** Women were only excluded for having an interval longer than 10 days. However, they did evaluate women

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			blighted ovum: tissue confirmation obtained from dilation and curettage **Ectopic pregnancy:** confirmed by tissue diagnosis after surgery **Abnormal pregnancy:** not requiring surgery		according to a slope of 0.016, corresponding to an increase of 63% over 48 hours. **Definition of "suspicion of EP" as an inclusion criterion** This is not defined in the methods, however the paper starts by discussing that suspicion of EP arises when a pregnant woman is clinically stable but complains of mild to moderate abdominal pain
Full citation Mol,B.W.J., Hajenius,P.J., Engelsbel,S., Ankum,W.M., van,derVeenF, Hemrika,D.J., Bossuyt,P.M.M., Serum human chorionic gonadotropin measurement in the diagnosis of ectopic pregnancy when transvaginal sonography is inconclusive, Fertility and Sterility, 70, 972-981, 1998	**Sample size** n=195 Note: 354 women are included in the study, but only 195 had repeated evaluation (i.e. a second hCG), and therefore they are the population of interest. **Characteristics** **Final diagnosis (number of women/total (%))** **a. in women whom a second hCG was used for**	**Tests** Serial serum hCG concentration **Test positive:** rise >50% in hCG **Test negative:** rise <50% or any decline in hCG	**Methods** Consecutive patients presenting with suspected ectopic pregnancy (see inclusion criteria) in two large teaching hospitals in Amsterdam were included. Transvaginal sonography was performed by one of the study investigators or, during shifts, by the resident on call. The intrauterine cavity was scanned, and an IUP diagnosed when an intrauterine gestational sac was visualised. When an intrauterine gestational sac could not be visualised, both adnexal regions were scanned for the presence	**Results** **Final diagnosis, split by pattern of hCG (n)** Rise > 50% - Viable IUP: 14 - EP: 12 - Non-viable pregnancy: 4 Rise < 50% - Viable IUP: 1 - EP: 15 - Non-viable pregnancy: 18 Decline < 50% - Viable IUP: 0 - EP: 11 - Non-viable pregnancy: 57	**Limitations** **Population** These women are a sub-set of the population of interest, who have hCG <1500 with an indeterminate ultrasound. Women with hCG>1500 with an indeterminate ultrasound have already left the pathway. Not all women presented with pain and bleeding. **Blinding**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ref Id

91712

Country/ies where the study was carried out

the Netherlands

Study type

Prospective cohort study

Aim of the study

To assess the accuracy of initial and repeated serum hCG measurements in the diagnosis of ectopic pregnancy in patients in whom transvaginal sonography is inconclusive, and to evaluate whether patient characteristics influence the accuracy of serum hCG measurements

Study dates

September 1993 to April 1996

Source of funding</td>
<td>diagnosis (population of interest for this review question)

Viable IUP: 15/195 (7.7)

EP: 38/195 (19.5)

Non-viable IUP: 16/195 (8.2)

Chemical pregnancy: 126/195 (64.6)

b. in whole study population

Viable IUP: 67/354 (18.9)

EP: 129/354 (36.4)

Non-viable IUP: 23/354 (6.5)

Chemical pregnancy: 135/354 (38.1)

<u>Presenting symptoms (number of women/total (%))</u>

Abdominal pain: 223/354 (63.0)

Vaginal bleeding: 228/354</td>
<td></td>
<td>of an ectopic gestational sac, an ectopic mass or fluid in the pouch of Douglas. An ectopic gestational sac was defined as the presence of a yolk sac, a foetal pole, or foetal cardiac activity. When an ectopic gestational sac was visualised, an EP was diagnosed. 824 women presented with a suspected EP, but 470 were excluded from analysis. Reasons for exclusion were that the pregnancy resulted from IVF (n=26), the patient presented with symptoms suggesting complete miscarriage (n=10), the ultrasound was diagnostic (n=407), haemodynamic instability (n=23) and missing data (n=4). This left 354 included patients, however only 195 of them had a second evaluation before diagnosis, and hence comprise the study population of interest for this review question.

After sonography was done, serum hCG concentration was determined using the Microparticle Enzyme Immunoassay. An EP was diagnosed in women with hCG concentration >1500 IU/l in patients in whom ultrasound failed to show an intrauterine or ectopic gestational sac. An exception was made for women presenting with a clinical picture</td>
<td>Decline > 50%
- Viable IUP: 0
- EP: 0
- Non-viable pregnancy: 63

<u>Diagnostic accuracy of serum hCG rise >50% for diagnosing viable intrauterine pregnancy</u>

AUC: 0.98 (0.94 to 1)

Sensitivity: 93.3 (80.7 to 100)

Specificity: 91.1 (87.0 to 95.3)

PPV: 46.7 (28.8 to 64.5)

NPV: 99.4 (98.2 to 100)

LR+: 10.50 (6.45 to 17.09)

LR-: 0.07 (0.01 to 0.49)

Rise >50%
<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>14</td><td>16</td></tr>
<tr><td>Predictive</td><td>1</td><td>164</td></tr>
</table>
</td>
<td>It is not reported whether the clinicians performing the reference test were blinded to the results of the index test.

<u>Gold standard</u>

Unclear how long they waited before intervening in the case of a miscarriage, and therefore, it is possible that some mistakes could have been made if they intervened too early.

<u>Final diagnosis</u>

Over 60% of the women that compose the population of interest (who had re-evaluation at 2 days) were finally diagnosed with a chemical pregnancy, and the location is not reported. However, as these pregnancies resolved without intervention, this may not be a clinically significant limitation, and for this reason it has not been downgraded in GRADE.</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Dutch Health Insurance Council, Amstelveen	(64.4) At least one risk indicator for EP: 134/354 (37.9) (note: the presenting characteristics for the women who required a second hCG are not reported separately) **Inclusion Criteria** Positive urine pregnancy test Patients with suspected ectopic pregnancy, who had one or more of the following criteria: - clinical symptoms (abdominal pain and/or vaginal bleeding) - presence of one or more risk indicators for EP (previous EP, known tubal pathology detected on hysterosalpingography and/or laparoscopy, previous tubal surgery, PID, diethylstilbestrol exposure in utero, and sterilisation/contraceptive device in situ at conception)		suggestive of complete miscarriage, who were managed expectantly and excluded from the study. If there was no gestational sac on ultrasound, but serum hCG was <1500 IU/l, the patients were re-evaluated 2 days later as outpatients. A diagnosis of viable IUP or EP was made if pregnancy was detected within or outside the uterine cavity, respectively. If ultrasound was repeatedly inconclusive, further management depended on hCG concentrations: - serum hCG concentrations of >1000 IU/l obtained 2-4 days after the start of the diagnostic process were assumed conclusive for EP - when three consecutive serum hCG were <1000 IU/l and ultrasound were repeatedly negative, the diagnosis of a non-viable pregnancy was made - if a plateauing serum hCG pattern emerged (a rise in two consecutive measurements or no decline in three consecutive measurements) then an EP was diagnosed **Patients in whom hCG was used to diagnose (population of interest for this review)**	<table><tr><td>**Test -ve**</td><td></td><td></td></tr></table>	**Other information** Calculations of diagnostic accuracy were performed by the technical team. **Sonographic findings** The authors recommend that in patients in whom ultrasound does not reveal a clear diagnosis, the presence of sonographic abnormalities should be taken into account when interpreting hCG levels.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	- routine sonography, performed after a gestational age of 6 weeks, that failed to show an intrauterine gestational sac - microscopic absence of chorionic villi after dilation and curettage **Exclusion Criteria** Haemodynamic instability Excluded from analysis: - pregnancy resulting from IVF - presenting with symptoms suggesting complete miscarriage - ultrasound was diagnostic (i.e. visualisation of an intra- or extra-uterine gestational sac) - missing data		Two hundred and eighty five patients underwent re-evaluation two days after the start of the diagnostic process. Of these, ultrasound led to a diagnosis in 63 patients (11 EP, 52 viable IUP). In the remaining 195, serum hCG was used to diagnose patients. (note: these numbers do not add up - it is likely to be a typo, and that 258 women underwent re-evaluation; otherwise they have lost patients) 136 patients underwent a second re-evaluation 4 days after the start of the process. Repeated ultrasound led to a diagnosis in 41 patients (17 EP, 24 IUP). In the remaining 95 patients, the serum hCG concentration was used to make a diagnosis. It is not reported whether % difference after 4 days is comparing the 4 day measurement to the first or the second hCG measurement. Therefore, diagnostic accuracy of the first hCG ratio is reported below. **Classification of final outcome** **EP:** verified by laparoscopy **IUP/miscarriage:** verified by		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			repeated ultrasound at a gestational age of 12 weeks, or by histopathologic evaluation in case of a miscarriage. When hCG declined, it was measured repeatedly until it declined below detection threshold (not reported, but there is a reference) The final diagnostic categories were: EP, viable IUP, and non-viable pregnancy (inclues non-viable IUP and chemical pregnancies that resolved without treatment) **Analysis** Analysis was limited to women in who ultrasound findings were inconclusive (i.e. gestational sac could not be visualised anywhere). Patients who conceived after IVF were also excluded because the transfer of multiple embryos could influence the cut-off levels for positive tests. Women with missing data were excluded. An ROC curve was constructed, and the AUC calculated, for diagnosis of EP. The authors also evaluated the diagnostic accuracy of serum hCG in association with patient		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			characteristis. Subgroups were defined based on presence/absence of abdominal pain, vaginal bleeding, and an ectopic mass and/or fluid in the pouch of Douglas. A p-value <0.05 was considered significant. For patients with serum concentrations of <1500 IU/l, the hCG concentrations obtained 2 days and 4 days after the start were compared with the final diagnosis. Diagnostic accuracy of these repeated serum hCG concentrations for diagnosing EP was evaluated using ROC curves of absolute serum concentration, absolute difference and % difference. (Note: Only the diagnostic accuracy of % difference in hCG will be reported here, as this was chosen by the GDG as the test of interest. % difference also had the highest AUC)		
Full citation Stewart,B.K., Nazar-Stewart,V., Toivola,B., Biochemical discrimination of pathologic pregnancy from early, normal intrauterine gestation in	**Sample size** N=77 **Characteristics** **<u>Final diagnosis</u>**	**Tests** Serum hCG concentration **Test positive:** rate of change of log hCG >	**Methods** Women with symptoms suggestive of ectopic pregnancy were identified through two sources: - A computer search of	**Results** **Note:** The mean slopes and standard deviations of the rate of the change of log hCG were not statistically significantly different for the ectopic pregnancy group when all hCG values were considered and when only the initial	**Limitations** **<u>Retrospective</u>** The patients were identified through a retrospective review of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
symptomatic patients, American Journal of Clinical Pathology, 103, 386-390, 1995 **Ref Id** 92050 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To examine the utility of using the rate of change of hCG level and the progesterone concentration to distinguish ectopic from normal intrauterine pregnancies. **Study dates** January 1989 to February 1992 **Source of funding** Not stated	**(number/total (%))** **a. In all women** EP: 37/77 (48.1) Normal intrauterine gestation: 21/77 (27.3) Inevitable miscarriage: 19/77 (24.7) **b. Among the pairs of hCG used for analysis** EP: 58/117 (49.6) Normal intrauterine gestation: 20/117 (17.1) Inevitable miscarriage: 39/117 (33.3) Note: this is not reported in the paper, but was established by the technical team from the graph. 3 values are missing. **Inclusion Criteria** Symptoms suggestive of ectopic pregnancy **Exclusion Criteria**	threshold **Test negative:** rate of change of log hCG < threshold	pathology records identified women with a diagnosis of ectopic pregnancy seen at the University of Washington Medical Centre (UWMC) or Harborview Medical Centre (HMC) from January 1989 to February 1192 - Patients for whom an EP screen had been ordered at either of the above facilities. These patients were either being followed at a fertility clinic or had presented acutely to the emergency room with little or no prenatal care. All women had symptoms suggestive of ectopic pregnancy. Their charts were reviewed to ascertain the outcome of the pregnancy, ultrasound findings, pathologic findings, whether any progesterone/hCG was administered and the time of any surgical intervention. 99 patients were identified through the sources, but 22 were excluded: 7 were not pregnant, 8 had no quantitative hCG done before surgery, 3 had no follow-up available, 1 only had outside lab values available, 1 was terminated before outcome was clear, 1 had ruptured corpus luteum and	pair of hCG values for each patient were considered. **Diagnostic accuracy of rate of change of log hCG > threshold for diagnosing a normal intrauterine pregnancy** **a. Using a threshold of 0.11 (95% CI)** Sensitivity: 80.0 (62.5 to 97.5) Specificity: 87.6 (81.1 to 94.2) PPV: 57.1 (38.8 to 75.5) NPV: 95.5 (91.2 to 99.8) LR+: 6.47 (3.65 to 11.47) LR-: 0.23 (0.09 to 0.55) **b. Using a threshold of 0.14 (95% CI)** Sensitivity: 65.0 (44.1 to 85.9) Specificity: 99.0 (97.0 to 100) PPV: 92.9 (79.4 to 100) NPV: 93.2 (88.3 to 98.1) LR+: 63.05 (8.74 to 454.93)	patients **Missing data** 36 women had multiple hCGs, but they had variables numbers of measurements taken and it is very poorly reported. The prevalence of EP, normal IUP and miscarriage among the 120 pairs of hCG used for analysis is not reported. This had to be estimated by the technical team using the graphical representation in the paper. However, only 117 out of 120 values could be accounted for. **Inclusion criteria** The "symptoms suggestive of ectopic pregnancy" are not defined further. It is also not reported whether women had an ultrasound prior to biochemical tests, and hence whether the participants are women with true pregnancy of

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>Not directly reported as "criteria", but they excluded women for the following reasons:

- not pregnant

- hCG not done before surgical intervention

- no follow-up

- outside lab used for tests

- termination before outcome is clear

- ruptured corpus luteum

- diagnosis of gestational trophoblastic disease</td>
<td></td>
<td>1 developed gestational trophoblastic disease.

<u>Classification of final outcome</u>

Patients were classified according to pregnancy outcome:

Normal intrauterine gestation: Patients had either a documented full term pregnancy, or a clinical impression of a normal viable foetus based on transvaginal ultrasound showing an intrauterine fetal sac with a fetal heart rate.

Ectopic pregnancy: Based on operative findings and pathology reports

Inevitable miscarriage: Based on a clinical impression of spontaneous or inevitable miscarriage, based on findings such as transvaginal ultrasound showing non-viable foetus, documented passage of products of conception, falling hCG levels and low progesterone levels.

Note: in some analysis, ectopic pregnancy and inevitable miscarriage have been grouped</td>
<td>LR-: 0.35 (0.19 to 0.64)

Rate of change of log hCG > 0.11
<table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td>16</td><td>12</td></tr><tr><td>Predictive Test -ve</td><td>4</td><td>85</td></tr></table>
Rate of change of log hCG > 0.14
<table><tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr><tr><td>Predictive Test +ve</td><td>13</td><td>1</td></tr><tr><td>Predictive Test -ve</td><td>7</td><td>96</td></tr></table></td>
<td>unknown location.

<u>Blinding</u>

It is not reported whether authors were blinded to final diagnosis when interpreting hCG.

Other information

The authors report that the thresholds were chosen for their own institution, and that it would be wise for other institutions to determine their own thresholds. They also only included hCG assays done at one specific lab.

<u>Progesterone</u>

Women also had their progesterone levels taken, however diagnostic accuracy is reported separately, not in conjunction with hCG, therefore this is not a test that the GDG were interested in.

<u>Interval between hCG</u></td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			together as **pathologic pregnancies** **<u>Tests performed</u>** Only values measured at the Endocrinology Laboratory in the Department of Laboratory Medicine of UWMC were used. No tests done following surgical intervention were included. Quantitative serum hCG was measured using a chemiluminometric sandwich immunoassay specific for the beta subunit of hCG. Quantitative serum progesterone was measured with a competitive binding radioimmunoassay. The rate of change of hCG was calculated using the formula: s = 1 / t[log (C2/C1)] where s is the slope, t is the time in days, C1 is the initial concentration and C2 is the concentration at the second time point which could be 2-7 days later. More than one pair of hCG values from overlapping time periods for the same patient were allowed. For example, if hCG concentrations were done on days 1, 4 and 7, then three time intervals were used: days 1		**<u>measurements</u>** The second hCG test could be up to 7 days after the first, however the slope was calculated **<u>Discrepancy with paper</u>** Calculations of diagnostic accuracy were performed by the technical team. They are different to those reported in the paper, as the paper reports the inverse comparison.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			to 4, days 1 to 7 and days 4 to 7. A total of 120 pairs of hCG values were obtained when overlapping time periods are allowed. If only the initial pair for each patient is considered, there are 36 pairs (some only had 1 hCG value). 61 patients had progesterone measured. **Analysis** ROC curves of cut-off values for progesterone and the s value for rate of change of hCG were calculated. Sensitivity and specificity were calculated as normal. Accuracy was calculated as: (TP + TN) / (TP + TN + FP + FN)		
Full citation Morse,C.B., Sammel,M.D., Shaunik,A., len-Taylor,L., Oberfoell,N.L., Takacs,P., Chung,K., Barnhart,K.T., Performance of human chorionic gonadotropin curves in women at risk for ectopic pregnancy: Exceptions to the rules, Fertility and Sterility,	**Sample size** N = 1005 **Characteristics** **Final diagnosis (n/total)** Ectopic pregnancy: 179/1005 IUP: 259/1005 Miscarriage: 567/1005 **Initial hCG level (n/total)**	**Tests** Serial hCG measurements Test positive: increase in hCG over a threshold % Test negative: other pattern of hCG change	**Methods** The study was done at 3 sites, all US universities. Data was collected using a centralised computerised database, and patients were entered in to it when the first presented with pain and/or bleeding in the first trimester. Patients were diagnosed with one of the following: - Ectopic pregnancy: included visualised and non-visualised ectopic pregnancies and treated	**Results** **Model performance for predicting IUP, split by expected 2-day increase for an IUP (% (95% CI)** **a. 35% increase in hCG** Sensitivity: 92.3 (89.0 to 95.6) Specificity: 94.0 (92.3 to 95.7) PPV: 84.2 (79.9 to 88.4) NPV: 97.2 (96.0 to 98.4) Accuracy: 93.5 (92.0 to 95.1) **b. 53% increase in hCG**	**Limitations** 167/1180 of patients who met the inclusion criteria were lost to follow-up Unclear whether anyone was blinded 65% of women presented with bleeding and 66% presented with pain. Therefore, it is unclear whether all of the participants of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
97, 101-106, 2012 **Ref Id** 156595 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To compare observed hCG curves to expected curves in a diverse set of patients with symptomatic early pregnancy and a PUL **Study dates** October 2007 to June 2009 **Source of funding** Some of the authors are supported by grants: R01-HD036455, K24HD060687, and the Doris Duke Clinical Research Fellowship	Ectopic pregnancy - 0-500: 82/179 - 501-2000: 70/179 - 2001-4000: 12/179 - > 4000: 15/179 IUP - 0-500: 117/259 - 501-2000: 89/259 - 2001-400: 39/259 - > 4000: 14/259 Miscarriage - 0-500: 235/567 - 501-2000: 146/567 - 2001-400: 79/567 - > 4000: 107/567 **Inclusion Criteria** Pain and/or bleeding in the first trimester of pregnancy No signs of an intrauterine or extrauterine gestation on TVS at presentation At least 2 hCG values at least 1 day apart Documented date of eventual definitive diagnosis		persistent PULs - Miscarriage: included spontaneously resolved PUL (resolution of serum hCG, two decreasing hCGs with the final level below 25 MIU/ml, or three declining levels with the final level below 500 mIU/ml) - Resolved persistent PUL - Histologic IUP hCG concentration measurements were done at the clinical laboratory of each centre. <u>Model based classification</u> Prediction rules did not impact care because they were applied retrospectively. The timing and frequency of serial hCG values was decided by the treating clinician. The trend of values was determined to be increasing or decreasing. For those with an initial increase, the rate was calculated and compared with the minimum expected gradient for an IUP. For patients whose hCG was initially declining, the decrease was compared with the decreased expected. If the change observed was between the minimum decrease	Sensitivity: 82.6 (78.0 to 87.3) Specificity: 97.2 (96.0 to 98.4) PPV: 91.1 (87.4 to 94.7) NPV: 94.2 (92.5 to 95.8) Accuracy: 93.4 (91.9 to 95.0) **<u>c. 71% increase in hCG</u>** Sensitivity: 72.6 (67.1 to 78.1) Specificity: 98.1 (97.1 to 99.1) PPV: 93.1 (89.5 to 96.6) NPV: 91.2 (89.2 to 93.1) Accuracy: 91.5 (89.8 to 93.3) Note: all of these use the 90% CI bounds for expected 2-day decrease for a miscarriage, corresponding to a decline of 36%-47% (depending on level)	study presented with pain and bleeding **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	Exclusion Criteria Diagnosed at presentation Never received a definitive diagnosis hCG level or more than 10000 MIU/ml		and the minimum increase, the patient was classified as a suspected EP by the model. If the observed hCG level was increasing or decreasing more than the threshold the process of classification was repeated based on the comparison of the next hCG with the previous one value. If later values the slope failed to increase or decrease as expected, or the slope switched directions, the woman was classified as a suspected EP. If the change did not deviate from 'normal' then diagnosis was made based on ultrasound findings, clinical symptoms, or resolution of hCG from serum. <u>Analysis</u> Confidence interval bounds representing the expected increase based on 95%, 99% and 99.9% CI for the slope of increasing IUPs were used. Lower limits represent an expected increase of 71%, 53% and 35% respectively, over 2 days. The expected decline for 90% and 95% CI was calculated based on decreasing miscarriage curves. The decrease expected was based on the value at presentation.		

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			The use of three hCG values was explored using patients with an initial increase. Sensitivity, specificity, PPV and NPV were calculated for each combination of bounds. The outcomes were IUP, miscarriage and EP. Disease positive was defined as the presence of one, and disease negative was the combination of the other two.		

What is the diagnostic accuracy of two or more hCG measurements plus progesterone for determining a viable intrauterine pregnancy in women with pain and bleeding and pregnancy of unknown location?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Hahlin,M., Sjoblom,P., Lindblom,B., Combined use of progesterone and human chorionic gonadotropin determinations for differential diagnosis of very early pregnancy, Fertility and Sterility, 55, 492-496, 1991 **Ref Id** 72394 **Country/ies where the study was carried out** Sweden **Study type** Prospective cohort study **Aim of the study** To evaluate the diagnostic potential of the combined application of progesterone and an increase in hCG in differentiating	**Sample size** N=307 **Characteristics** **Final diagnosis (number of women/total (%))** EP: 159/307 (51.8) Viable IUP: 73/307 (23.8) Miscarriage: 75/307 (24.4) Note: presenting symptoms are not reported **Inclusion Criteria** Positive urine hCG test Clinical suspicion of ectopic pregnancy (based on symptoms or the presence of risk factors) Initial serum hCG	**Tests** hCG score (calculated by plotting the initial hCG value against the rate of change of the serum level of hCG) Serum progesterone concentration **Positive test:** normal hCG score (falling above the curve that separates normal IUP and EP) in conjunction with a serum progesterone concentration >30 nmol/l **Negative test:** any other pattern of hCG and progesterone	**Methods** During the study period, two blood samples with an interval of 1-6 days (mean 2.2, SD 1.21) were obtained from patients meeting the inclusion criteria. In addition to the 307 patients eventually included, there were 18 patients whose final diagnosis was unknown because no chorionic villi or trophoblast cells were found intrauterinely or extrauterinely, despite temporarily elevated serum hCG levels in the range of 100-850 IU/l. Another 22 patients were excluded because their serum hCG declined rapidly below 50 IU/l without therapeutic measures. Finally, in 9 patients, it was not possible to wait for a second serum sample due to the patient's clinical condition. Blood samples were obtained from one of the antecubital veins and centrifuged. The serum was stored at -20 degrees Celsius until analysed. Serum progesterone and hCG were determined using time-resolved fluoroimmunoassay.	**Results** **Proportion of women with a normal hCG score and progesterone >30 nmol/l, split by final diagnosis (number/total (%))** Viable IUP: 68/73 (93.2) EP: 12/159 (7.5) Miscarriage: 1/75 (1.3) **Diagnostic accuracy of a normal hCG score in conjunction with progesterone concentration >30 nmol/l for diagnosing viable intrauterine pregnancy (95% CI)** Sensitivity: 93.2 (87.4 to 99.0) Specificity: 94.4 (91.5 to 97.4) PPV: 84.0 (76.0 to 91.9) NPV: 97.8 (95.9 to 99.7) LR+: 16.77 (9.85 to 28.54) LR-: 0.07 (0.03 to 0.17)	**Limitations** **Population** An unknown proportion of patients were analysed due to the suspicion of ectopic pregnancy based on risk factors. Therefore, not all of the women in this study presented with pain and bleeding, and may be outside the populatiion of interest for this review question. The population also only includes women with hCG of 100-4000 IU/l **Blinding** It is not reported whether the clinicians performing the reference tests were blinded to the results of the index test. **Progesterone** It is not reported whether the progesterone concentration from the first or second serum sample was used to judge against the threshold

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>viable intrauterine pregnancies from pathological pregnancies

Study dates

January 1987 to April 1989

Source of funding

Swedish Medical Research Council

Goteborg Medical Society, Goteborg</td>
<td>between 100 and 4000 IU/l (the lower limit was set to reduce the number of cases in which it was impossible to establish a definite diagnosis; the upper limit was set to exclude cases in which endovaginal sonography has high diagnostic accuracy)

Clinical examination, including vaginal sonography, failed to give clear diagnosis

Exclusion Criteria

Ovarian stimulation

Unknown final diagnosis

Rapid decline in hCG to below 50 IU/l without intervention

Aggravated clinical condition which prevented second serum sample being taken</td>
<td></td>
<td>The hCG score was calculated by plotting the initial hCG value against the rate of change in serum hCG levels. In a previous study, it was shown that a line with the equation $y = 12.31x^{0.46}$ discriminated normal intrauterine pregnancies and ectopic pregnancies, where y is the absolute daily change and x is the initial hCG value. A patient with an hCG score falling below the curve is designated as having an "abnormal" hCG score, whereas a patient with an hCG score above the curve has a "normal" hCG score. For daily use, copies of the curve on graph paper were prepared, and the data point of each patient was plotted to see where it falls in relation to the curve. Diagnostic accuracy of the test could then be calculated.

Progesterone was measured and compared to a threshold of 30 nmol/l, a threshold which has previously been shown to distinguish normal IUPs.

<u>Classification of final outcome</u>

Viable intrauterine pregnancy: The criteria was normal foetal development</td>
<td>Normal hCG score plus progesterone >30nmol/l

<table>
<tr><th></th><th>Reference Test +ve</th><th>Reference Test -ve</th></tr>
<tr><td>Predictive Test +ve</td><td>68</td><td>13</td></tr>
<tr><td>Predictive Test -ve</td><td>5</td><td>221</td></tr>
</table>
</td>
<td>of 30 nmol/l

<u>Gold standard</u>

It is unclear how long they waited before intervening in the case of a diagnosed miscarriage, i.e. whether all women received the gold standard of multiple ultrasounds. It is possible that viable intrauterine pregnancies could have been inadvertently terminated if clinicians intervened incorrectly or too early.

Other information

Calculations of diagnostic accuracy were performed by the technical team.

This paper's study period overlaps with that of Thorburn et al. 1992 and was conducted in the same hospital. Therefore some women may appear in both papers, particularly the women eventually diagnosed with ectopic pregnancy, as it is a rare event.</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			including heart activity in the 8th-10th gestational week, evaluated using vaginal sonography **Ectopic pregnancy:** Diagnosed based on laparoscopy, and confirmation of extrauterine trophoblast by histopathological examination **Miscarriage:** Diagnosis was based on histological confirmation of the presence of chorionic villi in curettage material		**Interval between hCG measurements** The interval between two consecutive measurements ranged from 1 to 6 days, however the mean was 2.2 days and the hCG score is calculated using a slope which accounts for different time intervals

What is the effectiveness of progesterone in improving outcomes in women with threatened miscarriage?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation El-Zibdeh,M.Y., Yousef,L.T., Dydrogesterone support in threatened miscarriage, Maturitas, 65 Suppl 1, S43-S46, 2009 **Ref Id** 65236 **Country/ies where the study was carried out** Jordan **Study type** Randomised clinical trial **Aim of the study** To determine whether treatment with dydrogesterone would help to preserve pregnancy in women with threatened miscarriage **Study dates** April 1999 to April 2001	**Sample size** Total n = 146 Dydrogestrone group n = 86 Untreated group n = 60 **Characteristics** No statistically significant differences were observed between the two groups in maternal age, parity and previous miscarriage in multiparous women. 15.3% in the dydrogesterone group and 16.3% in untreated group reported a previous miscarriage. **Inclusion criteria** Women with mild and moderate vaginal bleeding during the first trimester of their pregnancy **Exclusion criteria** Presence of a systemic illness or fever, the suspected passage of any fetal or pregnancy materials, the absence of a normal gestation sac at 5 weeks gestation age, a yolk sac at	**Interventions** Intervention: Oral dydrogesterone (Duphaston, Solvay Pharmaceuticals; 10 mg b.i.d.) Comparison: No treatment	**Details** Pregnant women who consecutively presented to Amman Islamic Hospital with mild or moderate vaginal bleeding were included in the study Randomisation Performed according to the day of the week that women attended the clinic. Women attending the clinic on Saturday, Monday or Wednesday were allocated to the dydrogestrone group and those attending on Sunday, Tuesday or Thursday were allocated to the no-treatment group. The randomisation was performed by the physician who gave the treatment to the women. Assessment All women that presented with bleeding underwent routine antenatal laboratory screening. The amount of blood loss was assesed by the number of pads used daily. An ultrasound was performed in order to exclude miscarriage and local causes for the bleeding. A further ultrasound was performed in all	**Results** Pregnancy outcomes: Miscarriage Dydrogesterone: 15/86 (17.5%) Untreated: 15/60 (25%) Preterm labour Dydrogesterone: 6/86 (7%) Untreated: 5/60 (8.3%) Full term delivery Dydrogesterone: 65/86 (75.5%) Untreated: 40/60 (66%)	**Limitations** Randomisation was done based on days of women attendance to the clinic Women and practitioners were not blinded to the study allocation although author claims, data were analysed under blinded conditions Funded by a pharmaceutical company **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Funded by Solvay Pharmaceuticals.	5.5 - 6 weeks gestational age, or cardiac activity at 7 weeks gestational age.		women after one week. <u>Treatment dydrogesterone group:</u> Treatment was started at presentation with bleeding and continued for 1 week after the bleeding had stopped. Women were given oral dydrogestrone 10 mg twice a day. Treatment was stopped early if vaginal bleeding became severe, there was passage of pregnancy material, there was an increase in body temperature, the gestational sac failed to grow after one week, the fetal pole was absent when the gestational sac was => 25 cm long or there was no cardiac activity when the crown to rump length was > 8 cm. In the majority of women, treatment was started during the 5th or 6th week of gestation (61%); in a further 34.8% of women, treatment started during the 7th or 8th week and 4.6% had the treatment after the 8th week. All women received iron, folic acid and multivitamin supplements and as much bed rest as possible was advised. Women were routinely followed-up in the antenatal clinic.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Gerhard,I., Gwinner,B., Eggert-Kruse,W., Runnebaum,B., Double-blind controlled trial of progesterone substitution in threatened abortion, Biological Research in Pregnancy and Perinatology, 8, 26-34, 1987 **Ref Id** 65260 **Country/ies where the study was carried out** Germany **Study type** Randomised control trial **Aim of the study** To assess the efficiency of progesterone substitution in women with bleeding in early pregnancy and the changes of pregnancy specific hormones in maternal serum **Study dates**	**Sample size** Total n = 56 Treatment group n = 27 Placebo n = 29 **Characteristics** There was no statistically significant differences between the two groups in mean age, nulliparity, previous abortion, ovulation induction, beginning of bleeding or grade of bleeding (mild, moderate and severe) <u>Gestational age</u> Gestational age 4 - 6 weeks Placebo: n = 9/26 Progesterone: n =14/26 Gestational age 7 - 10 weeks Placebo: n = 14/26 Progesterone: n =10/26 Gestational age ≥ 11 weeks Placebo: n = 3/26 Progesterone: n =2/26 **Inclusion criteria** Women with vaginal bleeding during the first trimester of pregnancy, and	**Interventions** <u>Intervention:</u> Bed rest and vaginal suppositories twice daily, containing either 25 mg progesterone <u>Comparison:</u> Only polyethylene glycol	**Details** n = 25 women (5th-6th week of pregnancy) were admitted to the study without regard to sonogram results. In another 25 women (7th-10th week of pregnancy) and 6 women (greater than or equal to 11th week of pregnancy) fetal heart action and movement could be demonstrated by ultrasound. Serial serum determinations of beta-hCG, estradiol-17 beta (E2), progesterone, and ultrasound were performed. Four patients had to be omitted from final analysis (two tubal pregnancies, one intrauterine infection, one section parva). Blood samples were taken weekly for the radioimmunological determination of β-hCG estradiol - 17β (E2) and progesterone. Sonogram examinations were routinely performed. <u>Treatment</u> All women were advised on bed rest and received a vaginal pessary twice daily until 14 days of being symptom-free <u>Analysis</u> The chi square, Wilcoxon matched pair and exact permutation test (Fisher) were used.	**Results** Total n = 52 Placebo: n = 26 Progesterone: n = 26 <u>Total miscarriages</u> Placebo: n = 5/26 (19%) Progesterone: n = 3/26 (11%) p = ns <u>Total deliveries</u> Placebo: n = 21/26 Progesterone: n = 23/26 **<u>Delivery and miscarriage rate based on the correlation parameters in two groups</u>** <u>Age ≤ 30</u> Total: n = 35/52 Delivery: Placebo: n = 17/35 no miscarriage Progesterone: n = 16/35 2 miscarriages <u>Age > 30</u> Total: n = 17/52 Delivery: Placebo: n = 4/17 5 miscarriages progesterone: n = 7/17 1 miscarriages <u>Previous abortion</u> Total: n = 29/52 Delivery: Placebo: n = 11/29 4 miscarriages progesterone: n = 13/29 1	**Limitations** Unclear randomisation Unclear allocation concealment Unclear blinding of the outcomes assessors No intention to treat analysis **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Between 1983 and 1984 **Source of funding** Not reported	with positive serum concentrations of beta-hCG **Exclusion criteria** Not reported			miscarriage <u>Ovulation induction</u> Total: n = 9/52 Delivery: Placebo: n = 3/9 1 miscarriage progesterone: n = 3/9 2 miscarriages Beginning of bleeding < 7th week Total: n= 23/52 Delivery: Placebo: n = 5/23 4 miscarriages progesterone: n = 11/23 3 miscarriages <u>Beginning of bleeding ≥ 7th week</u> Total: n = 29/52 Delivery: Placebo: n = 16/29 1 miscarriages progesterone: n = 12/29 0 miscarriages <u>Positive fetal heart action</u> Total: n = 35/52 Delivery: Placebo: n = 17/35 1 miscarriages progesterone: n = 17/35 0 miscarriages Progesterone treatment resulted in a significant elevation of serum progesterone concentrations ($p < 0.01$), while beta-hCG and E2 were unchanged	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Omar,M.H., Mashita,M.K., Lim,P.S., Jamil,M.A., Dydrogesterone in threatened abortion: pregnancy outcome, Journal of Steroid Biochemistry and Molecular Biology, 97, 421-425, 2005 **Ref Id** 65411 **Country/ies where the study was carried out** Malaysia **Study type** Prospective observational study **Aim of the study** To determine whether dydrogesterone treatment for threatened abortion in the first trimester of pregnancy will improve pregnancy outcomes and to evaluate the effectiveness of dydrogesterone in allowing the pregnancy to continue beyond 20	**Sample size** Total n = 194 were eligible according to the inclusion criteria, n = 40 (20.6%) of these women lost during follow-up, Therefore n = 154 women included n = 74 in the dydrogesterone group n = 80 in the control group **Characteristics** No statistically significant differences were observed between the two groups in race, mean age, mean gravida and mean gestational weeks. **Inclusion criteria** Women were included with mild or moderate vaginal bleeding, no history of loss of conception material, absence of systemic illness or fever, normal size and shape gestation sac at 5 weeks, presence of yolk sac at 5–6 weeks, presence of fetal heart at 7 weeks and gestational age less than 13 weeks.	**Interventions** Intervention: dydrogesterone 40 mg stat, followed by 10 mg twice a day until the bleeding stopped bed rest and received folic acid Comparison group: bed rest and folic acid only	**Details** The registration records of all pregnant women who presented to the Obstetric and Gynaecology Admitting Centre (OGAC) with vaginal bleeding before 20 weeks gestation were evaluated ((n = 678)) n = 205 were diagnosed with having threatened abortion at less than 13 weeks gestation who had no history of recurrent miscarriage. After reviewing the notes of these 205 cases, only 194 showed fetal viability with the correct size for the dates confirmed by ultrasound according to the inclusion criteria. n = 40 women defaulted during follow up, therefore n = 154 women were selected for comparison. Treatment group: n = 74 dydrogesterone bed rest and received folic acid Comparison group: n = 80 bed rest and folic acid only All women were advised to avoid sexual intercourse and women were followed up until 20 weeks gestation. Data analysis A pre-specified subgroup	**Results** Miscarriages Dydrogesterone: 3/74 (4.1%) Control: 11/80 (13.8%) Ongoing pregnancy rate at 20 weeks Dydrogesterone: 71/74 (95.9%) Control: 69/80 (86.3%) **Subgroup analysis of successful pregnancy outcomes at 20 weeks** **n (dydrogesterone/control) n = total(dydrogesterone/control)** Vaginal bleeding total n = 66 (29/37) Successful pregnancy outcomes: Dydrogesterone: 93.1% Control: 83.8% p = ns Vaginal spotting total n = 88 (45/43) Successful pregnancy outcomes: Dydrogesterone: 97.8% Control:88.4% p = ns Fetal heart activity total n = 65 (31/34) Successful pregnancy outcomes: Dydrogesterone: 97.8% Control: 91.8% p = ns Presence of yolk sac total n = 48	**Limitations** Unclear method of data collection and analysis **Other information** Miscarriage was defined as spontaneous loss ≤ 20 weeks gestation Recurrent miscarriages was defined as three or more consecutive miscarriages Continuing pregnancy was defined as an intrauterine pregnancy that had advanced beyond 20 weeks gestation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
weeks gestation **Study dates** From March 2002 to 28 February 2004 **Source of funding** Not reported	**Exclusion criteria** Women were excluded with empty sac of more than 26mm and history of recurrent miscarriage		analysis performed for the 'successful pregnancy outcomes at 20 weeks' and the 'miscarriage rate'. Data analysed using the Chi-square test.	(23/25) Successful pregnancy outcomes: Dydrogesterone: 100% Control: 95.1% p = ns **Subgroup analysis of miscarriage rate n (dydrogesterone/control) n = total(dydrogesterone/control)** Vaginal bleeding total n = 66 (29/37) Miscarriage: Dydrogesterone:n = 2/29 Control: n = 6/37 p = ns Vaginal spotting total n = 88 (45/43) Miscarriage: Dydrogesterone:n = 1/45 Control: n = 5/43 p = ns Foetal heart activity total n = 65 (31/34) Miscarriage: Dydrogesterone:n = 1/31 Control: n = 3/34 p = ns Presence of yolk sac total n = 48 (23/25) Miscarriage: Dydrogesterone:n = 0/23 Control: n = 1/25 p = ns	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Regular intrauterine gestational sac n = 12 (7/5) Miscarriage: Dydrogesterone:n = 2/7 Control: n = 3/5 p = ns The highest proportion of miscarriages (n = 5 [2/3]) occurred in the group with only a regular gestational sac at the time of presentation.	
Full citation Pandian,R.U., Dydrogesterone in threatened miscarriage: A Malaysian experience, Maturitas, 65, S47-S50, 2009 **Ref Id** 78346 **Country/ies where the study was carried out** Malaysia **Study type** Randomised trial **Aim of the study** To determine whether	**Sample size** Total: n = 191 women Dydrogesterone group: n = 96 Control group: n = 95 **Characteristics** No statistically significant differences observed between the two groups in maternal age, parity, race and gestation. There were also no statistically significant differences between the groups in pelvic examination, haematocrit values, white blood cell count and coagulation parameters **Inclusion criteria**	**Interventions** Intervention: Dydrogesterone (40 mg stat followed by 10 mg daily) Control: bed rest only	**Details** Women were randomised to receive either dydrogesterone or to have conservative management with bed rest only. Treatment was started within 24 h of diagnosis and within 2 h of an ultrasound being carried out. Treatment continued until 16 weeks of pregnancy and follow up were carried out until the end of the pregnancy. Analysis Data were analysed using Pearson Chi-square test and it performed under blind conditions. Power calculation to determined the sample size were performed (no further data provided)	**Results** Success rate (continuation of pregnancy beyond 20 weeks) Dydrogestrone: n = 84/96 (87.5%) Control: n = 68/95 (79.6%) Pregnancy outcomes Miscarriages Dydrogesterone: n = 12/96 (12.5%) Control: n = 27/95 (28.4%) p < 0.05 Successful delivery Dydrogesterone: n =84/96 (87.5%) Control : n = 68/95 (71.6%) p < 0.05 Caesarean section Dydrogesterone: n = 13/96 (13.5%) Control : n = 12/95 (12.6%) p = ns	**Limitations** Funded by a pharmaceutical company No clear blinding for participants and outcomes assessors **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
dydrogesterone was more effective than conservative management alone in preventing miscarriage in women with vaginal bleeding **Study dates** January 2003 to December 2005 **Source of funding** Solvey Pharmaceuticals	All women presenting with vaginal bleeding up to 16 week of pregnancy were assessed for inclusion. Inclusion criteria: No systemic illness or fever No loss of conception tissue Normal gestation sac morphology at 5 weeks gestation Presence of yolk sac and fetal cardiac activity at 6 weeks gestation or later **Exclusion criteria** History of recurrent miscarriages (≥ 3 previous miscarriages) Heavy bleeding (> 2 pads soaked) Cervical polyps Empty sac of more than 26 mm or multiple gestational sac shown on ultrasound			<u>Placenta praevia (> 28 weeks)</u> Dydrogesterone: n = 3/96 (3.1%) Control: n = 4/95 (4.2%) p = ns <u>Preterm birth (28-36 weeks)</u> Dydrogesterone: n = 6/96 (6.3%) Control : n = 4/95 (4.2%) p = ns <u>Antepartum haemorrhage</u> Dydrogesterone: n = 4/96 (4.2%) Control: n = 6/95 (6.3%) p = ns <u>Pregnancy induced hypertension</u> Dydrogesterone: n = 12/96 (12.5%) Control : n = 14/95 (14.7%) p = ns <u>Intrauterine death/congenital abnormality</u> Dydrogesterone: n = 0/96 Control: n = 0/95 p = ns <u>Low birth weight (< 2500g)</u> Dydrogesterone: n = 3/96 (3.1%) Control: n = 2/95 (2.1%) p = ns	
Full citation Duan,L., Yan,D., Zeng,W., Yang,X., Wei,Q., Effect of progesterone treatment due to threatened abortion in early	**Sample size** Total: 21,853 Progesterone treatment group n = 799 Normal pregnant group n =	**Interventions** <u>Intervention:</u> Progesterone injection (total accumulated dose in the ranges of 500 to 780 mg)	**Details** The study was conducted on 21,853 singleton women data in the Department of obstetrics, West China Second University	**Results** <u>Preterm delivery</u> Treated group: n = 66/532 (12.41%) Control group: n = 2257/21,054 (10.72%)	**Limitations** Control group consisted of women with a healthy pregnancy Uneven participants in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pregnancy for obstetric and perinatal outcomes, Early Human Development, 86, 41-43, 2010 **Ref Id** 124805 **Country/ies where the study was carried out** China **Study type** Retrospective observational study **Aim of the study** To analyse the effect of using high-dosage progesterone (the total accumulated dose ≥ 500 mg) in women with threatened miscarriage for obstetric and perinatal outcomes **Study dates** January 2002 to October 2008 **Source of funding**	21,054 **Characteristics** There were no statistically significant differences between the treatment group and the control group in age, gravidity, and parity. Women in the treatment group had had more previous miscarriages ($p < 0.0001$) and there were more incidences of ≥ 3 previous miscarriage compared with the control group ($p < 0.0001$) **Inclusion criteria** Singleton pregnant women **Exclusion criteria** Multiple pregnancies, severe uterine anomalies, thyroid dysfunction, glucose intolerance, kidney or liver disease, preexisting hypertension, a history of thrombosis, or autoimmune disease such as systemic lupus erthematosus	<u>Comparison:</u> Normal pregnant women with no treatment needed	Hospital for a period of 6 years. <u>Treatment group:</u> Women in treatment group received first 20 mg/day of intramuscular (IM) progesterone for 2 weeks, this was adjusted individually based on the clinical symptoms of vaginal bleeding. Then progesterone administration was changed at a dose of 20 mg every other day for 2 weeks and 20 mg twice a week for 2 weeks. n = 602/799 (75.3%) had their onset of progesterone treatment in the second month gestation. For n = 215 women treatment was stopped because of inevitable miscarriage (n = 11 had ≥ previous miscarriages; mean time of progesterone treatment was 6.9 ± 3.6 days). n = 197/799 had their onset of progesterone treatment in the third month gestation. For n = 52 women treatment stopped because of inevitable miscarriage (n = 5 had ≥ previous miscarriages; mean time of progesterone treatment was 5.7 ± 3.1 days). In total n = 532/799 (66.6%) women received progesterone under treatment	p = ns <u>Placental abruption</u> Treated group: n = 5/532 (0.94%) Control group: n = 153/21,054 (0.73%) p = ns <u>Placenta previa:</u> Treated group: n = 16/532 (3.01%) Control group: n = 718/21,054 (3.41%) p = ns <u>Hypertensive disorders in pregnancy</u> Treated group: n = 16/532 (3.01%) Control group: n = 974/21,054 (4.63%) p = ns <u>Gestational diabetes</u> Treated group: n = 37/532 (6.95%) Control group: n = 1141/21,054 (5.42%) p = ns <u>Intrahepatic cholestasis of pregnancy</u> Treated group: n = 51/532 (9.59%) Control group: n = 1712/21,054 (8.13%) p = ns	two groups Not clear if the viability of the fetus was confirmed before commencement of the progesterone treatment. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported			plan (total accumulated dose of progesterone in the ranges of 500 to 780 mg) and continued their pregnancy until delivery (n = 31 had ≥ 3 previous miscarriages) Control group Women received no treatment Analysis Performed using SPSS, Student's t-test was used for for quantitative and chi square test for categorical variables.		
Full citation Palagiano,A., Bulletti,C., Pace,M.C., DE,Ziegler D., Cicinelli,E., Izzo,A., Effects of vaginal progesterone on pain and uterine contractility in patients with threatened abortion before twelve weeks of pregnancy, Annals of the New York Academy of Sciences, 1034, 200-210, 2004 **Ref Id** 124812 **Country/ies where the study was carried out** Italy	**Sample size** Total n = 50 **Characteristics** Age mean (± SD) Total: 31.2 (± 6.3) Group A (treated group): 32.4 (± 6.0) Group B (placebo): 31.2 (± 6.3) p = ns Gestational age (wks) Group A (treated group): A:7.8 (± 2.2) Group B (placebo): 8.4 (± 1.2) p = ns	**Interventions** One dose of vaginal Crinone 8% per day (90 mg of progesterone) or placebo progesterone once a day for 5 consecutive days. Both groups were advised to observe bed rest for the 5 days.	**Details** Fifty women with a previous diagnosis of inadequate luteal phase and with both a biochemical and ultrasound diagnosis of threatened abortion between 6 and 12 weeks of pregnancy and with a detectable fetal heartbeat were included in the study. Evaluations were carried out on all women: First day (baseline): history recording, clinical evaluation, physical examination, ultrasound (US) to document the embryo's heart activity and the gestational age, blood losses, and UCs (Uterine contractility) detected by 3-min recordings of the sagittal scan	**Results** **Pain score mean (± SD)** Group A (treated) At the baseline: 2.6 (± 0.9) End of the 5-day treatment: 0.4 (± 0.7) p < 0.01 Group B (placebo) At the baseline: 2.5 (± 1) End of the 5-day treatment: 2.4 (± 0.8) p = ns **Frequency of the UCs (Uterine contractility) (mean ± SD)** Group A (treated) At baseline: 2.4 (± 1) End of the 5-day treat: 0.8 (± 0.8) p < 0.005 Group B (Placebo):	**Limitations** Randomisation not reported Loss to follow up not reported No intention to treat analysis **Other information** **Definition of threatended abortion** Threatened abortion was defined as a clinical condition of established pregnancy with ultrasonographic signs of live embryo, with uterine cramps and pain with or without blood loss. Cervical os was closed

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised clinical trial **Aim of the study** First, to establish the effects of vaginal progesterone (Crinone 8%) on uterine contractility, by assessing both cramps and pain, in women diagnosed with inadequate luteal phase and with threatened abortion; second, to evaluate the clinical outcomes of these pregnancies. **Study dates** Not reported **Source of funding** Not reported	**Inclusion criteria** Pregnant women between 6 and 12 weeks of amenorrhea, age ranging between 21 and 40 years, with a previous diagnosis of inadequate luteal phase and symptoms of threatened miscarriage (blood loss, uterine cramps, and ultrasound proof of an ongoing pregnancy) Positive fetal heartbeat Embryo's size ± 1 week of amenorrhea (CRL) Closed uterine cervix. Women who did not conclude the therapy were replaced in order to reach 25 patients in each group at the end of the study. **Exclusion criteria** Women with previous adequate luteal phase Women who were using hormonal treatment or other drugs affecting uterine contractility Women with vaginal infection Absence of fetal heartbeat Open cervix (>2 cm measured by U/S) Embryo's size one week more than the corresponding amenorrhea		of the uterus body. The frequency of UCs was analysed by two independent observers through a visual analysis of the recordings. From day 2 to day 5: ultrasound scan, blood losses evaluation, and UCs. Follow-up: Continued until delivery. Possible adverse effects were recorded. The treatment was stopped when the US established the absence of the embryo's heartbeat or when the patients reported adverse effects. **Evaluation of the pain** The evaluation of pain was assessed by a progressive score from 0 to 4 (0, no pain; 1, mild; 2, moderate; 3, severe; 4, extreme) recorded by the women for a length of time from 4 to 6 h. **Evaluation of blood loss** Blood loss was evaluated by the number of vaginal pads changed over time. **Evaluation of the uterine contractility** Uterine contractility was detected and recorded from the 1st to the 5th day of study by an ultrasound scan. The normal	At baseline: 2.3 (± 0.9) End of the 5-day treat: 2.3 (± 0.8 Spontaneous abortion (after 60 days) Group A (treated): 4/25 Group B (Placebo): 8/25 $p < 0.05$	(< 2 cm).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			condition was the absence of contractions per minute. After the establishment of the basal frequency of contractions, the decrease or the increase of uterine cramps in close association with the gel administration was considered as a response or no response. **Ultrasound** Ultrasound scan was performed every day for the 5 days of the study. The first one was used for the inclusion criteria, whereas the others were used to verify the continuation of the pregnancy. **Adverse effect** All possible adverse effects were established to be classified according to the WHO Adverse Reaction Dictionary. Women were requested to refer all possible adverse effects to the doctor responsible for this study.		

How effective is expectant management of miscarriage compared with active treatment for improving women's clinical and psychological outcomes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ngai,S.W., Chan,Y.M., Tang,O.S., Ho,P.C., Vaginal misoprostol as medical treatment for first trimester spontaneous miscarriage, Human Reproduction, 16, 1493-1496, 2001 **Ref Id** 65394 **Country/ies where the study was carried out** Hong Kong **Study type** Randomised controlled trial **Aim of the study** To compare vaginal misoprostol versus expectant treatment in women presenting with spontaneous miscarriage **Study dates** Unclear	**Sample size** n=60 women **Characteristics** Age, weight, menstrual delay, previous live birth, previous miscarriage and diagnosis of missed miscarriage or incomplete miscarriage at transabdominal US on admission were not significantly different between the two groups Proportion of women who have had a termination of pregnancy (TOP) was higher in the group randomised to misoprostol as compared to the expectant group (46.7% vs. 20.0%, p=0.03) **Inclusion criteria** >16 years old Good past health Positive pregnancy test Gestation age ≤12 weeks	**Interventions** Active management (Misoprostol) n=30 Expectant management n=30 **Comparisons** Active management vs. expectant management	**Details** <u>Sample size calculation</u> Total required sample was 58 women (29 in each group), based on the assumptions that the use of misoprostol would achieve a complete miscarriage rate of 60% and that the chance of spontaneous resolution in the expectant group was 20% (type 1 error of 0.05 and power of 0.85 were considered acceptable) <u>Randomisation and allocation concealment</u> A randomisation table was constructed as described by Meinert (1986). The grouping allocation number was put into an opaque envelope that was serially labelled. Each patient with consent for randomisation was assigned to the latest numbered envelope. <u>Recruitment</u> One patient in the expectant group was excluded from analysis. This patient was recruited in error because an	**Results** (Except for "days of bleeding" all outcomes are reported as proportion of women in each group and their corresponding percentages) <u>Treatment success</u> Active: 25/30 (83.3) Expectant: 14/29 (48.3) p<0.05 (No statistically significant difference was found between the two groups for any of the following outcomes but p values were not reported) <u>Incidence of side effects/complications</u> a. Nausea Active: 14/30 (46.7) Expectant: 7/29 (24.1) b. Vomiting Active: 7/30 (23.3) Expectant: 4/29 (13.8) c. Diarrhoea	**Limitations** No intention to treat analysis carried out Selective outcome reporting: data on dose of analgesic requirement and patients' acceptability were not reported Confounders: authors acknowledged that the fact that more patients presenting with a missed miscarriage were included in the active management group than in the expectant group (83.3% vs. 63.3%) suggested that the actual clinical benefit from the former was likely to be larger than which has been demonstrated by the study Signs and symptoms at presentation not reported: unclear how women with a missed miscarriage (as per ultrasound) presented with a "spontaneous" miscarriage Assessment of outcomes: unclear who measured the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Committee on Research and Conference Grants, the University of Hong-Kong	Ultrasound confirmed diagnosis of missed miscarriage: -intrauterine gestational sac with a mean sac diameter of ≥2 cm without fetal pole -presence of fetal pole with no cardiac pulsation -the gestational sac was < 2cm with no interval growth or persistence absence of fetal cardiac pulsation on rescanning 7 to 10 days later Incomplete miscarriage was diagnosed with incomplete cervical os and ultrasound findings of an endometrial echo showing mixed echogenicity **Exclusion criteria** Severe blood loss Sepsis Known allergy to prostaglandins Transvaginal scan showing thin endometrial echo suggesting complete miscarriage or extrauterine pregnancy		ultrasound scan showed that the fetal parameter was >13 weeks gestation. She subsequently passed the fetus spontaneously <u>Interventions</u> 1. Active management: 400 µg vaginal misoprostol daily, given every other day on an outpatient basis. On day 1 administration of the misoprostol was followed by a 4h observation period in the day care centre. Patients were discharged if there was no excessive vaginal bleeding. The same procedure was repeated in day 3 and day 5. Sexual intercourse was avoided in the following 2 weeks. Emergency suction evacuation was arranged where excessive blood loss or abdominal pain occurred. The decision for emergency suction evacuation was made by the on-call medical officer based on clinical judgement. All women were advised to record and bring back the tissue mass if it was passed at home. Oral analgesia was given. 2. Expectant management On day 1 women were	Active: 4/30 (13.3) Expectant: 1/29 (3.4) d. Infection rate Active: 0 Expectant: 0 e. Postoperative complications Active: 0 Expectant: 0 <u>Pain</u> Active: 11/30 (36.7) Expectant: 7/29 (24.1) <u>Days of bleeding (mean)</u> Active: 14.6 Expectant: 15.0 <u>Need for unplanned intervention</u> (In all cases excessive bleeding requiring suction evacuation) Active: 1/30 (3.3 Expectant: 3/29 (10.3) <u>Need for blood transfusion</u> Active: 0 Expectant: 0	outcomes **Other information** For those women who required suction evacuation prophylactic antibiotics were not given Four women in each group had not menstruated by day 42. Extra follow-up was arranged for them until menstruation returned

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			discharged if there was no excessive vaginal bleeding. They were advised to come back if excessive bleeding was noted. They were followed up on day 3 and day 5. If they had passed tissue masses, transvaginal ultrasonography was performed to check for retained gestational products. Outcomes assessed 1. Treatment success/failure: Initially assessed on day 15 by ultrasound. If findings were compatible with a missed miscarriage (identified gestational sac without fetal activity) suction evacuation was performed. If the findings were compatible with complete or incomplete miscarriage no further action was taken. Al women were followed up on day 43. If menstruation did not return an additional follow-up visit was arranged. Those who did not require suction evacuation up to the time of normal menstruation were considered successful. Failure was defined as the recourse to surgical treatment either due to method failure or change of patients' decision 2. Incidence of side effects (nausea, vomiting and abdominal pain) and		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			complications, including infection rate: Women were given standardised questionnaires during and after the miscarriage to report on side effects 3. Duration of vaginal bleeding: The amount of blood loss was assessed clinically by the on-call doctor. Objective measurement of blood loss was not done 4. Dose of analgesic required: Dose and frequency of medication taken was recorded (no other details provided) 5. Patients' acceptability: Women were given standardised questionnaires during and after the miscarriage to report on acceptability <u>Statistical analysis</u> Chi square or Fisher's exact test were used to analyse the differences between discrete variables		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Nielsen,S., Hahlin,M., Expectant management of first-trimester spontaneous abortion, Lancet, 345, 84-86, 1995 **Ref Id** 65396 **Country/ies where the study was carried out** Sweden **Study type** Randomised controlled trial **Aim of the study** To evaluate pregnant women in whom both clinical and transvaginal ultrasound examination had identified an inevitable or incomplete spontaneous miscarriage and to assess clinical outcome after expectant management or D&C in a prospective randomised trial **Study dates** Women recruited during the 16	**Sample size** n=155 women **Characteristics** There were no statistically significant differences between both groups at baseline regarding: age, gestational age, parity, previous miscarriages, previous legal abortions, estimated intrauterine volume and hormonal values (serum progesterone and serum hCG) **Inclusion criteria** Vaginal bleeding and/or abdominal pain in the presence of a positive urinary pregnancy test Good health with a normal blood count Estimated gestational age less than 13 weeks Having been seen at the time of entry and followed-up by one of the authors of the trial Clinical examination and transvaginal ultrasound	**Interventions** Expectant management n=103 Active management (surgical management: D&C) n=52 **Comparisons** Expectant vs. active management	**Details** <u>Randomisation</u> After consent was obtained patients were randomised to expectant management or D&C in a ratio 2 to 1 by drawing a sealed envelope from a box <u>Allocation concealment</u> Unclear <u>Interventions</u> -Expectant management: patients were asked to avoid bathing and sexual intercourse for 2 weeks. They were informed that they might expect some bleeding and pain. In case of pain they were recommended to use paracetamol alone or in combination with codeine. Prophylactic antibiotics were not given. After 3 days and at 2 weeks patients returned for a gynaecological examination including transvaginal ultrasonography. If examination showed retained products of conception with a diameter of more than 15 mm the patient underwent D&C. If the patient experienced unacceptable bleeding and/or pain she was advised to return to the clinic	**Results** <u>Incidence of adverse effects/complications (number of women and percentage)</u> a. Total complication rate Expectant (n=103): 3 (3) (the 3 women were diagnosed with PID. One of them had undergone D&C 3 days after inclusion for RPOC and PID was diagnosed 2 days after the operation) Active (n=52): 6 (11) (5 were infections (1 tubo-ovarian access and 4 PID) and another patient experienced heavy bleeding during D&C and was unable to return to work for 3 weeks) There were NS between both groups (p=0.08) b. Infections Expectant (n=103): 3 (3) (the 3 women were diagnosed with PID. One of them had undergone D&C 3 days after inclusion for RPOC and PID was diagnosed 2 days after the operation)	**Limitations** No sample size calculation was reported Unclear why patients were randomised in a ratio 2 to 1 Not always reported how outcomes were assessed and who assessed them **Other information** In both groups women who were Rhesus negative received 625 IU of anti-D immunoglobulin

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
months before April 1994 **Source of funding** Grants from the Swedish Medical Research Council (B95-17X-11237-01A)	showing inevitable or incomplete miscarriage Ultrasound criteria: -intrauterine tissue with an anterior-posterior diameter of 15 to 50 mm (the lower limit was chosen since pregnancy tissue with a diameter of less than 15 mm would not have been considered for D&C as a routine procedure in the authors' department; the upper limit was arbitrarily chosen and pregnancies with retained tissue of more than 50mm had D&C) **Exclusion criteria** Non viable intrauterine pregnancy diagnosed on ultrasound but without clinical signs of miscarriage		for a D&C -Active management (D&C): Curettage was done under general anaesthesia. Prophylactic antibiotics were not given and patients left hospital after 2 to 4 hours. In case of pain they were also recommended to use paracetamol alone or in combination with codeine. They were also asked to avoid bathing and sexual intercourse for 2 weeks. After 3 days and at 14 days patients returned for a examination Outcomes assessed 1. Total complication rate (in particular Pelvic Inflammatory Disease-PID): PID defined by 3 or more of the following criteria being observed within one month of inclusion: purulent vaginal discharge, temperature above 38 degree Celsius for more than 24 h, tenderness over the uterus or adnexa on pelvic examination, erythrocyte sedimentation rate above 30 mm and/or increase in CRP of more than 5mg/L 2. Days of bleeding: Defined as number of days with vaginal bleeding that required sanitary protection	Active (n=52): 5 (10) (1 tubo-ovarian access and 4 PID) Days of bleeding (mean, SD) Expectant (n=103): 8.79 (3.01) Active (n=52): 7.53 (3.06) p<0.02 Days of pain (mean, SD) Expectant (n=103): 1.92 (1.47) Active (n=52): 1.69 (1.46) p>0.03 Need for unplanned interventions (number of women and percentage) Expectant (n=103): 22 (21.4) (19 women underwent D&C because of RPOC with a diameter of more than 15mm 3 days after inclusion. 3 women underwent D&C 1 day after inclusion: 1 because of bleeding, 1 because of pain and 1 because she wished to) Active (n=52): 2 (3.8) (The two patients were readmitted to hospital (1 for tubo-ovarian access and 1 for PID and RPOC)) Hospital admissions (number	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			3. Days of pain: Defined as number of days with pain that required analgesics 4. Need for unplanned intervention: Not defined 5. Hospital admissions: Not defined Statistical analysis Comparisons between groups were done by Fisher's permutation test. Two-tailed tests were used	of women and percentage) Expectant (n=103): 22 (21.4) (These figures refer to all the women who underwent D&C for the reasons stated above. The paper does not clearly state that but it is assumed that women were admitted in order to have any D&C) Active (n=52): 2 (3.8) (The two patients were readmitted to hospital (1 for tubo-ovarian access and 1 for PID and RPOC))	
Full citation Nielsen,S., Hahlin,M., Moller,A., Granberg,S., Bereavement, grieving and psychological morbidity after first trimester spontaneous abortion: comparing expectant management with surgical evacuation, Human Reproduction, 11, 1767-1770, 1996 **Ref Id** 65397 **Country/ies where the study was carried out**	**Sample size** n = 86 women **Characteristics** There were no significant differences between both groups with regard to age, parity, marital status, gestational age, urban population, planned pregnancy, estimated intrauterine volume or hormonal values at inclusion. None of the following variables differed significantly between the two randomized patient groups	**Interventions** Expectant management n=58 Active management (surgical management: D&C) n=28 **Comparisons** Expectant vs. active management	**Details** Recruitment The patients included in this study were also included in a previously published comparison of clinical results between the two treatment groups (Nielsen and Hahlin, 1995). Of 87 patients who fulfilled the entry criteria and were informed about the study, 86 agreed to take part. Outcomes assessed -Anxiety All patients included completed a brief anxiety status inventory, Spielberger State Anxiety	**Results** Emotional and psychological outcomes -Anxiety (Spielberg scores, mean (SD)) Expectant (n=58): 57.5 (12.4) Active (n=28): 57.5 (14.0) NS (p>0.30) -Subgroup analysis in expectant group Expectant and complete spontaneous miscarriage within 3 days (n=43): 56.1 (12.3) Expectant and dilatation and curettage within 3 days (n =	**Limitations** Unclear why one woman refused to participate in the study Unclear who administered the questionnaire and in which context it was completed by the women Unclear whether the Spielberg SAI is a validated instrument. In any case it should had been piloted in a similar population to the one included in the study Women undergoing expectant management

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Sweden **Study type** Follow-up survey of a randomised controlled trial (See Nielsen 1995) **Aim of the study** To compare bereavement, grieving and psychological morbidity following first trimester spontaneous miscarriage managed either expectantly (defined as no medical or surgical treatment) or using D&C **Study dates** Women recruited during the 16 months before April 1994 **Source of funding** Grants from the Swedish Medical Research Council (B95-17X-11237-01A), the Swedish Medical Society and the Merchant Hjalmar Svensson Foundation	after either management: convalescence time, the time during which the patients experienced bleeding, the time during which the patients experienced pain or the rate of complications. **Inclusion criteria** Please refer to Nielsen 1995. In this follow-up study only Swedish speaking women were included **Exclusion criteria** Please refer to Nielsen 1995 Non Swedish speaking women		Inventory (form x) (Spielberger, 1983) immediately after the follow-up visit 14 days after inclusion. It consisted of a list of 30 adjectives or descriptions of affective states. The patient was asked to state which adjectives or statements described her present feelings best. Each answer was given a weighted score of 1 to 4, where a rating of 4 indicated the presence of a high level of anxiety, e g. 'I feel frightened'. The scoring weights for the 'anxiety absent' items were reversed, e.g. 'I feel calm'. The scores were added together to give a minimum of 30 and a maximum of 120. The means and SD for 210 healthy working females aged 19 to 39 years have been shown to be 54 ± 12 (Spielberger, 1983). <u>Statistical analysis</u> The patient group randomized to expectant management (n = 58) was compared with the patient group randomized to primary D&C. Moreover, patients randomized to expectant management who had an empty uterine cavity following 3 days of expectancy (n = 43) were compared with patients randomized to expectant management who	15): 61.6 (12.3) p=0.046	were over-represented in the study population as it was a 2:1 randomisation **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			had to undergo D&C within 3 days of expectancy in = 15). Comparisons between patient groups were made using Fisher's permutation test. Two-tailed tests were used.		
Full citation Nielsen,S., Hahlin,M., Platz-Christensen,J., Randomised trial comparing expectant with medical management for first trimester miscarriages, British Journal of Obstetrics and Gynaecology, 106, 804-807, 1999 **Ref Id** 65398 **Country/ies where the study was carried out** Sweden **Study type** Randomised controlled trial **Aim of the study** To compare a combination of mifepristone and misoprostol with expectant management for outpatient treatment of first	**Sample size** n = 122 women **Characteristics** There were no significantly different characteristics between both groups at baseline regarding: age, parity, previous miscarriages, previous legal abortions, pregnancy length, progesterone levels, packed cell volume (%), intrauterine diameter (mm), empty gestational sac, gestational sac with foetal structure and complex mass (deformed gestational sac) **Inclusion criteria** Women attending a hospital outpatient clinic with symptoms of threatened or inevitable miscarriage (bleeding and/or pain) and: - Good health with a normal blood count - Estimated gestational age of less than 13 weeks	**Interventions** Expectant management n=62 Active management (medical: mifepristone oral misoprostol) n=60 **Comparisons** Expectant vs. active management	**Details** <u>Sample size calculation</u> Based on their previous experience authors calculated that approximately 25% of the women undergoing expectant management would need surgery with the proposed endpoint (< 15 mm in the antero-posterior diameter of the uterine cavity). To be worthwhile, pharmacological treatment should reduce the need for surgery to below 5%. The power of predicting a difference in the number of women having to undergo surgical evacuation will be at least 80% at the 5% level (two-tailed test) with a sample size of 55 women in each group. To allow for withdrawals 122 women were included. <u>Randomisation and allocation concealment</u> Not described <u>Interventions</u>	**Results** <u>Proportion of women with an empty uterine cavity within 5 days after inclusion (and percentage)</u> Expectant: 47/62 (76) Active: 49/60 (82) NS OR of complete miscarriage (active vs. expectant): 1.41 (95 CI: 0.59 to 3.41) <u>Pain (degree) (VAS scores, mean (SD)</u> Expectant: 62.0 (30.1) Active: 66.1 (26.3) NS (p value not reported) <u>Bleeding (duration in days, mean, (SD)</u> Expectant: 10.3 (3.11) Active: 11.0 (3.26) NS (p value not reported) <u>Need for unplanned interventions (proportion of women and percentage)</u>	**Limitations** Randomisation and allocation concealment methods not described Unclear who measured the outcomes **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trimester miscarriages **Study dates** Unclear **Source of funding** Not stated	- Clinical examination, including transvaginal ultrasound, showed an inevitable or incomplete miscarriage The following were considered the three main ultrasound characteristics of a pathological pregnancy: 1. an intact but empty gestational sac; 2. a gestational sac with a non-viable fetal structure or; 3. a complex mass where the gestational sac is deformed with the presence of blood clots within the uterus Women included in the study had retained products of conception with an anterior-posterior diameter between 15 and 50 mm. The lower diameter was chosen because retained tissue with a diameter of less than 15 mm would not have been considered for surgical evacuation of the uterus as a routine procedure in the authors' department. The upper limit was chosen on the basis of previous studies. At inclusion, all women had a closed cervix on clinical examination		1. Expectant management: Refer to general management for both groups below 2. Active management: women received mifepristone 400 mg orally at the clinic followed by a single oral dose of 400 pg misoprostol 48 hours later taken at home General management: Both groups were informed about expected bleeding and were recommended to use paracetamol in combination with codeine if they had pain. They were advised to return to the clinic for surgical evacuation if they had unacceptable symptoms such as severe bleeding or pain. Anti-D immunoglobulin was given to all rhesus-negative women. All women returned for a follow up visit, including transvaginal ultrasound, five days after inclusion. If they had retained intrauterine products of conception with an antero-posterior diameter above 15 mm, surgical evacuation was performed <u>Outcomes assessed</u> 1. Proportion of women with an empty uterine cavity within 5 days after inclusion	Expectant: 3/62 (5) Active: 1/60 (2) OR=0.33 (CI 0.03 to 3.30) (active vs. expectant) One woman randomised to expectant management was admitted for emergency evacuation due to severe bleeding two days after inclusion. Three women underwent surgical evacuation owing to retained products of conception five days after inclusion, two in the group randomised to expectant management and one in the group randomised to medical treatment <u>Incidence of adverse effects/complications (proportion of women and percentage)</u> a. PID Expectant: 2/62 (3) Active: 1/60 (2) (p value not reported as the way this outcome is reported in the paper reflects what we call in the guideline “need for unplanned interventions”. We are not including severe bleeding in our list of side	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Women with retained tissue of more than 50 mm underwent surgical evacuation.		2. Pain (degree): Five days after inclusion, the women marked on a visual analogue scale their maximum experience of pain (0 = no pain, 100 = unbearable pain) 3. Bleeding (duration): Bleeding was defined as the time in days that sanitary protection was required 4. Need for unplanned interventions 5. Incidence of adverse effects/complications 6. Satisfaction: Fourteen days after inclusion, women marked on a visual analogue scale their satisfaction with the medical interventions in connection with the miscarriage (0=positive, 100 negative) <u>Statistical analysis</u> Comparisons between groups were performed by Fisher's permutation test. Two tailed tests were used and $p < 0.05$ was considered significant	effects/complications) <u>Satisfaction with the management (VAS scores, mean (SD)</u> Expectant: 25.2 (25.6) Active: 28.6 (24.8) NS (p=0.1744)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Shelley,J.M., Healy,D., Grover,S., A randomised trial of surgical, medical and expectant management of first trimester spontaneous miscarriage, Australian and New Zealand Journal of Obstetrics and Gynaecology, 45, 122-127, 2005 **Ref Id** 65485 **Country/ies where the study was carried out** Australia **Study type** Randomised controlled trial **Aim of the study** To compare the effectiveness and safety of medical and expectant management with surgical management for first trimester incomplete or inevitable miscarriage **Study dates** June 1999 to December 2000	**Sample size** n=39 women **Characteristics** There were no marked or systematic differences between the groups with regards to gestation, woman's age, reproductive history, method of diagnosis, days of bleeding, pain, haemoglobin or white cell count. No further details are reported. **Inclusion criteria** Women presenting to the emergency departments of five metropolitan hospitals and diagnosed with inevitable or incomplete miscarriage and with the following characteristics: Gestational age of 13 weeks or less Bleeding not excessive Haemodynamic system stable Temperature not more than 37.5 degrees Celsius	**Interventions** Expectant management n=15 Active management (vaginal misoprostol) n=12 Active management (surgical evacuation) n=12 **Comparisons** Expectant management vs.	**Details** <u>Randomisation and allocation concealment</u> Women were randomised to curettage, medical or expectant management via a centralised computer-based enrolment and randomisation service. The randomisation schedule was generated by a coordinating centre using the biased coin method of maintaining balance between study arms and was stratified by hospital and gestation (<7 weeks, 8-10 weeks, 11-13 weeks <u>Interventions</u> a. Expectant: Women were given a contact phone number to ring if unsure or anxious and an information sheet with details of expected symptoms/signs and indications that further care was required. They were then discharged b. Active-medical: Two tablets of 200 microgram misoprostol were placed into the posterior fornix of the vagina. A repeat dose was given 4-6 hours later if miscarriage was still incomplete. c. Active-surgical: Either	**Results** (Unless a p value is reported there were no significant differences amongst the 3 groups) **<u>Need for unplanned intervention (proportion of women and percentage)</u>** Expectant: 3/15 (20) (1 had surgical evacuation following the detection of small amount of RPOC at 10 to 14 day follow-up. 1 had ongoing blood loss and was later diagnosed with molar pregnancy for which she received appropriate treatment. 1 re-presented with heavy bleeding 7 days after randomisation. She had RPOC removed from the os and surgical evacuation without confirmation of retained products by ultrasound) Medical: 2/10 (20) (1 had surgical evacuation due to retained products visible at 10 to 14 day follow-up; 1 had surgical evacuation due to patient request after not passing any products after 2 doses of misoprostol)	**Limitations** **<u>Loss to follow-up and cross-overs</u>** By the time the primary outcome of treatment success was being evaluated, 1 woman had been lost from the medical arm. For some outcomes, such as side effects, it is unclear what the size of the population is, because the point at which the side effects were reported is unknown. For satisfaction in the medical group, the denominator is only 7. Expectant: 15 women were randomised to expectant management but one requested medical management 2 weeks after randomisation and 1 was lost to follow-up by 8 weeks Medical: 13 women were initially randomised to medical treatment, but 1 withdrew after randomisation, and is not included in the analyses. 1 woman had a complete evacuation before misoprostol was given. Therefore, 11 women received misoprostol. 1

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Department of Human Services, Victoria Best Practice Initiatives Grant MBF Medical Research Award	No history of current serious systemic medical or surgical condition Use of prostaglandins not contraindicated (allergy, mitral stenosis, diabetes, blood dyscrasia, haemolytic disease, glaucoma, sickle cell anaemia, hypertension, epilepsy or severe asthma) 18 years or older Not taking anticoagulants or oral corticosteroids Singleton pregnancy No intrauterine device in situ Sufficient familiarity with English to complete written questionnaires **Exclusion criteria** Non-viable intrauterine pregnancy diagnosed on ultrasound but no vaginal bleeding	active management	aspiration curettage or D&C was done under general anaesthetic. Pain relief, Rh immunisation, use of prophylactic antibiotics and provision of information followed usual hospital procedure Suspected retained products of conception were confirmed by ultrasound prior to unplanned surgical evacuation (as experience with medical and expectant care was limited at most of the participating hospitals and because unplanned surgical evacuation was the primary trial outcome)All women were requested to return for a follow-up visit at the hospital or with their local doctor 10-14 days later. <u>Outcomes assessed</u> 1. Efficacy by 10 to 14 days and by 8 weeks A successful evacuation of the uterus without unplanned surgical evacuation of RPOC occured if neither the woman's clinical record or the questionnaires indicated she had received further treatment. 2. Need for unplanned intervention	Surgical: 0/11 (0) **<u>Incidence of side effects/complications</u>** a. Confirmed infection (proportion of women and percentage) Expectant: 0/15 (0) Medical: 2/11 (1.8) Surgical: 0/12 (0) b. Suspected infection (proportion of women and percentage) Expectant: 1/15 (6.7) Medical: 1/11 (9.1) Surgical: 1/12 (8.3) c. Nausea (number of women) Expectant: not reported Medical: 2 Surgical: 1 (the paper does not specifically state at what time point this outcome was measured, therefore due to loss to follow-up between 10-14 days and 8 weeks, the denominator cannot be stated) d. Vomiting (number of women)	further woman was lost by 14 day follow-up, and 1 more by 8 weeks. Surgical: 11 women received surgery. 1 woman did not receive surgery because she requested medical management following randomisation. 1 was lost to follow-up by 8 weeks. **<u>Lack of intention-to-treat</u>** 12 women were initially randomised to the surgical group, however 1 woman elected to have medical treatment rather than surgery. For the primary outcome of success of treatment (i.e. need for further intervention), the n for surgical group has been reported as n=11. However, in the outcome of infection, she is included in the analysis. Similarly, the denominator varies for the medical group where one woman (out of 11 who were randomised) had a complete miscarriage before misoprostol was administered. Finally one woman of 15 randomised to expectant care requested medical treatment 2 weeks after

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			Hospital staff recorded details of further investigations and treatment at 10-14 days or any unsecheduled hospital visit using standardised forms and patients completed questionnaires at 10-14 days and 8 weeks.When care was provided elsewhere, details were obtained from the practitioner. 3. Incidence of side effects/complications Infection was confirmed if vaginal swabs showed evidence of infection, or two of the following criteria were met: white cell count of 15x109/mL or higher, fever, smelly vaginal discharge or prescription of antibiotics. If one criterion was met, a suspected infection was recorded. Incidence of infection is reported within 2 weeks of treatment. Nausea, vomiting and diarrhoea appeared to have been reported at the 10-14 day follow-up visit, although this is not categorically stated. 4. Need for a blood transfusion Haemorrhage is defined as the need for a blood transfusion. 5. Duration of bleeding	Expectant: not reported Medical: 1 Surgical: 0 (the paper does not specifically state at what time point this outcome was measured, therefore due to loss to follow-up between 10-14 days and 8 weeks, the denominator cannot be stated) e. Diarrhoea (number of women) Expectant: not reported Medical: 1 Surgical: 0 (the paper does not specifically state at what time point this outcome was measured, therefore due to loss to follow-up between 10-14 days and 8 weeks, the denominator cannot be stated) <u>Need for a blood transfusion (proportion of women and percentage)</u> Expectant: 0/14 (0) Medical: 0/12 (0) Surgical: 0/12 (0) <u>Duration of bleeding/days (proportion of women and percentage)</u>	randomisation as she was still bleeding and was about to go on holidays. She was completeley excluded from the primary outome analysis and from all the other outomes assessed apart from infection and mental health and anxiety at 2 weeks 1 woman in the expectant group who experienced heavy bleeding was later diagnosed with molar pregnancy for which she received appropriate treatment (no further details reported). Technically speaking she would not be included in our guideline but she was included in the ITT analysis by the authors (whenever this was conducted) therefore we have included her as well **<u>Small sample size</u>** The original trial was planned to be 831 women. Recruitment stopped because after repeated attempts to enlist support from hospital staff, fewer than 50% of eligible women were being approached to participate and only 22% of those

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Hospital staff recorded bleeding at the 10-14 day visit or any unsecheduled hospital visit using standardised forms, and patients completed questionnaires at 10-14 days and 8 weeks. However, it is unclear which results were used to judge duration and degree of bleeding 6. Pain Hospital staff recorded pain at the 10-14 day visit or any unsecheduled hospital visit using standardised forms, and patients completed questionnaires at 10-14 days and 8 weeks. However, it is unclear which results were used to judge duration and degree of pain. Severity was measured using a modified form of the Brief Pain Inventory (no further details given). 7. Satisfaction Measured as the number of women who, if time went backwards, would choose the same method again. 8. Emotional and psychological outcomes Anxiety was measured at the 10-14 day visit using Hospital Anxiety and Depression Scale	Expectant: ≤3: 0/14 (0.0) 4-8: 7/14 (50.0) ≥9: 7/14 (50.0) Medical: ≤3: 2/8 (25.0) 4-8: 3/8 (37.5) ≥9: 3/8 (37.5) Surgical: ≤3: 6/11 (54.6) 4-8: 1/11 (9.1) ≥9: 4/11 (36.4) p=0.004 (expectant vs. surgical at ≤3 days) (Unless a p value is reported there were no significant differences amongst the 3 groups) <u>(proportion of women and percentage)</u> <u>Pain</u> a. Duration/days (median (range)) Expectant: 3.0 (0.0 to 11.0) Medical: 3.0 (0.2-16.0) Surgical: 2.0 (0.2-12.0) b. Severity (median (range)) Expectant: 3 (1 to 7)	agreed to be randomised **<u>Reporting of mental health</u>** It is unclear whether authors are reporting the "mental health" subscale of the SF-36, or whether they have combined the various components of mental health within the SF-36 to give a combined score. **Other information**

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			(HADS). Anxiety is reported as the number of women in each group scoring over 11. General mental health is reported using results of the SF-36 scale, using a questionnaire completed at 2 weeks. The technical team looked for information on how to interpret the results of the emotional and psychological outcomes as this was not reported in the paper. Anxiety is reported as the number of women in each group scoring over 11, which is a score considered to be "abnormal." General mental health is reported using results of the SF-36 scale, using a questionnaire completed at 2 weeks. The scale is scored out of 100, with lower scores indicating greater impairment <u>Sample size calculation</u> Authors had planned a considerable larger study with a sample size of 831 women. This would have provided 80% power to detect a difference in the rate of succesful evacuation of 5% (99% to 94%) at a 0.05 level of significance <u>Statistical analysis</u>	Medical: 3 (1-8) Surgical: 3 (1-10) <u>Reported satisfaction (proportion of women and percentage)</u> "Would choose again" Expectant:8/14 (57.1) Medical: 3/7 (42.9) Surgical: 6/11 (54.5) (reasons why some women were not satisfied are not reported) <u>Emotional and psychological outcomes</u> a. Mental health/100 (mean (SD)) Expectant: 37.1 (13.0) Medical: 36.7 (13.8) (n=11) Surgical: 42.0 (14.5) (n=11) b. Anxiety (proportion of women and percentage) Expectant: 3/15 (20.0) Medical: 2/11 (18.2) Surgical: 3/11 (27.3)	

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			Differences in simple proportions of outomes between treatment groups were examined. Rate ratios were calculated and non-parametric tests carried out to compare treatment groups. In each case the surgical group was compared with one of the other 2 groups The data analyst had access to unblinded data but no contact with any study participants.		
Full citation Smith,L.F., Frost,J., Levitas,R., Bradley,H., Garcia,J., Women's experiences of three early miscarriage management options: a qualitative study, British Journal of General Practice, 56, 198-205, 2006 **Ref Id** 65493 **Country/ies where the study was carried out** UK **Study type** Qualitative follow-up to a randomised controlled trial	**Sample size** n=72 women 56 of these women are the participants of the original trial, however, this qualitative study also includes 16 non-participants who had decided not to participate in the trial and whose management methods are not reported) **Characteristics** Individual characteristics are not given for each group **Inclusion criteria**	**Interventions** Expectant management n=18 Active management (medical) n=18 Active management (surgical) n=20 **Comparisons** Expectant vs. active management	**Details** (Full details of the trial, and management given, can be found in Trinder et al. 2006) <u>Recruitment</u> The qualitative study included trial participants and those who had decided not to participate. Women were recruited from 3 out of the 7 trial centres (Southmead and St Michael's Hospital in Bristol and Royal United Hospital in Bath). Women were initially informed of the research when they were contacted 8 weeks after miscarriage, and they were reapproached 8-12 months later, allowing them to opt out if desired.	**Results** **The key themes identified by the authors were: feelings about the intervention, pain and bleeding, a need for finality, feelings about the 'baby,' and experience of the care they received** **<u>Intervention</u>** **Appropriateness / necessity:** There were many comments about the issue of whether intervention was appropriate or not. The majority of women who mentioned appropriateness queried if the intervention was necessary:	**Limitations** It would have been interesting if the authors had comapred the experiences of the women who had decided not to participate in the trial vs. those who accepted randomisation This paper is a qualitative follow-up of a small number of participants in the MIST trial (Trinder et al. 2006). However, it also includes 16 non-participants, and the distribution of management methods within this group is unclear. Apart from stating that in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(See Trinder 2006) **Aim of the study** To assess the social and personal impact of different management methods (expectant, medical and surgical) on women's experience of first trimester miscarriage **Study dates** September 1999 to June 2000 (Recruitment for the original trial occurred May 1997 to December 2001) **Source of funding** S&W Executive Project Grant	Women linked to the MIST trial and 16 non-participants who had decided not to participate in the trial **Exclusion criteria** Not stated		<u>Data collection</u> The topic guide consisted of: Demographic details (age, social class as indicated by own and partner's occupation, marital status, number of children, family situation, ethnicity and nationality);previous reproductive history and experience; history of the recent miscarriage; experience of the mode of management and of other related healthcare services; support from family, doctors and midwives; feelings before and after miscarriage; subsequent feelings; effects on partner and other family members; coping strategies; and future reproductive hopes and plans.Most interviews were carried out by one of the authors, with fewer than 10% being undertaken either jointly or solely by two other experienced qualitative interviewers. Women were interviewed in their homes, the interviews taped and subsequently transcribed verbatim. Where women expressed a preference for being interviewed with their partner, a friend, or a relative, this was respected due to the potentially distressing nature of the research.	*'I didn't want a D & C, I didn't … I know it sounds silly, 'cos the baby was already dead, but I don't agree with abortion, and things like that, and to me it felt the same; I wanted to do it on my own, and I got the D & C.' (woman who received s*urgical management (S)) *'... and however uncomfortable, or however emotionally, you know, painful it was, I didn't want to speed the process up, I didn't want this unnatural or chemical way, so I, I knew I definitely didn't want a D & C.'*(Woman who received expectant management (E)) A minority were strongly in favour of something being done to help them, to bring the miscarriage to completion quickly. Some in the medical group also were glad that they had been assisted to miscarry naturally: *'I remember thinking about the three options, and coming to the conclusion that, at least a D & C was quick … because at the time I'd been off work for 3 weeks already … and I just thought:*	each occasion one of the researchers conducted the interviewes there are no other details reported on the people who collected the data <u>Hawthorne effect</u> The women may have been contrasting the care shown them as part of the trial with previous experiences where they felt the treatment had been less caring. The women were also given a follow-up session to talk about future reproductive issues, which is not a normal part of NHS care. **Other information**

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			<u>Data analysis</u> The interviews, once anonymised, were analysed using NUDIST . The analysis involved a process of close iterative readings. Transcripts were shared between the five members of the research team. Each interview was read individually and summaries produced on a proforma: demographic and treatment details were recorded along with what were identified as potential themes or issues of significance. After a batch had been completed the whole team read the summaries and discussed them at a meeting and a set of themes were then included on subsequent proformas. Subsequent transcripts were read looking for more on these themes, but this did not preclude the identification of new themes. The discussions guided the development of the topic guide for later interviews. Transcripts were also subjected to iterative readings by the team to ensure that no major issues had been overlooked. The key themes identified were subsequently used to encode all the transcripts using NUDIST.	*I don't want to wait anymore, particularly as I don't know what's going to happen.'* (S) *'… it happened the next morning* [when] *I came home … and it was a sense of relief really, ... it's ended … the medical treatment, it's just speeding it up … it's not actually anyone else going in my body … it's just a little magic tablet … it's midpoint… it's a kind treatment … it's not your baby whipped out of you, which is what a D & C feels like to me.' (*Woman who received medical management (*M))* A majority of women in all groups wished to be allowed to miscarry, because they felt it was more "natural." Similarly, women from the surgical group felt that they had been denied a choice in the management of their miscarriage. **Awareness of the event:** Some women felt that there was benefit in consciously experiencing the miscarriage, in terms of grieving, saying goodbye and performing rites of passage:	

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				'… it's very clean, very quick, wonderful operation, but, in a way, I think probably letting it miscarry helps to grieve in a funny way, because you're going through your grief all of the time that you are waiting for it to go, and then it goes, and you do a sort of mental realignment or whatever, you know, you have time to sort of prepare yourself.'(M) However, there was also a counter-balancing group of women who preferred surgery, to avoid consciousness of the miscarriage and so preferred a D & C (this is the term that women uniformly used to describe the operation of evacuation of retained products of conception — an ERPC — from the uterus): **E:** *'… but, it was just awful, having to wait, like wait ...'* **Researcher:** *'And was it on your mind all of the time?'* **E:** *'A lot of the time, yeah … yeah, you know, I was walking around, waiting to lose my baby.'* **Fear of intervention:** The authors state that there was near uniform fear of intervention, especially	

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				anaesthetic. Hospitalisation and surgery were seen as inherently traumatic events, and women wanted to avoid being "messed about with." *"I was more worried about the anaesthetic, that sort of worries me, just sort of being knocked out, and I'm always afraid about not waking up again...." (S)* "*...yeah... I didn't really want to have anything done. I thought it was bad enough having lost it, without having to have any more fiddling around." (S)* Women viewed medical management particularly badly when they still had to have a surgery. In comparison those women who had had no initial intervention, that is, the expectant group, rarely mentioned the need for a subsequent D & C as an issue for them: **E:** *'That was another reason for doing it, because I hate hospitals, I hate injections, and I was working, I just couldn't see how it was all going to fit in.'* **Researcher:** *'So, you didn't want to have the D and C?'*	

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				E: *'No, I didn't !'* **<u>Pain and bleeding</u>** **Pain:** Pain was mentioned mostly by the medical and expectant groups. There were very variable experiences, ranging from severe pain like labour or contractions, to tolerable pain like bad period pains: *'I don't remember actually, it was more like period pain and I'd get the odd backaches … I think that I had a hot water bottle, I just needed something warm on my tummy, and if I moved ... then I was fine.'*(E.) *'They said it would be like a contraction, but I mean, it wasn't like a contraction at all, really … it was like very strong period pain … I likened it to when I first started my periods, when I was sort of 13.' (M)* *'I didn't actually feel I was prepared for what was coming, because, come the Saturday, when I started miscarrying even more, em, I had like contraction pains, which I would say were as*	

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				bad as childbirth.'(E.) *'I suppose to all intents and purposes, I had gone through labour, although, obviously a different version, but I did feel, my body did feel as though I'd gone through labour, and of course, I had nothing to show for it.' (M)* **Bleeding:** Only women in medical and expectant groups mentioned bleeding as an issue, generally referring to it as "severe", "flooding" and "lots of clots." *'… I mean, looking back on it, I bled for about 40 hours, and had 40 hours of pain and bleeding; but I think that the actual psychological support I had was so much better, that it didn't seem that bad.' (M)* *'I started a bit of bleeding on the Saturday evening, and then Sunday, it was just … you know … sort of gushing, it was horrid and it was definitely, definitely, definitely worse than just a normal period.'*(E) **Lack of information:**	

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				Women in medical and expectant groups felt that they were not given information about the degree of pain and bleeding to expect. Women in all groups mentioned that they generally had not known what to expect from their method. **<u>Medical management</u>** Women who had medical management expressed particular concerns. Many women talked about the time the process took: women with missed miscarriage were given tablets and sent home for 48 hours, then women with any miscarriage had to wait for a free bed to be admitted, then they had to wait for the tablets to work. Some women felt they were not given enough information about the effect of the tablets, and how long it might take them to work. **<u>Finality / need for an ending</u>** **Predictability:** The two themes were firstly that it should come to a predictable end so that they	

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				can get on with their lives, and secondly that there should be predictability to their experience, i.e. symptoms and management. *'I would have preferred to have a D & C, although I'm not sure what that would be like, exactly what that is, but, at least there would be an end to that, like you know: one minute you're pregnant, and the next minute, it's finished and you can get on with your life.'* (M) *'And it was like: I wanted it done, I wanted it done now. I wanted to get home for tea, sort of thing, that was how I was: can't we just do it.' (S)* *'… but we had tickets to go out, and we had the baby sitter organised, and we were having a weekend away on our own, and it meant that we couldn't go, so it was more the inconvenience ... as opposed to actually having to go in, and go through it.' (S)* *'… after it had happened, I just thought: let's get this sorted, you know, and get back to normal, rather than thinking: oh, what's gonna*	

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				happen now then, you know, and worrying about it, I thought: let's get the tablets and get it over with, or have an operation and get it over with and then I can go home.' (E.) **Need for information:** Women wished to know what to expect in terms of bleeding and pain, and more accurate and precise details on timings of interventions. *'… well, I was tired, and I didn't know it would happen did I? I just went for a wee and wiped myself and there it was ... I was shocked, and I just held it, touched it, examined it, and I did feel a bit sick.'* (M) *'… and I just thought: I don't want to wait any more, particularly because I don't know what's going to happen, and, oh, the first time I'd read a book about miscarriage, and it, the most awful stories always get in there, I mean I was, you always get those sorts of stories and you think, "oh my God, you know, what on earth is going to happen?" So I just thought: right, I'll go for the most invasive was of*	

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				doing it [laughs], *which at least, gets it over with.' (S)* *'I wanted to. I didn't want to sort of just go home and wait for a miscarriage, erm, ... because I, I didn't know what to expect at all.'* (S) *'If I'd never had a miscarriage, I think the thought of an expectant miscarriage is quite alarming, because you really don't know what to expect at all.'*(E.) **Feelings about the 'baby'** **Seeing the 'baby':** Many women expressed views about seeing the baby. Some were worried and scared about what they might see, and how to avoid it. Others felt it was important to see the baby, to say goodbye, and to finish the miscarriage on their own terms: *'… but you know, I just sort of thought: what's that there? You know and, then, sort of waited, and then when you pull the flush, it's like a real goodbye, you know.' (M)* *'… and now this little one had got so far, and I couldn't*	

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				protect her either, because, I mean I was able to have [name], but this was different, because I felt that this baby … I mean, what was left of the baby was being taken away from me.'(E.) **Fear of accidentally killing the 'baby':** A few women wanted to avoid intervention, because they felt that if there was a misdiagnosis then they were somehow involved in the killing of the baby: *'I was very relieved that it had miscarried naturally 'cos I could cope with it dying naturally, that wasn't a problem, with the thought of having it killed on purpose, that's how I would have seen it.' (M)* The authors also state that some women expressed a kind of horror about carrying something dead around inside them: *'I think that that's one of the scariest things: knowing that something inside of you is dead.'*(E.) *'… but I remember, when they first told me, I remember*	

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				I was sort of like sitting on the bed, and I just sort of thought: god, get it out of me! And, it was; that felt really strange you know what I mean, because at that time, they hadn't explained that it wasn't actually growing.'(E.) **<u>Experiences of care received</u>** A <u>small</u> number of women in surgical and medical groups felt there was a lack of caring, and that they were part of a "conveyor belt." *'... you know, nobody came and showed us any care, apart from when they came to take the commode away, but nobody came in to see us.'* (M) *'... and I hated it! The whole thing was cold! It was so insensitive, it was horrible! I will never forget how insensitive, and cold it felt.' (S)* *'… you felt like you were ... sort of on a conveyor belt and they just whacked this mask over my face, it was almost like, you know: get through, lie down, shut up* [laughs] *and we can get on with it, because you are*	

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				slowing down the process … ' (S) *'… and they were just icy cold towards us, weren't they? I couldn't believe it really, it was just like when you take your car in for an MOT, they could have been telling us anything ... they didn't show any emotions.' (M)* These comments were not frequent. However, the authors considered them significant due to the difficulty that patients have in passing negative comments about their doctors or nurses. In contrast, several women in the expectant group commented that although the experience was upsetting for them they found it reassuring to be at home: *'… so, you know, I thought: no, I'll be at home, I'll be safe, and if there's any real problems, I've got a phone number to ring, or my GP, or we'll just call, if I was really frightened, or worried that it was too heavy … there is something I can do, and I had some stronger pain killers.'* (E.)	

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Full citation Trinder,J., Brocklehurst,P., Porter,R., Read,M., Vyas,S., Smith,L., Management of miscarriage: expectant, medical, or surgical? Results of randomised controlled trial (miscarriage treatment (MIST) trial), BMJ, 332, 1235-1240, 2006 **Ref Id** 65526 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To ascertain whether a clinically important difference exists in the incidence of gynaecological infection between surgical management and expectant or medical management of miscarriage **Study dates** Recruitment occurred May	**Sample size** n=1198 **Characteristics** No significant differences were found at baseline between the 3 groups regarding the following: - age - gestational age - type of miscarriage (missed/incomplete) - bleeding at entry - pain - median anteroposterior diameter on ultraosund scan **Inclusion criteria** Pregnancy of <13 weeks gestation, diagnosed as either: - an incomplete miscarriage (defined as areas of mixed echogenicity within the uterine cavity, with or without a disordered gestation sac) - early fetal demise (defined as a fetus >6mm crown-rump length with no heart activity on transvaginal ultrasound) - early embryonic demise (defined as an intact gestation sac >20mm mean diameter with no other	**Interventions** Active management (surgical) n=402 Expectant n=398 Active management (medical) n=398 **Comparisons** Expectant vs. active management	**Details** <u>Recruitment</u> Of 3905 women attending the early pregnancy clinics, authors recruited and randomised 1200 (31%) women; 1620 women refused trial entry and were offered routine surgical management; 1085 women were not eligible for entry to the study. The number of women recruited to the trial was lower than that needed to meet the original sample size calculation. Recruitment was slower than anticipated and despite an additional 33 months of recruitment, authors recruited a total of 1200 women. Two women recruited to the trial were subsequently found to have a viable pregnancy <u>Sample size calculation</u> On the basis of the one published trial before the MIST trial started, authors expected the incidence of the primary outcome in the standard care group (surgical management) to be 10%. To detect a 50% lower incidence of this outcome in the surgical group, compared with the expectant or medical management group, authors needed to recruit 474	**Results** <u>Duration of bleeding/days (median (IQR))</u> Expectant: 12 (7 to 15) Medical: 11 (7 to 15) Surgical: 8 (4 to 14) <u>Pain</u> a. Pain They report no significant difference between medical and surgical groups but give no further details. b. Extra analgesia taken (number of women/total (%)) Expectant: 177/398 (44) Medical: 98/398 (24.6) Surgical: 71/402 (17.7) <u>Unscheduled vists to a medical facility (number of events/total (%))</u> Expectant: 196/398 (49.0) Medical: 72/398 (18.0) Surgical: 32/402 (8.0) (Note: The above numbers relate to unplanned admission. The paper also states that the number of unplanned hospital consultations (without admission) was similar in the	**Limitations** <u>Loss to follow-up</u> Expectant: 5/398 (1.2%) by 10-14 days; 11/398 (2.8%) by 8 weeks Medical: 9/398 (2.3%) by 10-14 days; 12/398 (3.0%) by 8 weeks Surgical: 8/402 (2.0%) by 10-14 days; 10/402 (2.5%) by 8 weeks <u>Outcomes assessed</u> It is unclear how some of the outomes reported were assessed Lack of reporting of specific figures for some outcomes **Other information** <u>Intention-to-treat</u> Out of the 402 women randomised to surgery, 356 (89%) had surgical curettage. 46 did not, because 30 miscarried before admission, and 16 declined surgery following randomisation. However, 12 subsequently had curettage. Out of the 398 women randomised to medical

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1997 to December 2001 **Source of funding** South and West NHS Executive research and development grant Donation of £20,000 from Exelgyn (manufacturers of mifepristone)	internal structures) **Exclusion criteria** Severe haemorrhage or pain Pyrexia >37.5 degrees Severe asthma, haemolytic disease or blood dyscrasias Current anticoagulation or systemic corticosteroid treatment Twin or higher order pregnancy Smoker aged over 35 Inability to understand written English		women to each group, giving a total sample size of 1422 women. This sample size would have 80% power to detect the treatment effect significant at the 5% level Randomisation Randomisation was by a central telephone system. Authors used minimisation to ensure comparability between women with respect to participating centre, parity, type of miscarriage, and gestation. Interventions All women were given a specific information sheet, 30 co-dydramol tablets and an emergency telephone number 1. Expectant management: Women were allowed home with no intervention 2. Active mangement-medical: Women with an incomplete miscarriage were admitted to hospital and given a single vaginal dose of 800 microgram misoprostol. Women with early foetal/embryonic demise were pre-treated with a single oral dose of 200mg mifepristone, and then admitted to hospital 24-48 hours later for a single vaginal dose of 800 microgram	groups, but gives no further details) Emotional and psychological outcomes They report that there was no differences between anxiety scores or any of the subscales of the SF-36. Raw scores are not reported. Need for unplanned intervention (number of women/total (%)) Expectant: 177/398 (44) (reasons not stated) Medical: 142/398 (35.6) (90 as a result of the failure of the failure of the medical protocol; 52 had an unplanned curettage, of which 11 were an emergency procedure prior to admission. Reason not stated for the remaining group) Surgical: 22/402 (5.5) (the main indications for unplanned curettage were retained products on the scan and excess bleeding) (expectant management not compared to active management) Incidence of side	management, 12 women miscarried spontaneously (but 2 later had curettage). Trial management A research fellow based at one of the centres coordinated the day to day activity of the seven participating centres. Randomisation, data management, and analyses were done at the National Perinatal Epidemiology Unit, Oxford. A multidisciplinary steering committee oversaw the trial. Authors established an independent data monitoring committee, which met annually during the period of recruitment to review interim analyses; its terms of reference stated that interim results should not be revealed to the steering committee unless a strong reason to alter the protocol or stop the trial emerged.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			misoprostol. A surgical evacuation of retained products of conception was offered if expulsion had not started within 8 hours of misoprostol insertion. 3. Active management-surgical: Women were admitted for surgical suction curettage under general anaesthetic. Prophylactic antibiotics were not used. In all three groups, blood was taken for full blood count. Rhesus negative women were offered 250 IU of anti-D irrespective of their allocated management. A follow-up appointment was arranged 10-14 days after trial entry for a transvaginal ultrasound scan, full blood count, consultation with the study nurse, and examination by a gynaecologist if symptoms of infection were present. Retained products of conception were diagnosed if areas of mixed echogenicity within the uterine cavity were seen. A surgical curettage was offered if retained products of conception were present. Clinical symptoms were also taken into account; individual doctors in the early pregnancy clinics made the decision to offer curettage, in association	<u>effects/complications (number of women/total (%))</u> a. Surgical complications Expectant: 4/398 (1.0) Medical: 4/398 (1.0) Surgical: 9/402 (2.2) (no differences between the 3 groups; type of surgical complication is not reported) b. Infection specified by criteria (by 10-14 days) Expectant: 11/398 (3.0) Medical: 9/398 (2.3) Surgical: 12/402 (3.0) c. Infection specified by criteria (by 8 weeks) Expectant: 14/398 (4) Medical: 12/398 (3) Surgical: 16/402 (4) d. Antibiotic use for presumed infection (by 10-14 days) Expectant: 17/398 (4.0) Medical: 31/398 (7.8) Surgical: 34/402 (8.5) e. Antibiotic use for presumed infection (by 8 weeks) Expectant: 31/398 (8.0)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			with the women. <u>Outcomes assessed</u> 1. Need for unplanned intervention: In the paper this is reported as the number of women with an "unplanned curettage" in the surgical group, and "any curettage" in the medical and expectant groups (indicated by failure of the management protocol, or as an emergency procedure prior to admission) within 8 weeks. 2. Incidence of side effects/complications: The primary outcome was gynaecological infection, defined as two or more of: purulent vaginal discharge, pyrexia above 38.0 degrees, tenderness over the uterus on abdominal examination, and a white cell count above 15x109/l. The outcome is reported at both 10-14 day follow-up and 8 week follow-up. Infection specified by the prescription of antibiotics is also reported. Vomiting and diarrhoea were assessed by the medical staff 3. Need for a transfusion: Method of data collection not reported.	Medical: 43/398 (10.8) Surgical: 44/402 (10.9) f. Vomiting and diarrhoea The paper reports that there was no significant difference between the medical and surgical groups, but gives no further details. <u>Need for a blood transfusion (number of women/total (%))</u> Expectant: 7/398 (2) Medical: 4/398 (1.0) Surgical: 0/402 (0) % Risk difference (95% CI): −1.8 (−3.6 to −0.4) (surgical vs. expectant)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			4. Duration of bleeding: Unclear at what point, and how, this was assessed. 5. Pain: Pain was assessed by the medical staff. Additional analgesia taken was used as a proxy of the need for analgesia in an outpatient setting, however the dose or method of analgesia is not reported. 6. Unscheduled visits to a medical facility: This is the number of unplanned hospital admissions within the first 8 weeks after randomisation 7. Emotional and psychological outcomes: The women completed questionnaires (standard UK SF-36 and Hospital Anxiety and Depression Scale) at 8 weeks after treatment. Method of administration of the questionnaires is not stated. <u>Statistical analysis</u> The differences between groups were expressed as risk differences with 95% confidence intervals.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wieringa-de,Waard M., Hartman,E.E., Ankum,W.M., Reitsma,J.B., Bindels,P.J., Bonsel,G.J., Expectant management versus surgical evacuation in first trimester miscarriage: health-related quality of life in randomized and non-randomized patients, Human Reproduction, 17, 1638-1642, 2002 **Ref Id** 65550 **Country/ies where the study was carried out** The Netherlands **Study type** Survey as follow-up of a randomised controlled trial and an observational study (See Wieringa 2002, RefID 81242) **Aim of the study** To measure general and specific quality of life in women with miscarriages who were managed either expectantly or by surgical evacuation in a randomised controlled trial and to compare these results with	**Sample size** n=229 women (82 randomised, 147 non-randomised (preference group)) **Characteristics** No significant differences in sociodemographic or clinical characteristics, prior experience with one of the management options, education, native country or anxiety (STAI) were present neither between the randomised nor between the preference groups. At baseline there were no significant differences in mental health (MCS) between the two randomised groups (data not shown) however, women preferring expectant management showed significantly better scores on the MCS than women preferring curettage (mean score 66 vs. 57 respectively) (no SD or p values provided) **Inclusion criteria** Women included in a	**Interventions** Expectant management n=107 (46 randomised; 61 non-randomised) Active management (D&C) n=122 (36 randomised; 86 non randomised) **Comparisons** Expectant vs. active management Randomised vs. non-randomised groups	**Details** <u>Recruitment</u> Of the 427 women (including randomised as well as non randomised) participating in the medical outcomes analysis (see Wieringa 2000 ref ID 81242) 198 were excluded (see exclusion criteria). The remaining 229 women (54%) returned two or more questionnaires and were included in the present study. Responders more often originated from Western European countries than the excluded women (72% vs. 46%, no p value given) and also showed a higher degree of education. No significant differences between responders and non-responders were found in age, prior experience with any of the management options or interval between enrolment in the study and curettage or spontaneous loss of pregnancy (data not shown). <u>Sample size calculation</u> The SF-36 was used for the power calculation. Assuming a five-point difference in the summary PCS or MCS measures as being clinically	**Results** <u>Emotional and psychological outcomes</u> <u>1. Mental health (MCS scores)</u> a. randomised group (n=82) Mean difference between expectant management group vs. active (surgical) treatment, all time points together: 7.4 in favour of expectant management p=0.004 The difference at 12 weeks was still 6.3 (no p values reported) b. Preference group (n=147) No statistically signicant differences between expectant vs. active management (no p values reported) <u>2. Anxiety (STAI scores)</u> a. randomised group (n=82) No statistically signicant differences between expectant vs. active management (p=0.09)	**Limitations** Other than expressing a strong preference for a specific management option it is unclear whether randomised and non-randomised women were different regarding any other variables Mean values for all scores at different assessment times were not reported as figures in the text but only in graphs from which it is impossible to extract accurate values Selective outome reporting (anxiety not reported in the comparison between randomised and preference groups) **Other information** Reference scores for the SF-36 sub-scales were obtained from published data of a Dutch population sample (16 to 40 years of age) (Ware et al., 1993, 1994, 1998; Aaronson et al., 1998)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
those of women who, because of a treatment preference, were managed according to their own choice (the asumption being that quality of life might well be influenced by patients' treatment preference) **Study dates** April 1998 and September 2000 **Source of funding** Grants from the Dutch Health Research and Development Council (ZON) and the Dutch Ministry of Health, Welfare and Sports	previous study comparing expectant with surgical management (see Wieringa 2002 (Ref ID 81242)) **Exclusion criteria** Insufficient Dutch or English language skills Refusal to participate in this part of the research Returned only one questionnaire of the five that were sent to them		relevant, 33 women were needed in each randomised group to detect this difference (alpha=0.05, beta=0.2) <u>Outcomes</u> 1. Emotional and psychological outomes (Health Related Quality of Life (HRQL) in the paper) a. Mental Health (Mental Component Summary scale-MCS) Assessed by the generic Medical Outome Study 36-Item Short-Form Health Survey (SF-36) Scores of the eight sub-scales of the SF-36 which range to zero (worst health) to 100 (best health) were aggregated into the standardised MCS scale and Physical Component Summary scale (PCS) both with a mean 50, SD 10 (PCS not relevant to our outomes therefore results not reported in this table). Subscales are: physical problemas, mental health, role limitations because of emtional problems, role limitations because of physical problems, social functioning, bodily pain, vitality and general health perception.	b. Preference group (n=147) No statistically signicant differences between expectant vs. active management (no p values reported) All of the previous individual scores at different assessment times were only reported in graphs from which it is impossible to obtain accurate results) -Randomised vs. preference groups a. Expectant (n=46; n=61 respectively) No significant differences either for mental health or for anxiety between randomised and preference groups b. Active (n=36; n=86 respectively) A significant overall five-point difference (p=0.03) was found in the MCS when comparing randomised women to those who preferred curettage. Women treated according to randomised allocation performed worse than those who received the same treatment at their own	No correlation was found between the time taken to achieve pregnancy and MCS scores at 12 weeks No differences were found between the proportion of high responders (women who returned four to five questionnaires) and low responders (women who returned two or three questionnaires) in the randomised and in the preference group Designated 2002b

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			b. Anxiety Assessed by the domain-specific State-trait Anxiety Inventory (STAI) The STAI contains two 20-item scales covering both current (state) and background (trait) anxiety. Items are rated on a 4-point scale with total scores ranging from 20 to 80 where higher scores represent higher levels of anxiety. Both questionnaires were completed by the patients at home and were returned in a pre-stamped envelope (immediately after inclusion and 2, 4, 6 and 12 weeks later). Reminders were sent to non-responders once after each time point. <u>Statistical analysis</u> Changes in HRQL over time in the four groups were analysed in a repeated measurements mixed model	request Results for anxiety were not reported -Additional analysis No differences were found between the any of the scores in women allocated to the treatment for which they expressed a slight preference before randomisation and those not allocated to their preferred treatment	
Full citation Blohm,F., Hahlin,M., Nielsen,S., Milsom,I., Fertility after a randomised trial of spontaneous abortion managed by surgical evacuation or expectant	**Sample size** n=113 women **Characteristics**	**Interventions** Expectant management n=76 Active management (surgical	**Details** <u>Recruitment</u> 127 women were sent a questionnaire and 113 returned it (89% response rate). 13% of the women who had	**Results** <u>Cumulative conception rates (figures are estimates taken from a graph as they were not reported in the text)</u> a. at 6 months	**Limitations** <u>Recruitment</u> Unclear if women who responded to the questionnaire were significantly different from

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treatment, Lancet, 349, 995, 1997-, 1997 **Ref Id** 77951 **Country/ies where the study was carried out** Sweden **Study type** Survey follow-up of a randomised controlled trial (See Nielsen 1995 Ref ID 65396) **Aim of the study** Not clearly stated **Study dates** 1996 (no other details provided) **Source of funding** Not stated	Not stated **Inclusion criteria** Women included in randomised controlled trial comparing expectant management with primary surgical evacuation for miscarriages less than 13 weeks (See Nielsen 1995) **Exclusion criteria** Women: -aged 45 or more -not identifiable in the population registry -who were tourists visiting Sweden at the time of their miscarriage -who reported that they did not intend to become pregnant again	management: D&C) n=37 **Comparisons** Expectant vs. active management	experienced expectant management did not respond as compared to 8% of the women who had experienced surgical management (unclear whether this was statistically significant) <u>Outcomes assessed</u> 1. Cumulative conception rates 2. Pregnancy outcomes A questionnaire was sent to the women asking about their desire to become pregnant, whether or not they had a partner, months at risk of pregnancy and pregnancy history. Fertility during the 24 months after the miscarriage was evaluated. Information on the outcome of subsequent pregnancies (birth weight, duration of pregnancy at time of delivery and form of delivery) was obtained from hospital records	Expectant: 0.70 Active: 0.60 b. at 12 months Expectant: 0.80 Active: 0.75 c. at 18 months Expectant: 0.90 Active: 0.82 d. at 24 months Expectant: 0.93 Active: 0.89 No significant differences between both groups (p values not reported) -Subgroup analysis (cumulative conception rates %) Women managed expectantly who later required surgical evacuation for retained products: 93 Women managed expectantly only: 91 Women managed by primary surgical evacuation: 88 Pelvic inflammatory disease (PID) had been diagnosed in 3 of the women originally managed expectantly, 2	those who did not <u>Methods</u> Statistical analysis carried out not described <u>Outcomes and results</u> Selective outcome reporting **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				were present in this follow-up and both had given birth. Of the 5 women originally managed surgically who were diagnosed with PID 3 were followed up and two had given birth Pregnancy outcomes No significant differences between both groups (data or p values not reported)	
Full citation Chipchase,J., James,D., Randomised trial of expectant versus surgical management of spontaneous miscarriage, British Journal of Obstetrics and Gynaecology, 104, 840-841, 1997 **Ref Id** 78010 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study**	**Sample size** n=35 women **Characteristics** There were no significant differences between both groups at baseline regarding age, gestational age and anterior-posterior diameter **Inclusion criteria** Women in early pregnancy with vaginal bleeding Good health with a normal haemoglobin and haemodynamically stable Estimated gestational age of	**Interventions** Expectant management n=19 Active management (surgical evacuation) n=16 **Comparisons** Expectant vs. active management	**Details** Randomisation and allocation concealment Not described Sample size calculation Not reported Interventions Expectant: Women were informed they might expect some further bleeding and pain and were recommended to use simple analgesia Active: Women were booked for an evacuation of retained products of conception.	**Results** Duration of bleeding (days, median and range) Expectant: 4 (0 to 7) Active: 2 (0 to 7) NS (p values not reported) Duration of pain (days, median and range) Expectant: 0 (0 to 5) Active: 0 (0 to 2) NS (p values not reported) Incidence of side effects/complications (proportion of women and percentage)	**Limitations** Small sample size and no sample size calculation reported Management strategies not described in detail Selective outcome reporting (no data on patients' preference of management options) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare expectant with surgical management of first trimester spontaneous miscarriage, in both the short term and the medium term **Study dates** Unclear **Source of funding** Not stated	< 13 weeks Anterior-posterior diameter of retained products < 50 mm on a transvaginal ultrasound **Exclusion criteria** Complete and recurrent miscarriages		Products of conception were confirmed by histopathology in all cases <u>Outcomes assessed</u> All women were reviewed at one week, two weeks and six months after inclusion 1. Duration of bleeding: Number of days with vaginal bleeding necessitating sanitary protection 2. Duration of pain: Number of days requiring analgesia 3. Incidence of side effects/complications: Not defined 4. Subsequent conceptions: Time taken for the next spontaneous pregnancy 5. Women's satisfaction: Patients' satisfaction with and preference of management options <u>Statistical analysis</u> Undertaken using nonparametric methods (x2 test with Yates' correction for comparison of frequencies and	-Infection: Expectant: 1/19 (0.5) Active: 1/16 (0.63) (In both cases women were diagnosed with pelvic infection) <u>Subsequent conceptions (number of pregnancies/number attempted and percentage)</u> Expectant: 9/12 (75) Active: 6/9 (66) <u>Women's satisfaction (proportion of women satisfied and percentage)</u> Expectant: 19/19 (100) Active: 14/16 (88) (2 women not satisfied due to the length of time between diagnosis and operation)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Mann-Whitney for comparison U test of medians).		
Full citation Smith,L.F.P., Ewings,P.D., Quinlan,C., Incidence of pregnancy after expectant, medical, or surgical management of spontaneous first trimester miscarriage: Long term follow-up of miscarriage treatment (MIST) randomised controlled trial, BMJ, 339, 910-, 2009 **Ref Id** 78470 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To compare fertility rates after three methods of managing early miscarriage in women recruited to the MIST randomised controlled trial **Study dates**	**Sample size** n=762 women **Characteristics** Details of the characteristics of the three groups are not given **Inclusion criteria** See Trinder et al. 2006 **Exclusion criteria** See Trinder et al. 2006 Opting out of follow-up Original GP advised against follow-up	**Interventions** Expectant management n=247 Active management (medical) n=252 Active management (surgical) n=263 **Comparisons** Expectant vs. active management	**Details** (For full details, see Trinder et al. 2006) <u>Recruitment and data collection</u> A preliminary survey involving the general practitioners of 99 of the original participants was undertaken to assess ease of contacting women. This achieved a response rate of 79%. Subsequently, in 2005-7, women who completed the original trial and their general practitioners were sent a postal questionnaire; the only exclusions were women who opted out of any follow- up or for whom the original general practitioner advised against follow-up. When questionnaire packs were returned "addressee unknown," authors used the Office for National Statistics tracing services to identify the woman's current health authority information. Health authorities were then requested to forward a pack to her general practitioner for subsequent forwarding. The mailing period extended over	**Results** <u>Live birth rate (number of women/total (%)</u> Expectant: 177/224 (79.0) Medical: 181/230 (78.7) Surgical: 192/235 (81.7)	**Limitations** <u>Population</u> Population denominators include women who did not want to conceive again, and the proportion of such women in each group was not reported. **Other information** Of the 1199 women recruited to the original trial, authors sent questionnaires to 1128 women and their GPs. For the 71 remaining there was no consent from the patient or her original general practitioner for such follow-up. Questionnaires providing subsequent pregnancy details were returned for 762 women (68% response rate), from the woman herself, her general practitioner, or both. With data recorded as part of the original MIST trial protocol, respondents to this follow up survey were compared with non-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Recruitment occurred May 1997 to December 2001. Follow-up was done in 2005-2007. **Source of funding** BMA Claire Wand Fund. Sponsorship and research governance was provided by East Somerset Research Consortium			two years because of the time delay in obtaining tracing authorisation from all four countries in the United Kingdom. Women's general practitioners were also asked for details of subsequent pregnancies; women's replies were used if there were discrepancies between the two. The questionnaire was sent with a consent form, covering letter, and freepost envelope for return. <u>Sample size calculation</u> Authors estimated from published studies that the MIST trial cohort would give 80% power to detect a hazard ratio of about 0.7 in fertility rates between any two of the management methods <u>Interventions</u> For full details of the three management interventions, see Trinder et al. 2006. <u>Outcomes assesed</u> Live birth rate The only outcome reported separately for the different		respondents (including the 71 not sent a questionnaire as well as those not returning questionnaires). The respondents were broadly representative of the MIST trial population, with no significant differences between respondents and non-respondents. Age was associated with low birth rate, however respondents and non-respondents were not significantly different in terms of age.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			management groups is % of women with a live birth within 5 years of the index miscarriage Statistical analysis To assess representativeness, authors compared respondents and non-respondents (including those not consenting to follow-up) using either $\chi 2$ test or Student's t test. Separate analyses were undertaken for live births Quoted denominators are sometimes different due to occasional non-response to certain questions.		
Full citation Wieringa-de,Waard M., Vos,J., Bonsel,G.J., Bindels,P.J., Ankum,W.M., Management of miscarriage: a randomized controlled trial of expectant management versus surgical evacuation, Human Reproduction, 17, 2445-2450, 2002 **Ref Id** 81242 **Country/ies where the study was carried out**	**Sample size** n=122 women **Characteristics** Age, parity, prior spontaneous miscarriage, prior curettage, gestational age, presence of intact gestational sac, diagnosis of incomplete miscarriage, presence of vaginal bleeding, number of days bleeding until inclusion, number of days with pain until inclusion and native country were not significantly	**Interventions** Expectant management n=64 Active management (D&C) n=58 **Comparisons** Expectant vs. active management	**Details** Recruitment Study was conducted in two city hospitals. GPs working in the health districts covered by those hospitals were asked to refer women with first trimester vaginal bleeding for an ultrasound assessment. All women attending the A&E department or outpatient clinics of both hospitals because of first-trimester vaginal bleeding were also asked to participate	**Results** Treatment success (efficacy) at 6 weeks (proportion of women and percentage) Expectant: 30/64 (46.9) Active: 55/58 (95) p<0.001 Treatment success (efficacy) after 6 weeks (intention-to-treat analysis including cross-overs) (evacuation rate, %) Expectant: 92	**Limitations** Inclusion criteria: this study included women with a gestational age up to 16 weeks and the guideline only includes women up to 13 weeks (a total of 33 women (54.4.%) had a gestational age between 12 and 16 weeks. 7 women (11.5 had an uncertain gestational age) Outcomes: unclear who assessed and analysed the outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
The Netherlands **Study type** Randomised controlled trial **Aim of the study** To compare expectant management with surgical uterine evacuation for women with a miscarriage **Study dates** April 1998 to September 2000 **Source of funding** Grants from the Dutch Health Research and Development Council (ZON) and the Dutch Ministry of Health, Welfare and Sports	different between the two groups **Inclusion criteria** First trimester vaginal bleeding Established diagnosis of early fetal demise or incomplete miscarriage at a gestational age of <16 completed weeks Transvaginal sonographic criteria for early fetal demise were: -mean gestational sac diameter >15 mm without measurable embryonic pole -embryo without cardiac activity or -gestational sac diameter <15 mm, not showing any growth after a 7-day interval Incomplete miscarriage diagnosed in case of ultrasound evidence of retained products of conception (RPOC)> 15 mm anteroposterior (AP) diameter		Inclusion criteria All transvaginal scans were performed by trained physicians using a transvaginal 6.5 MHz sonographic probe Sample size calculation Total required sample to be randomised was 162 (power of 0.80), based on the assumption that there would be no substantial differences between the two treatments in terms of safety and complications. The aim was to demonstrate a 20% difference in efficacy (65% for expectant management and 85% for active management) Randomisation After informed consent was given women were randomised by the attending physician to either expectant management or surgical evacuation using central electronic randomisation. Randomisation was stratified for referral setting (directly by general practitioners vs. outpatient clinics) and for gestational age (4 to 8, 8 to 12 and 12 to 16 weeks of amenorrhoea)	Active: 100 NS Time until evacuation (days, median, interquartile range) Expectant: 7 (3 to 16) Active: 5 (2 to 7) p<0.001 Incidence of complications, including infection rate and surgical complications (proportion of women and percentage) a. Infection Expectant: 0 Active: 0 NS b. Cervical tear Expectant: 1/64 (1.6) Active: 0 NS c. Uterine perforation Expectant: 0	**Other information** Eligible women who expressed a strong preference for one of the treatment options and refused informed consent for randomisation were invited to participate in an observational study and received the treatment of their choice. They were asked to consent to the same follow-up procedures as applied in the randomised patients. Data on efficacy for this group of women is not reported in this table Among 1101 women referred for an early pregnancy assessment, 652 were excluded because of their diagnoses (viable pregnancy, complete miscarriage, and other reasons) and 449 were excluded because of severe bleeding or pain necessitating immediate curettage. Of the 427 remaining women 122 accepted randomisation while 305 expressed their own treatment preference and gave consent for data collection and follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Age < 18 years Inability to understand the Dutch or the English informed consent form and/or Severe bleeding, pain or fever necessitating immediate surgical evacuation		<u>Allocation concealment</u> Not reported <u>Interventions</u> 1. Active management Surgical uterine evacuation using suction curettage was performed within a week after inclusion in the study under local or general anaesthesia in daytime surgery. Planning of surgery depended on the availability of theatre facilities only. General anaesthesia was used whenever cardiopulmonary monitoring was required or when requested by the patient. Patients left the hospital after 2 to 4 hours of postoperative observation 2. Expectant management Involved bi-weekly scheduled visits to the outpatient clinic. Further management depended on clinical developments. Women who became impatient while being managed expectantly and requested surgical evacuation were scheduled to undergo	Active: 0 NS <u>Need for unplanned interventions (proportion of women and percentage)</u> a. Second curettage Expectant: 2/64 (3.1) Active: 3/58 (5.2) NS b. Emergency curettage Expectant: 7/64 (10.9) Active: 6/58 (10.3) NS Emergency curettages occurred in the expectant group because of intolerable bleeding and pain. Second curettages occurred in the active group because of incompleteness of the first procedure. (unclear why second curettages were needed in the expectant group and why emergency curettages were needed in the active group,	Baseline characteristics between randomised patients and those managed according to their preference did not differ Rhesus negative patients undergoing curettage received 375 IU anti-D immunoglobin whilst in hospital Approximately 25% of women did not have vaginal bleeding at inclusion. Outcomes on efficacy and complications however, were identical to those in women with vaginal bleeding at inclusion In the group allocated to expectant management 2 women experienced a complete loss after 6 weeks and 25 (39%) underwent surgical evacuation on their own request. In 10 women allocated to active treatment a spontaneous loss occurred before the scheduled curettages No difference was found in the efficacy of expectant management between

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			curettage within a week All women had access to a telephone consultation at all times and emergency admission could be arranged if necessary <u>Outcomes assessed</u> 1. Treatment success (efficacy): Expectant management was considered to be successful if a spontaneous loss had occurred within 6 weeks. Active management was considered successful if the curettage vs. performed without the need for repeated curettage. Additional analysis compared uterine evacuation rates after 6 weeks including cross-overs (intention to treat) 2. Time until evacuation: All women were assessed clinically and sonographically during bi-weekly appointments until a complete evacuation of the uterus was established 3. Incidence of complications, including infection rate and surgical complications 4. Duration of vaginal bleeding: Patients reported amount of	although presumably the same reasons reported above also apply here) <u>Time to stop pain days, median, interquartile range</u> Expectant: 14 (7 to 24) Active: 11 (6 to26) NS <u>Time to stop bleeding days, median, interquartile range</u> Expectant: 17 (10 to 26) Active: 13 (9 to 17) P=0.04 <u>Need for blood transfusion (proportion of women and percentage)</u> Expectant: 1/64 (1.6) Active: 0 NS	women at >12 and ≤12 weeks of age This study has been designated 2002a

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			bleeding using a standardised diary. Bleeding was registered daily on a validated pictorial blood loss assessment chart 5. Duration of pain: Patients reported degree of abdominal pain using a standardised diary. Pain was scored on a visual analogue scale 6. Need for blood transfusion 7. Need for unplanned interventions: Emergency curettage was defined as the need to perform an unscheduled curettage because of severe bleeding or pain <u>Statistical analysis</u> Complication rate and duration of clinical symptoms were analysed according to the intention to treat principle. Outcome measures were analysed with the application of the t-test, Chi Square and Wilcoxon-Mann-Whitney test as appropriate. For the analysis of time until evacuation and time until bleeding or pain stopped, conventional survival analysis methods were applied and appropriate comparative tests		

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			(log-rank test) used. Medians were 50% cumulative probabilities as estimated with Kaplan-Meier analysis unless stated otherwise (25% and 75% respectively are shown in parentheses in the outcomes reported here)		

How effective is surgical management of miscarriage compared with medical management for improving women's clinical and psychological outcomes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Demetroulis,C., Saridogan,E., Kunde,D., Naftalin,A.A., A prospective randomized control trial comparing medical and surgical treatment for early pregnancy failure, Human Reproduction, 16, 365-369, 2001 **Ref Id** 65212 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To assess the effectiveness of single dose, 800 microgram, misoprostol delivered vaginally, compared with surgical evacuation for the treatment of early	**Sample size** N=80 **Characteristics** There were no statistically significant differences between the two groups, in terms of age, gestational age, parity, previous miscarriage, haemoglobin, and proportion of incomplete/missed miscarriages. **Age/years (mean (SD))** Medical: 30.4 (6.4) Surgical: 28.4 (6.6) **Gestational age/weeks (mean (SD))** Medical: 10.4 (1.8) Surgical: 9.5 (2.6) **Previous miscarriage (number/total)** Medical: 11/40 Surgical: 11/40 **Type of miscarriage (number/total (%))** **Medical:**	**Interventions** Medical management n=40 **Comparator** Surgical management n=40	**Details** 249 patients were seen for early pregnancy problems during the study period, of which 94 were eligible. However, 14 declined to participate. Participants were suitably randomised. Medical Patients were given 800 micrograms of misoprostol vaginally. After 8-10 hours, patients were assessed clinically and an ultrasound was done. Patients were discharged if their uterus had fully evacuated, otherwise they were booked for surgery. Surgical Patients were booked for surgical evacuation using "conventional methods". (no further details given) All patients were seen 10 days later. A repeat full blood count was done, and they were checked for infection and other possible complications. Variables were compared using chi-squared, student's t-test or Fisher's exact test.	**Results** **Need for unplanned intervention (number of events/total (%))** Medical: 7/40 (17.5) (all were surgical evacuations due to failure of medication) Surgical: 0/40 (0) p=0.005 **Incidence of side effects/complications (number of events/total (%))** **a. Nausea** Medical: 6/40 (15) Surgical: 22/40 (55) p<0.001 (no test statistic reported) **b. Vomiting** Medical: 3/40 (7.5) Surgical: 6/40 (15) Not significant **Need for a blood transfusion (number of events/total (%))**	**Limitations** **Loss to follow-up** Four patients from the medical group did not attend 10-day follow-up appointment. One was traced and declared no problems, but the other three could not be contacted. Five patients from the surgical group did not attend follow-up appointment, out of which three were traced and declared no problems. Those that were contacted by phone only reported satisfaction levels, not other outcomes such as duration of bleeding and side effects, therefore loss to follow-up for some outcomes is 10% for medical group, and 12.5% for surgical group. **Other information** Includes all types of miscarriage (incomplete, missed and anembryonic gestation) Time to passage of products of conception could not be

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pregnancy failure **Study dates** Not stated **Source of funding** Not stated	Incomplete: 14/40 (35) Missed/anembryonic sac: 26/40 (65) **Surgical:** Incomplete: 16/40 (40) Missed/anembryonic sac: 24/40 (60) **Inclusion criteria** Diagnosis of either: - spontaneous incomplete miscarriage (history of passage of tissue and/or heterogeneous echogenic material in the uterine cavity with a thickness of >15mm) - missed miscarriage (intrauterine gestation with a foetal pole measuring >6mm and no heart movements) - anembryonic gestation (diameter of gestational sac >20mm and no foetal pole visible) Up to 13 weeks gestation **Exclusion criteria** Complete miscarriage High temperature (>37.5 degrees) Low haemoglobin (<10.0 g/dl) History of serious medical or surgical condition History of medical condition		A sample size calculation was done, and the numbers needed were exactly met. (N=80) **<u>Outcomes reported</u>** **1. Need for unplanned intervention:** Surgical evacuation due to failure of treatment **2. Incidence of side effects/complications:** Nausea and vomiting were reported immediately after treatment. Method of assessment is not clear, however both were categorised as "mild". **3. Need for a blood transfusion** **4. Vaginal bleeding:** Patients were checked for signs of bleeding at 10 day follow-up appointment **5. Pain:** Self reported at 10 day follow-up **6. Unscheduled visits to a medical facility:** Reported as the number of women who visited their general practioner between the treatment and the follow-up period. However, it is unclear whether these visits were self-reported, or information was gained from	Medical: 0/40 (0) Surgical: 0/40 (0) **<u>Duration of bleeding/days (mean (SD))</u>** Medical: 4.7 (2.4) Surgical: 4.9 (3.0) (Not significant) **<u>Pain</u>** **a. Incidence (number of events/total (%))** Medical: 19/36 (52.7) Surgical: 26/35 (74.3) **b. Duration/days (mean (SD))** Medical: 4.7 (2.4) n=36 Surgical: 2.8 (1.6) n=35 **<u>Unscheduled visits to a medical facility</u>** **a. Visits - outpatient (number of events/total (%))** Medical: 2/36 (5.6) (both due to vaginal bleeding - they were prescribed antibiotics) Surgical: 5/35 (14.3) (2 due to offensive discharge (given antibiotics), 2 due to vaginal bleeding (given antibiotics),	reported, because many of the patients noticed that they had miscarried while they slept.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	which is a contraindication to prostaglandin treatment (asthma, hypertension, glaucoma, sickle cell disease, mitral stenosis) Heavy bleeding requiring evacuation of the uterus Under 16 years old Unable to give informed consent		medical records. **7. Satisfaction:** Reported at 10 day follow-up appointment.	1 due to abdominal pain (given analgesics only)) **Measures of satisfaction** **a. Reported satisfaction (number of women/total (%))** Medical: 33/37 (89.2) (all these were women who had successful medical treatment) Surgical: 22/38 (57.9) (long waiting time for operation was the main reason for dissatisfaction, as well as uncertainty of the time of the operation) p=0.000007	
Full citation Egarter,C., Lederhilger,J., Kurz,C., Karas,H., Reisenberger,K., Gemeprost for first trimester missed abortion, Archives of Gynecology and Obstetrics, 256, 29-32, 1995 **Ref Id** 65227 **Country/ies where the**	**Sample size** N=87 **Characteristics** **Age/years (mean)** Medical: 29.8 Surgical: 30.6 **Gestational age/weeks (mean)** Medical: 10.1 Surgical: 10.1	**Interventions** Medical management n=43 **Comparator** Surgical management n=44	**Details** Serum hCG was determined pre-operatively, and when there was doubt concerning the last menstrual period, hCG was repeated to rule out intact early pregnancy. If hCG levels failed to increase by at least 200mIU/ml per day, an abnormal intra-uterine pregnancy was assumed. Eligible patients were randomly assigned (method not stated) to each group.	**Results** **Need for unplanned intervention (number of events/total (%))** Medical: 10/43 (23.2) (3 for failure of up to 6 doses of medical treatment, 2 for incomplete miscarriage, 2 for persistent bleeding, 1 for severe pain, 2 expelled a hydatidiform mole and needed curettage on days 15 and 30 for	**Limitations** **Methods** Method of randomisation not stated. Method of data collection is not stated in many cases, e.g. for side effects and complications Length of follow-up period is not reported **Population** Participants include one

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Austria **Study type** Randomised controlled trial **Aim of the study** To compare the application of a prostaglandin E_1 derivative with conventional surgical termination of pregnancy by cervical dilation and curettage. **Study dates** Not stated **Source of funding** Not stated	**Inclusion criteria** Patients with 8-12 weeks of amenorrhea with two ultrasonograms which failed to show progressive intrauterine pregnancy **Exclusion criteria** Not stated		<u>Medical</u> 1mg synthetic PGE_1 derivative (gemeprost suppository) was given every 3 hours up to a maximum daily dose of 3mg for 2 days. Patients were given surgery if gemeprost failed. <u>Surgical</u> Cervical dilation under general anaesthesia with evacuation by curettage. The tissues obtained during surgery and expelled after medical treatment were examined. Determination of hCG levels were performed on the day after expulsion and again after that until hCG was no longer detectable. Bleeding and pain in each group were treated according to "established clinical guidelines." Statistical analysis was performed using ANOVA and student's t-test. **<u>Outcomes reported</u>** **1. Need for unplanned intervention** Any further intervention reported, including surgery for failure of treatment, further investigation or due to surgical	persistent mild bleeding) Surgical: 4/44 (9.1) (1 perforation occurred during dilation requiring laparotomy, 1 fundal perforation occurred requiring enterotomy with end-to-end anastomosis, 1 required repeat curettage due to persistent bleeding, and 1 complained of abdominal pain and had a laparoscopy revealing a tubal ectopic pregnancy) **<u>Incidence of side effects/complications (number of events/total (%))</u>** **a. Surgical complications** Medical: NR Surgical: 2/44 (4.5) (perforations, see details above) **b. Nausea** Medical: 7/43 (16.3) Surgical: 4/44 (9.1) **c. Vomiting** Medical: 2/43 (4.7) Surgical: 0/44 (0) **<u>Duration of bleeding/days (mean (SD))</u>** Medical: 3.7 (4.8)	woman who was found to have an ectopic pregnancy, and two patients had a hydatiform mole. **Other information** Missed miscarriage only Mean time to expulsion following administration of $PGE_1$was 8.8 (SD 4.5) hours (range 3.5-29.7)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			complications. **2. Incidence of side effects/complications** Method of assessment and data collection is not stated. Follow-up period is not stated **3. Duration of bleeding** Reported as duration of "moderate to mild" bleeding. Follow-up period is not stated **4. Pain** The time scale for the reported abdominal pain is unclear. **5. Length of hospital stay** Reported in days. Method of data collection not stated.	Surgical: 2.9 (3.2) **Pain** **a. Incidence of abdominal pain (number of women/total (%))** Medical: 1/43 (2.3) Surgical: 2/44 (4.5) **Length of hospital stay/days (mean (SD))** Medical: 3.9 (1.1) Surgical: 3.4 (1.9)	
Full citation Harwood,B., Nansel,T., National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial., Quality of life and acceptability of medical versus surgical management of early pregnancy failure, BJOG: An International Journal of Obstetrics and Gynaecology, 115, 501-508, 2008	**Sample size** N=607 **Characteristics** There were no significant differences between the two groups. Further details can be found in Zhang et al. 2005. **Inclusion criteria** Inclusion in original trial (see	**Interventions** Medical management n=457 **Comparator** Surgical management n=150	**Details** This is a planned secondary analysis of Zhang et al. 2005, therefore, full details of the medical treatment and surgical methods can be found elsewhere in the evidence table. Participants completed questionnaires assessing Quality of Life and treatment acceptability on their visit 2 weeks after treatment. The questionnaires were completed in private and and all	**Results** **Emotional and psychological outcomes** **a. Social functioning/100 (mean (SD))** Medical: 44.53 (10.72) Surgical: 45.12 (11.51) p=0.57 (t=-0.57)	**Limitations** **Single measurement** No baseline or long term information is available **Loss to follow-up** Loss to follow-up from initial trial was 6.9%. Those who did not complete the quality of life questionnaire were younger (mean age 27.4 vs. 30.2, p=0.02) and a greater percentage were of lower education status (p=0.04).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 65286 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To compare quality of life and acceptability of medical versus surgical treatment of early pregnancy failure **Study dates** March 2002 to March 2004 **Source of funding** National Institute of Child Health and Human Development National Institutes of Health	Zhang et al. 2005) Received study treatment Follow-up diary and questionnaire data available for analysis **Exclusion criteria** See Zhang et al. 2005		participants were given instructions for completion, and the option of having a member of the research team read it to them. If women did not present for their follow-up visit, the questionnaires were not done at another time, but every effort was made to contact them, and collect their symptoms diaries (completed daily between treatment and follow-up). **<u>Outcomes measured</u>** **1. Emotional/psychological outcomes** Social functioning is reported as part of the Short Form-36 Revised (SF-36R) quality of life scale. The questionnaire was administered on the follow-up visit 2 weeks after treatment. Social functioning measures the extent to which health problems interfere with usual social activities. It is measured on a scale of 1-100, in which 1 corresponds to total impairment and 100 corresponds to no impairment. (Note: this paper also reported bodily pain as a component of the SF-36R scale, however it is not reported here, because pain has already been reported for the same population in Zhang et al. 2005)		**Other information** This is a secondary analysis of Zhang et al. 2005. Original trial participants were randomised in a 3:1 ratio.

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Full citation Moodliar,S., Bagratee,J.S., Moodley,J., Medical vs. surgical evacuation of first-trimester spontaneous abortion, International Journal of Gynaecology and Obstetrics, 91, 21-26, 2005 **Ref Id** 65379 **Country/ies where the study was carried out** South Africa **Study type** Randomised controlled trial **Aim of the study** To determine whether management of incomplete first-trimester miscarriage with vaginal misoprostol in an under-resourced setting is a viable treatment option. **Study dates** October 2003 to April 2004	**Sample size** N=94 **Characteristics** Not reported, but they report that groups were "well matched" for demographic and clinical data. **Inclusion criteria** Incomplete miscarriage, diagnosed by: - positive pregnancy test - history of passage of tissue and blood - open cervical os with palpable retained products of conception - heterogenous material with a thickness greater than 15mm in the uterine cavity on ultrasound examination Up to 13 weeks of pregnancy **Exclusion criteria** Complete miscarriage (endometrial thickness	**Interventions** Medical management n=47 **Comparator** Surgical management n=47	**Details** Women presenting to the Gynaecology Outpatients Department at King Edward VII Hospital, Durban were eligible if they fulfilled the inclusion criteria. A sample size calculation calculated that a study with 80% power to show a difference of 20% would require 94 women. 119 women presented with bleeding in early pregnancy, of which 19 did not meet the inclusion criteria and 6 elected not to participate. 94 women were suitably randomised. <u>Medical</u> 600 micrograms of misoprostol was inserted in to the posterior fornix of the vagina on day 0. They were prescribed an analgesic if they experienced pain. Alll women were examined and had an ultrasonographic examination the next day. They were discharged if a complete miscarriage was diagnosed (i.e. a closed cervical os and endometrial thickness <15mm). Those who did not have a complete miscarriage received a second dose of misoprostol on day 1, and were told to	**Results** **<u>Need for unplanned intervention (number of events/total (%))</u>** Medical: 4/47 (8.5) (4 women required surgery after 1 week due to failure of the medical treatment) Surgical: 0/47 (0) Success rate was not significantly different (p=0.12) **<u>Incidence of side effects/complications (number of events/total (%))</u>** **a. Infection (endometritis)** Medical: 0/47 (0) Surgical: 0/47 (0) Note: White blood cell counts were also done on day 14, and there was no significant difference between the two groups. (Mean difference of 0.221 (95% CI: -0.51 to 0.96)) **b. Nausea** Medical: 0/47 (0) Surgical: 1/47 (2.1) **c. Vomiting** Medical: 0/47 (0) Surgical: 1/47 (2.1)	**Limitations** **Other information** Incomplete miscarriage (bleeding is part of the inclusion criteria) **<u>Intention-to-treat</u>** All women received the treatment that they were allocated to. There was no loss to follow-up at 2 weeks.

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Source of funding Not stated	<15mm and closed cervical os) Fever (>37.5 degrees) Haemoglobin <10g/dL Contraindication to prostaglandin therapy (asthma, hypertension, glaucoma, mitral stenosis) Profuse bleeding after manual removal of products of conception from the external cervical os		report after a week. After a week, if miscarriage was not complete, surgical management was performed. <u>Surgical</u> Women received an IV infusion of 20U of oxytocin per litre of normal saline solution. Sharp curettage was then performed under general anaesthesia within 6 hours. No antibiotic prophylaxis was given. Oral analgesia was prescribed and the oxytocin infusion was continued for 6 hours post-operatively. All women were discharged the next day and seen 2 weeks later. All women in the study were seen 14 days after a diagnosis of complete miscarriage. They had a full blood count and were checked for the presence of hCG. If present, they were seen weekly until a negative result was obtained. Pearson chi-squared and Man-Whitney tests were used to test significance. **<u>Outcomes reported</u>** **1. Need for unplanned intervention**	**d. Diarrhoea** Medical: 1/47 (2.1) Surgical: 0/47 (0) **<u>Duration of bleeding/days (mean (SD))</u>** Medical: 7.0 (3.4) Surgical: 4.4 (3.2) Significant (MD=2.57 (95% CI: 1.2-3.9)) **<u>Pain</u>** **a. Severity/10 (mean (SD))** Medical: 5.6 (2.7) Surgical: 4.1 (3.1) Not significant. (MD=1.55 (95% CI 0.36-2.75)) **<u>Measures of satisfaction</u>** **a. Satisfaction score/10 (mean (SD))** Medical: 8.43 (2.1) Surgical: 7.30 (1.87) Not significant (MD=1.13 (95% CI 0.332-1.92) **b. "Would choose again" (number of events/total (%))** Medical: 44/47 (93.6) Surgical: 19/47 (40.4) p<0.05 (RR=2.32 (95% CI 1.62-3.30)	

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			The number of women requiring further surgery as a result of failure of the initial treatment. **2. Incidence of side effects/complications** This was self-reported at the 2 week follow-up visit. Infection is reported as the number of women with endometritis. White blood cell counts were also done. (note: surgical complications are not reported) **3. Duration of bleeding** Reported at 2-week follow-up visit. **4. Pain** Measured using visual analogue scale. **5. Measures of satisfaction** Satisfaction was measured using visual analogue scale. Women were also asked if they would elect to have the same treatment if they were to have a miscarriage again.		
Full citation Muffley,P.E., Stitely,M.L., Gherman,R.B., Early intrauterine pregnancy failure: a randomized trial of medical versus surgical treatment, American	**Sample size** N=50 **Characteristics**	**Interventions** Medical management n=25 **Comparator**	**Details** The trial was conducted at the Naval Medical Centre, Portsmouth. Patients were referred by resident and staff providers from the hospital's obstetrics and gynaecology	**Results** **<u>Need for unplanned intervention (number of events/total (%))</u>** Medical: 10/25 (40)	**Limitations** **<u>Loss to follow-up</u>** One patient from each arm (4%) was lost to follow-up due to military transfer, however the point at which they were lost is not reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Obstetrics and Gynecology, 187, 321-325, 2002 **Ref Id** 65384 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To determine whether medical treatment of early pregnancy failure represents a reasonable alternative to surgical therapy **Study dates** June 1999 to March 2000 **Source of funding** Supported by the Chief, Navy Bureau of Medicine and Surgery, Washington DC, Clinical Investigation Program	**Age/years (mean (SEM))** Medical: 29.7 (1.2) Surgical: 25.5 (0.9) (p=0.009) **Gravidity (mean (SEM))** Medical: 2.6 (0.3) Surgical: 2.3 (0.3) **Estimated gestational age/weeks (mean (SEM))** Medical: 8.2 (0.4) Surgical: 8.3 (0.4) **Previous miscarriage (number/total (%))** Medical: 9/25 (36) Surgical: 6/25 (24) **Initial hCG titre/ mIU/mL(mean (SEM))** Medical: 37684 (6066) Surgical: 18509 (3967) (p=0.02) **Inclusion criteria** Aged 18-50 years old Proved failed intrauterine	Surgical management n=25	clinics. All patients underwent a transvaginal ultrasound prior to enrolment, to confirm foetal non-viability. Patients were then suitably randomised to medical or surgical treatment. Medical 800 micrograms (four x 200 microgram tablets) were placed within the posterior vaginal fornix. Patients then remained in a semi-prone position and were observed in the clinic for a minimum of two hours. Patients were given prescriptions for acetaminophen with codeine (instructions to take every 4-6 hours) and ibruprofen (to take every 4 hours). They were contacted 6-10 hours after medication dosing and asked about bleeding, diarrhoea, fever, chills, nausea or emesis. Patients were asked to return 24 hours later, and another ultrasound was done. If there was evidence of persistent pregnancy tissue, another 800 microgram dose of misoprostol was given. 16/25 patients required two doses. 24 hours later, on study day 3, another	(10 underwent curettage after failure of medical treatment. Note - they also later report that one woman had curettage for haemorrhage, but she appears to have been included in the 10 women previously reported to have had curettage) Surgical: 1/25 (4) (1 woman, who had previously undergone cryotherapy and two cervical loop electrocautery excisional procedures, had a uterine perforation, requiring exploratory laparotomy with bowel repair and primary repair of the uterine defect) **Incidence of side effects/complications (number of events/total (%))** **a. Surgical complications** Medical: 0/25 (0) Surgical: 2/25 (8) (1 woman, who had previously undergone cryotherapy and two cervical loop electrocautery excisional procedures, had a uterine perforation, requiring exploratory laparotomy with bowel repair and primary repair of	2 patients in the surgery group had spontaneous pregnancy loss before their scheduled procedure, Intention-to-treat analysis was done in the paper, and is reported here. **Sample size** Their sample size calculation assumed a success rate of 90% in the misoprostol group. Because they only had a sucess rate of 60%, they calculate that a sample size of 814 patients would be needed to achieve 80% power. **Variable misoprostol administration** Some of the vaginal misoprostol doses were coadministered with a vaginal lubricant, which could have resulted in non-uniformity of dosing or variable absorption patterns. **Other information** Missed miscarriage only Mean time to initial tissue expulsion in misoprostol group was 12.6 hours (SEM 2.7) after medication insertion.

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	pregnancy, defined as one out of: - embryonic pole 5-14mm with no embryonic cardiac activity - irregular intrauterine gestational sac with a mean diameter of >16mm and no embryonic pole - abnormal growth on ultrasound image over a minimum of 7 days - yolk sac present with an abnormal increase in hCG (<50%) over a 48 hour period. <12 weeks gestation, as determined by ultrasonographic dating **Exclusion criteria** Inability to confirm pregnancy failure or intrauterine location of the gestation Inability or refusal of patients to adhere to study follow-up requirements Excessive vaginal spotting (defined as soaking more		vaginal ultrasound scan was done, and if the gestational sac was present, medical treatment was considered a failure and patients underwent surgery. <u>Surgical</u> Surgical evacuation was completed by suction curettage. Surgery was performed by obstetric residents in the operating room under direct staff supervision. Subjects were administered by either paracervical blockade, intravenous sedation, spinal anaesthesia or general anaesthesia. After all treatments, patients had hCG and complete blood counts. hCG was monitored weekly until negative values were achieved. In the medical arm, if the hCG did not become negative, the patient underwent surgery. A sample size calculation required a population of 38, however they planned to enrol 50 to account for drop-out. All subjects were analysed on an intention-to-treat basis, and statistical analysis was done using unpaired t-tests, chi-squared analysis, Fisher's	the uterine defect. 1 had a 2-L haemorrhage that resolved only after IM 15-methyl prostaglandin F2-alpha administration) **b. Nausea** Medical: 12/25 (48) Surgical: NR **c. Vomiting** Medical: 1/25 (4) Surgical: NR **d. Diarrhoea** Medical: 12/25 (48) Surgical: NR **<u>Need for a blood transfusion (number of events/total (%)</u>** Medical: 0/25 (0) Surgical: 0/25 (0)	**<u>Satisfaction</u>** The trial did not directly report satisfaction as an outcome, however the authors note in the discussion that there was a high degree of contentment among women who received medical treatment.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	than one vaginal pad per hour) Anaemia (defined as haemoglobin concentration of <10mg/dL) Unstable vital signs (tachycardia or hypotension) Maternal coagulopathy Signs or symptoms of infection History of asthma or cardiac disease Known allergy to prostaglandins or previous adverse reaction <18 or >50 years old Foetal gestational age of >12 weeks Open cervical os on speculum examination (as defined by allowing passage of a ring forceps)		exact test and Mann-Whitney test were used as appropriate. **Outcomes reported** **1. Need for unplanned intervention** Reports need for further surgery due to failure of treatment or complications **2. Incidence of side effects/complications** Women in the medical arm were contacted 6-10 hours after treatment and asked about symptoms. It is not reported if surgical patients were contacted. **3. Need for a blood transfusion** Criteria for judging need is not reported.		
Full citation Niinimaki,M., Jouppila,P., Martikainen,H., Talvensaari-Mattila,A., A	**Sample size** N=98	**Interventions** Medical management n=49	**Details** The study was conducted at the Department of Gynaecology and Obstetrics of	**Results** **Need for unplanned intervention (number of**	**Limitations** **Loss to follow up** 6% women were lost to follow up for the outcomes of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage, Fertility and Sterility, 86, 367-372, 2006 **Ref Id** 65399 **Country/ies where the study was carried out** Finland **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy of medical treatment to surgical uterine evacuation, and patient satisfaction in each group **Study dates** February 4th 2003 to 8th December 2004 **Source of funding** Not stated	**Characteristics** **Age/years (mean (SD))** Medical: 30.9 (6.9) Surgical: 29.3 (6.7) **Gestation/days (mean (SD))** Medical: 74.7 (14.2) Surgical: 73.6 (13.5) **Previous miscarriages (mean (SD))** Medical: 0.4 (0.7) Surgical: 0.4 (1.0) **Anembryonic pregnancies (number/total (%))** Medical: 25/49 (51.0) Surgical: 24/49 (49.0) **Inclusion criteria** Aged >18 years old Positive pregnancy test (urine or serum hCG) One of the following: - an inhomogeneous mass with diameter of 15-50mm in	**Comparator** Surgical management n=49	Oulu University Hospital. Clinical examination and transvaginal ultrasonography were performed on each patient to confirm eligibility. The amount of bleeding and opening stage of cervix were evaluated at the clinical examination. A power calculation found a required sample size of 40 patients in each group. 98 patients were suitably randomised to either surgical or medical treatment. Medical Patients received 200mg of mifepristone orally at the primary visit to the clinic. Patients were advised to come to the clinic 24-72 hours later, when the nurse applied 0.8mg (4 tablets) of misoprostol in to the posterior fornix of the vagina. Observation was for a minimum of 4 hours. Patients were routinely given prophylactic oral analgesia (combination of paracetamol and codeine or metamitsol and pitofenon) before administration of misoprostol. Oral paracetamol (with or without codeine) or IM tramadol/pethidine were given during observation at the patients' request.	**events/total (%))** Medical: 6/49 (12.2) (5 curettages due to failure of medical treatment, 1 emergency curettage following randomisation due to bleeding) Surgical: 1/49 (2.0) (1 emergency curettage following randomisation, due to bleeding) No statistical test is reported for this difference, however the difference between the number of curettages due to failure of primary treatment (5 vs. 0) was calculated by the authors to be non-significant. **Incidence of side effects/complications (number of events/total (%))** **a. Infection (2 month follow-up)** Medical: 1/49 (2.0) Surgical: 7/49 (14.3) p=0.03 (CI 0.97-35.57) (Note: 1 surgical patient was admitted for IV antibiotics, but the others were given oral antibiotics) *This outcome is currently not included in the meta-analysis, due to the long length of follow-up in*	satisfaction and pain, however the loss was equal in both groups. **Other information** Includes incomplete miscarriage, missed miscarriage and anembryonic pregnancy **Intention-to-treat** Medical: Out of 49 women allocated to medical treatment, 48 received the allocated intervention. 1 woman received an emergency curettage for bleeding. Surgical: Out of 49 women allocated to surgery, 47 received it. 1 woman had an emergency curettage, and 1 had a complete miscarriage prior to planned curettage. **Population** This paper does not specifically state that women had to be <13 weeks gestation, however later in the paper it mentions "first trimester miscarriages." It includes all kinds of miscarriages, including spontaneous miscarriages with incomplete expulsion. The authors state

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	the uterine cavity (incomplete miscarriage) - empty amnion sack with diameter >15mm (anembryonic pregnancy) - crown-rump length more than 5mm without signs of foetal heart function (missed miscarriage) **Exclusion criteria** Profuse bleeding Signs of endometritis Allergies to either mifepristone or misoprostol Severe asthma Suspected case of molar or extra uterine pregnancy		<u>Surgical</u> Curettage was performed with IV propofol anaesthesia within 0-5 days of the primary examination. Pre-operative misoprostol (0.4mg) was given at least 2 hours before to ripen the cervix, if it was necessary (mostly for nulliparous patients). All patients were given IV fentanyl and a non-steroid anti-inflammatory or paracetamol per rectum during the operation. Post-operative observation in the day care unit was for a minimum of two hours. Additional analgesia (fentanyl 50 micrograms) was given during the operation if needed (pain reaction during intervention) or afterwards at patients request (fentanyl, ketoprofein or paracetamol). Clinical outcomes were evaluated by confirming urine pregnancy test 5-6 weeks later at the follow-up visit. Treatment was considered successful when no subsequent intervention (curettage) was needed. Transvaginal ultrasonography was not routinely performed. At the point of treatment, women were given a questionnaire to be returned at the 5-6 week visit. Total follow-up was 2	*comparison to other studies.* <u>**Pain**</u> **a. Incidence of pain (number of events/total (%))** Medical: 29/46 (63.0) Surgical: 17/46 (37.0) p=0.02 <u>**Unscheduled visit to a medical facility**</u> **a. Admission (number of women/total (%))** Medical: 3/49 (6.1) (the three women were admitted for intensive pain during treatment: 1 after mifepristone, 2 after misoprostol) Surgical: 1/49 (2.0) (patient was admitted for 3 days, for treatment with IV antibiotics for infection) *Admissions for issues other than pain and infection are not reported, therefore this outcome has not been included in the meta analysis.* <u>**Measures of satisfaction (number of women/total (%))**</u> **a. Reported satisfaction** Medical: 37/42 (88.1) Surgical: 44/44 (100) p=0.02	that their high success rate, compared to previous papers studying missed miscarriage/anembryonic pregnancies, could potentially be due to biased selection of study population. No further details regarding proportion of incomplete miscarriages are given.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			months, and complications during this period were obtained from hospital records. Statistical analysis was performed using Fisher's exact test. **<u>Outcomes reported</u>** **1. Need for unplanned intervention** Includes women who required surgery due to failure of initial treatment, or required an emergency surgery following randomisation. **2. Incidence of side effects/complications** Details of complications were obtained from hospital records, up to a follow-up of 2 months. **3. Pain** Self-reported in a questionnaire given to patients, that they returned during a follow-up visit 5-6 weeks after treatment. Pain was defined as either "none or mild" or "moderate or intensive," and the incidence reported here is the reported incidence of	(This analysis excludes women who were neither satisfied or dissatisfied, which was 4 women in the medical group and 2 women in the surgical group) **b. "Would choose again"** Medical: 32/46 (70.0) Surgical: 42/46 (91.3) p=0.02	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			"moderate or intensive" pain. **4. Unscheduled visit to a medical facility** The number of women who had to be admitted during treatment, or following treatment as a result of infection. **5. Satisfaction** Self-reported in a questionnaire given to patients, that they returned during a follow-up visit 5-6 weeks after treatment. Measured by satisfaction, and the proportion who would choose the method again.		
Full citation Sahin,H.G., Sahin,H.A., Kocer,M., Randomized outpatient clinical trial of medical evacuation and surgical curettage in incomplete miscarriage.[Erratum appears in Eur J Contracept Reprod Health Care 2002 Mar;7(1):iv], European Journal of Contraception and Reproductive Health Care, 6, 141-144, 2001 **Ref Id**	**Sample size** N=80 **Characteristics** There were no significant differences between the two groups in terms of age, gravida, parity, gestational age or anterior-posterior diameter. **Inclusion criteria** History of vaginal bleeding	**Interventions** Medical management n=40 **Comparator** Surgical management n=40	**Details** Women were randomised to either medical or surgical management (method of randomisation not stated). Medical Women were given 200 micrograms of misoprostol four times daily, after the application of 200 micrograms intravaginal misoprostol for five days. They were recommended to use simple analgesia. Surgical Surgical curettage was	**Results** **Need for unplanned intervention (number of events/total (%))** Medical: 1/40 (1 woman had surgical curettage after the end of the observation period. An additional woman had bleeding lasting 3 weeks, but she refused surgery and was well by the end of the third week) Surgical: 0/40 *(Note: they state that medical management failed*	**Limitations** **Randomisation** Method not stated **Anaesthesia** An unknown proportion of women in the surgical group received local not general anaesthesia, which affected measures of satisfaction. **Other information** Incomplete miscarriage (inclusion criteria were history of vaginal bleeding and passage of some products of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
65460 **Country/ies where the study was carried out** Turkey **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy and safety of misoprostol in outpatient medical evacuation with surgical curettage in uncomplicated spontaneous miscarriage **Study dates** Not stated **Source of funding** Not stated	Cramping abdominal pain Passage of some products of conceptus Good health Haemoglobin level >9g/dl Haemodynamically stable Estimated gestational age of 10 weeks or less Anterior-posterior diameter of retained products of the conceptus were <50mm No contraindication to prostaglandin treatment **Exclusion criteria** Foul-smelling products of the conceptus Temperature above 37.5 degrees Excessive vaginal bleeding requiring immediate surgical evacuation Haemodynamic instability		performed. Due to lack of facilities, general anaesthesia could not be used in all cases, therefore local anaesthesia was sometimes used (proportion not stated). All women were reviewed 10 days later. Outcomes were analysed using Mann-Whitney U and chi-squared tests. **Outcomes reported** **1. Need for unplanned intervention** They report the need for further intervention due to failure of the medical protocol. **2. Incidence of side effects/complications** This was reported at the 10 day follow-up visit. **3. Duration of bleeding** This was reported at the 10 day follow-up visit, as the number of days with bleeding requiring sanitary protection. **4. Measures of satisfaction** The paper reports dissatisfaction rate, as measured at 10 days after treatment.	*in 2 women, as detailed above, however then they report a success rate of 93.33% for medical management (not 95%) - reasons for this discrepancy are not stated)* **Incidence of side effects/complications (number of events/total (%))** **a. Infection** Medical: 1/40 (2.5) Surgical: 2/40 (5) (The authors report that the patients recovered quickly with broad-spectrum antibiotic therapy. There is no report of whether treatment was inpatient or outpatient.) Note: they also state that no important side effects were noted in the medical group, but give no further details **Duration of bleeding/days (mean (SD))** Medical: 6.45 (2.23) Surgical: 4.90 (2.19) p=0.002 (no test statistic given)	the conceptus)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				<u>Measures of satisfaction</u> **a. Reported satisfaction (number of events/total (%))** Medical: 39/40 (97.5) Surgical: 26/40 (65) (Dissatisfaction in the surgical group was as a result of the lack of general anaesthesia) p=0.001	
Full citation Shelley,J.M., Healy,D., Grover,S., A randomised trial of surgical, medical and expectant management of first trimester spontaneous miscarriage, Australian and New Zealand Journal of Obstetrics and Gynaecology, 45, 122-127, 2005 **Ref Id** 65485 **Country/ies where the study was carried out** Australia **Study type** Randomised controlled trial **Aim of the study**	**Sample size** N=24 **Characteristics** There were no marked or systematic differences between the groups with regards to gestation, woman's age, reproductive history, method of diagnosis, days of bleeding, pain, haemoglobin or white cell count. No further details are reported. **Inclusion criteria** Gestational age of 13 weeks or less Bleeding not excessive Haemodynamic system	**Interventions** Medical management n=12 **Comparator** Surgical management n=12	**Details** Women presenting to the emergency departments of five Melbourne metropolitan hospitals were assessed for eligibility. They were suitably randomised to curettage, medical or expectant management, stratified by hospital and gestation (<7 weeks, 8-10 weeks, 11-13 weeks). <u>Medical</u> Two tablets of 200 microgram misoprostol were placed into the posterior fornix of the vagina. A repeat dose was given 4-6 hours later if miscarriage was still incomplete. <u>Surgical</u> Either aspiration curettage or D&C was done under general anaesthetic. Pain relief, Rh	**Results** **<u>Need for unplanned intervention (number of events/total (%))</u>** Medical: 2/10 (20) (1 surgical evacuation due to retained products visible at 10-14 day follow-up; 1 surgical evacuation due to patient request after not passing any products after 2 doses of misoprostol) Surgical: 0/11 (0) **<u>Incidence of side effects/complications</u>** **a. Confirmed infection by 2 weeks (number of events/total (%))** Medical: 2/11 (1.8) Surgical: 0/12 (0) *(This is the outcome used for the meta-analysis of infection)* **b. Suspected infection by**	**Limitations** **<u>Loss to follow-up and missing data</u>** Medical: 13 women were initially randomised to medical treatment, but 1 withdrew after randomisation, and is not included in the analyses. 1 woman had a complete evacuation before misoprostol was given. Therefore, 11 women received misoprostol. 1 further woman was lost by 14 day follow-up, and 1 more by 8 weeks. Surgical: 11 women received surgery. 1 woman did not receive surgery because she requested medical management following randomisation. 1 was lost to follow-up by 8 weeks. For various outcomes, there

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare the effectiveness and safety of medical and expectant management with surgical management for first trimester incomplete or inevitable miscarriage **Study dates** June 1999 to December 2000 **Source of funding** Department of Human Services, Victoria Best Practice Initiatives Grant MBF Medical Research Award	stable Temperature not more than 37.5 degrees No history of current serious systemic medical or surgical condition Use of prostaglandins not contraindicated (allergy, mitral stenosis, diabetes, blood dyscrasia, haemolytic disease, glaucoma, sickle cell anaemia, hypertension, epilepsy or severe asthma) 18 years or older Not taking anticoagulants or oral corticosteroids Singleton pregnancy No intrauterine device in situ Sufficient familiarity with English to complete written questionnaires **Exclusion criteria** Non-viable intrauterine pregnancy diagnosed on ultrasound but no vaginal bleeding		immunisation, use of prophylactic antibiotics and provision of information was done. All women were requested to return for a follow-up visit at the hospital or with their doctor 10-14 days later. Suspected retained products of conception were confirmed by ultrasound prior to unplanned surgical evacuation. Some outcomes were also assessed at 8 weeks post-recruitment. **Outcomes reported** **1. Need for unplanned intervention** Hospital staff recorded details of further investigations and treatment at 10-14 days. When care was provided elsewhere, details were obtained from the practitioner. A successful treatment was assumed if neither the woman's clinical record or the questionnaires indicated that she had received further treatment. **2. Incidence of side effects/complications** Infection was confirmed if vaginal swabs showed evidence of infection, or two of the following criteria were met: white cell count of $15x10^9$/mL	**2 weeks (number of events/total (%))** Medical: 1/11 (9.1) Surgical: 1/12 (8.3) **c. Confirmed infection by 8 weeks (number of events/total (%))** Medical: 2/10 (20) Surgical: 0/11 (0) **d. Suspected infection by 8 weeks (number of events/total (%))** Medical: 1/10 (10) Surgical: 2/11 (18.2) **e. Nausea (number of women)** Medical: 2/11 Surgical: 1/12 **f. Vomiting (number of women)** Medical: 1/11 Surgical: 0/12 **g. Diarrhoea (number of women)** Medical: 1/11 Surgical: 0/12 **Need for a blood transfusion (number of events/total (%))** Medical: 0/12 (0)	is unexplained missing data, e.g. duration of bleeding. **Lack of intention-to-treat** 12 women were initially randomised to the surgical group, however 1 woman stated a preference for misoprostol. For the primary outcome of success of treatment (i.e. need for further intervention), the n for surgical group has been reported as n=11, and similarly for psychological outcomes. **Small sample size** The original trial was planned to be 831 women. Recruitment stopped because, after repeated attempts to enlist support from hospital staff, fewer than 50% of eligible women were being approached to participate. **Other information** Incomplete miscarriage only (excludes women who had no vaginal bleeding) **Scales used for psychological outcomes and pain** The technical team looked for

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			or higher, fever, smelly vaginal discharge or prescription of antibiotics. If one criterion was met, a suspected infection was recorded. Incidence of infection is reported within 2 weeks of treatment. Nausea, vomiting and diarrhoea appear to have been reported at the 10-14 day follow-up visit, although this is not categorically stated; therefore the technical team had to assume the denominator. **3. Need for a blood transfusion** Haemorrhage is defined as the need for a blood transfusion. **4. Duration of bleeding** Hospital staff recorded bleeding at the 10-14 day visit, and patients completed questionnaires at 10-14 days and 8 weeks. However, it is unclear which results were used to judge duration and degree of pain. **5. Pain** Hospital staff recorded pain at the 10-14 day visit, and patients completed questionnaires at 10-14 days and 8 weeks. However, it is unclear which results were used to judge duration and degree of pain. Severity was	Surgical: 0/12 (0) **Duration of bleeding/days (number/total (%))** **Medical:** <3: 2/8 (25.0) 4-8: 3/8 (37.5) >9: 3/8 (37.5) **Surgical:** <3: 6/11 (54.6) 4-8: 1/11 (9.1) >9: 4/11 (36.4) **Pain** **a. Duration/days (median (range))** Medical: 3.0 (0.2-16.0) Surgical: 2.0 (0.2-12.0) They state "no difference" but no p-value or test statistic is reported **b. Severity (median (range))** Medical: 3 (1-8) Surgical: 3 (1-10) Significance is not reported for this measure, only for degree of worst pain (not significant) **Measures of satisfaction** **a. "Would choose again" (number of women/total (%))**	information on how to interpret the results of the emotional and psychological outcomes as this was not reported in the paper. Anxiety is reported as the number of women in each group scoring over 11, which is a score considered to be "abnormal." General mental health is reported using results of the SF-36 scale, using a questionnaire completed at 2 weeks. The scale is scored out of 100, with lower scores indicating greater impairment. The technical team also had to research the range of scores possible in the Brief Pain Inventory. It is out of 10, with 10 indicating worse pain. **Reporting of mental health** It is unclear whether they are reporting the "mental health" subscale of the SF-36, or whether they have combined the various components of mental health within the SF-36 to give a combined score.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			measured using a modified form of the Brief Pain Inventory (no further details given). **6. Satisfaction** Measured as the number of women who, if time went backwards, would choose the same method again. 7**. Emotional and psychological outcomes** Anxiety was measured at 2 weeks using Hospital Anxiety and Depression Scale (HADS). Anxiety is reported as the number of women in each group scoring over 11. General mental health is reported using results of the SF-36 scale, using a questionnaire completed at 2 weeks. The scale is scored out of 100, with lower scores indicating greater impairment.	Medical: 3/7 (42.9) Surgical: 6/11 (54.5) **<u>Emotional and psychological outcomes</u>** **a. Mental health/100 (mean (SD))** Medical: 36.7 (13.8) (n=11) Surgical: 42.0 (14.5) (n=11) (These denominators have been assumed, due to the number of women completing anxiety measures at the same time point) **b. Anxiety (number of women/total (%))** Medical: 2/11 (18.2) Surgical: 3/11 (27.3) Not significant (no p-value or test statistic reported)	
Full citation Smith,L.F., Frost,J., Levitas,R., Bradley,H., Garcia,J., Women's experiences of three early miscarriage management options: a qualitative study, British Journal of General Practice, 56, 198-205, 2006 **Ref Id**	**Sample size** N=38 (These 38 are participants of the original trial; however, this qualitative study also includes 16 non-participants, whose management methods are not reported. Therefore, the actual population of medically and surgically managed women is	**Interventions** Medical management n=18 (plus an unknown number of non-participants who received medical management)	**Details** Full details of the trial, and methods of surgical and medical management, can be found in Trinder et al. 2006. The qualitative study included trial participants and some of those who had decided not to participate. Women were recruited from 3 out of the 7 trial centres (Southmead and	**Results** The key themes identified by the authors were: feelings about the intervention, pain and bleeding, a need for finality, feelings about the 'baby,' and the care they received **<u>Intervention</u>** **Appropriateness /**	**Limitations** **<u>Hawthorne effect</u>** The women may have been contrasting the care shown them as part of the trial with previous experiences where they felt the treatment had been less caring. The women were also given a follow-up session to talk about future reproductive issues, which is

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
65493 **Country/ies where the study was carried out** UK **Study type** Qualitative follow-up to a randomised controlled trial **Aim of the study** To assess the social and personal impact of different management methods (expectant, medical and surgical) on women's experience of first trimester miscarriage. **Study dates** September 1999 to June 2000 (Recruitment for the original trial occurred May 1997 to December 2001) **Source of funding** S&W Executive Project Grant	unknown. In addition, 18 women who received expectant management were interviewed, however they are not included in the population size.) **Characteristics** Individual characteristics are not given for each group. **Inclusion criteria** Women linked to the MIST trial **Exclusion criteria** Not stated	**Comparator** Surgical management n=20 (plus an unknown number of non-participants who received surgical management)	St Michael's Hospital in Bristol and Royal United Hospital in Bath). Women were initially informed of the research when they were contacted 8 weeks after miscarriage, and they were reapproached 8-12 months later, allowing them to opt out if desired. The topic guide consisted of: Demographic details (age, social class as indicated by own and partner's occupation, marital status, number of children, family situation, ethnicity and nationality); previous reproductive history and experience; history of the recent miscarriage; experience of the mode of management and of other related healthcare services; support from family, doctors and midwives; feelings before and after miscarriage; subsequent feelings; effects on partner and other family members; coping strategies; and future reproductive hopes and plans. Most interviews were carried out by one of the authors, with fewer than 10% being undertaken either jointly or solely by two other experienced qualitative interviewers. Women were interviewed in their homes, the	**necessity:** The majority of women who mentioned appropriateness queried if the intervention was necessary: Surgical: *'I didn't want a D & C, I didn't … I know it sounds silly, 'cos the baby was already dead, but I don't agree with abortion, and things like that, and to me it felt the same; I wanted to do it on my own, and I got the D & C.'* A minority were strongly in favour of something being done to help them, to bring the miscarriage to completion quickly. Some in the medical group also were glad that they had been assisted to miscarry naturally: Surgical: *'I remember thinking about the three options, and coming to the conclusion that, at least a D & C was quick … because at the time I'd been off work for 3 weeks already … and I just thought: I don't want to wait anymore, particularly as I don't know what's*	not a normal part of NHS care. **<u>Lack of quantitative detail</u>** The authors do not report the number of women in each group that discussed each theme, instead using general terms like "majority" and "minority." Therefore, it is quite hard to judge how representative the views are. **<u>Inclusion of non-participants</u>** There is no separation of participants and non-participants, and no discussion of the management method chosen by non-participants. Randomised and non-randomised women may have different opinions and experiences. **Other information** This paper is a qualitative follow-up of a small number of participants in the MIST trial (Trinder et al. 2006). However, it also includes 16 non-participants, and the distribution of management methods within this group is

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			interviews taped and subsequently transcribed verbatim. Where women expressed a preference for being interviewed with their partner, a friend, or a relative, this was respected due to the potentially distressing nature of the research. The interviews, once anonymised, were analysed using NUDIST . The analysis involved a process of close iterative readings. Transcripts were shared between the five members of the research team. Each interview was read individually and summaries produced on a proforma: demographic and treatment details were recorded along with what were identified as potential themes or issues of significance. After a batch had been completed the whole team read the summaries and discussed them at a meeting and a set of themes were then included on subsequent proformas. Subsequent transcripts were read looking for more on these themes, but this did not preclude the identification of new themes. The discussions guided the development of the topic guide	*going to happen.'* Medical: *'… it happened the next morning* [when] *I came home … and it was a sense of relief really, ... it's ended … the medical treatment, it's just speeding it up … it's not actually anyone else going in my body … it's just a little magic tablet … it's midpoint… it's a kind treatment … it's not your baby whipped out of you, which is what a D & C feels like to me.'* A majority of women in all groups wished to be allowed to miscarry, because they felt it was more "natural." Similarly, women from the surgical group felt that they had been denied a choice in the management of their miscarriage. **Awareness of the event:** Some women felt that there was benefit in consciously experiencing the miscarriage, in terms of grieving, saying goodbye and performing rites of passage:	unclear.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			for later interviews. Transcripts were also subjected to iterative readings by the team to ensure that no major issues had been overlooked. The key themes identified were subsequently used to encode all the transcripts using NUDIST.	Medical: *'… it's very clean, very quick, wonderful operation, but, in a way, I think probably letting it miscarry helps to grieve in a funny way, because you're going through your grief all of the time that you are waiting for it to go, and then it goes, and you do a sort of mental realignment or whatever, you know, you have time to sort of prepare yourself.'* However, there was also a counter-balancing group of women who preferred surgery, to avoid consciousness of the miscarriage. **Fear of intervention:** The authors state that there was near uniform fear of intervention, especially anaesthetic. Hospitalisation and surgery were seen as inherently traumatic events, and women wanted to avoid being "messed about with." Surgical: *"I was more worried about the anaesthetic, that sort of worries me, just sort of*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				being knocked out, and I'm always afraid about not waking up again...." Surgical: "...*yeah... I didn't really want to have anything done. I thought it was bad enough having lost it, without having to have any more fiddling around."* Women viewed medical management particularly badly when they still had to have a surgery. **<u>Pain and bleeding</u>** **Pain:** Pain was mentioned mostly by the medical (and expectant) groups. There were very variable experiences, ranging from severe pain like labour or contractions, to tolerable pain like bad period pains. Medical: *'They said it would be like a contraction, but I mean, it wasn't like a contraction at all, really … it was like very strong period pain … I likened it to when I first started my periods,*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				when I was sort of 13.' Medical: *'I suppose to all intents and purposes, I had gone through labour, although, obviously a different version, but I did feel, my body did feel as though I'd gone through labour, and of course, I had nothing to show for it.'* **Bleeding:** Only women in medical (and expectant) groups mentioned bleeding as an issue, generally referring to it as "severe", "flooding" and "lots of clots." Medical: *'… I mean, looking back on it, I bled for about 40 hours, and had 40 hours of pain and bleeding; but I think that the actual psychological support I had was so much better, that it didn't seem that bad.'* **Lack of information:** Women in medical (and expectant) groups felt that they were not given information about the degree of pain and bleeding to expect. Women in all	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				groups mentioned that they generally had not known what to expect from their method. **<u>Medical management</u>** Women who had medical management expressed particular concerns. Many women talked about the time the process took: women with missed miscarriage were given tablets and sent home for 48 hours, then women with any miscarriage had to wait for a free bed to be admitted, then they had to wait for the tablets to work. Some women felt they were not given enough information about the effect of the tablets, and how long it might take them to work. **<u>Finality / need for an ending</u>** **Predictability:** The two themes were firstly that it should come to a predictable end so that they can get on with their lives, and secondly that there should be predictability to their experience, i.e.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				symptoms and management. Medical: *'I would have preferred to have a D & C, although I'm not sure what that would be like, exactly what that is, but, at least there would be an end to that, like you know: one minute you're pregnant, and the next minute, it's finished and you can get on with your life.'* Surgical: *'And it was like: I wanted it done, I wanted it done now. I wanted to get home for tea, sort of thing, that was how I was: can't we just do it.'* Surgical: *'… but we had tickets to go out, and we had the baby sitter organised, and we were having a weekend away on our own, and it meant that we couldn't go, so it was more the inconvenience ... as opposed to actually having to go in, and go through it.'* **Need for information:** Women wished to know what to expect in terms of	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				bleeding and pain, and more accurate and precise details on timings of interventions. Medical: *'… well, I was tired, and I didn't know it would happen did I? I just went for a wee and wiped myself and there it was ... I was shocked, and I just held it, touched it, examined it, and I did feel a bit sick.'* Surgical: *'… and I just thought: I don't want to wait any more, particularly because I don't know what's going to happen, and, oh, the first time I'd read a book about miscarriage, and it, the most awful stories always get in there, I mean I was, you always get those sorts of stories and you think, "oh my God, you know, what on earth is going to happen?" So I just thought: right, I'll go for the most invasive was of doing it* [laughs]*, which at least, gets it over with.'* Surgical: *'I wanted to. I didn't want to sort of just go home and wait for a miscarriage, erm, ...*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				because I, I didn't know what to expect at all.' **<u>Feelings about the 'baby'</u>** **Seeing the 'baby':** Many women expressed views about seeing the baby. Some were worried and scared about what they might see, and how to avoid it. Others felt it was important to see the baby, to say goodbye, and to finish the miscarriage on their own terms: Medical: *'… but you know, I just sort of thought: what's that there? You know and, then, sort of waited, and then when you pull the flush, it's like a real goodbye, you know.'* **Fear of accidentally killing the 'baby':** A few women wanted to avoid intervention, because they felt that if there was a misdiagnosis then they were somehow involved in the killing of the baby. Medical: *'I was very*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				relieved that it had miscarried naturally 'cos I could cope with it dying naturally, that wasn't a problem, with the thought of having it killed on purpose, that's how I would have seen it.' The authors also state that some women expressed a kind of horror about carrying something dead around inside them, however all the illustrative quotes are from the expectant management group. **Experiences of care received** A small number of women in surgical and medical groups felt there was a lack of caring, and that they were part of a "conveyor belt." Medical: *'... you know, nobody came and showed us any care, apart from when they came to take the commode away, but nobody came in to see us.'* Surgical:*'... and I hated it!*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				The whole thing was cold! It was so insensitive, it was horrible! I will never forget how insensitive, and cold it felt.' Surgical: *'… you felt like you were ... sort of on a conveyor belt and they just whacked this mask over my face, it was almost like, you know: get through, lie down, shut up* [laughs] *and we can get on with it, because you are slowing down the process …'* Medical: *'… and they were just icy cold towards us, weren't they? I couldn't believe it really, it was just like when you take your car in for an MOT, they could have been telling us anything ... they didn't show any emotions.'* These comments were not frequent. However, the authors considered them significant due to the difficulty that patients have in passing negative comments about their doctors or nurses.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Trinder,J., Brocklehurst,P., Porter,R., Read,M., Vyas,S., Smith,L., Management of miscarriage: expectant, medical, or surgical? Results of randomised controlled trial (miscarriage treatment (MIST) trial), BMJ, 332, 1235-1240, 2006 **Ref Id** 65526 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To ascertain whether a clinically important difference exists in the incidence of gynaecological infection between surgical management and expectant or medical management of miscarriage **Study dates**	**Sample size** N=800 **Characteristics** **Age/years (mean (SD))** Medical: 31.2 (5.9) Surgical: 31.5 (5.8) **Gestational age/days (number/total (%))** **Medical:** <56: 18/398 (5) 56-76: 168/398 (42) >77: 155/398 (39) Unknown: 57/398 (14) **Surgical:** <56: 25/402 (6) 56-76: 173/402 (43) >77: 147/402 (37) Unknown: 57/402 (14) **Type of miscarriage (number/total (%))** **Medical:** Missed 308/398 (77)	**Interventions** Medical management n=398 **Comparator** Surgical management n=402	**Details** This trial had seven participating hospitals, all of which had an early pregnancy clinic. 3905 women attended, of which 1085 were ineligible and 1620 refused trial entry. 1200 were recruited, but 399 received expectant management and therefore their outcomes are not reported here. A prior sample size calculation calculated that 474 would be needed in each group to have 80% power to detect a 50% difference in the primary outcome of infection within 10-14 days. Women were suitably randomised, and minimisation was used to ensure comparability between women with respect to centre, parity, type of miscarriage and gestation. All women were given a specific information sheet, 30 co-dydramol tablets and an emergency telephone number. Medical Women with an incomplete miscarriage were admitted to hospital and given a single vaginal dose of 800 microgram	**Results** **Need for unplanned intervention (number of events/total (%))** Medical: 142/398 (35.6) (90 as a result of the failure of the failure of the medical protocol; 52 had an unplanned curettage, of which 11 were an emergency procedure prior to admission) Surgical: 22/402 (5.5) (the main indications for unplanned curettage were retained products on the scan and excess bleeding) **Incidence of side effects/complications (number of events/total (%))** **a. Surgical complications** Medical: 4/398 (1.0) Surgical: 9/402 (2.2) (type of surgical complication is not reported) **b. Infection specified by**	**Limitations** **Loss to follow-up** Medical: 9/398 (2.3%) by 10-14 days; 12/398 (3.0%) by 8 weeks Surgical: 8/402 (2.0) by 10-14 days; 10/402 (2.5%) by 8 weeks **Other information** Includes incomplete and missed miscarriages. **Intention-to-treat** Out of the 402 women randomised to surgery, 356 (89%) had surgical curettage. 46 did not, because 30 miscarried before admission, and 16 declined surgery following randomisation. However, 12 subsequently had curettage. Out of the 398 women randomised to medical management, 12 women miscarried spontaneously (but 2 later had curettage). Intention-to-treat analysis was done.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Recruitment occurred May 1997 to December 2001 **Source of funding** South and West NHS Executive research and development grant. Donation of £20,000 from Exelgyn (manufacturers of mifepristone)	Incomplete 90/398 (23) **Surgical:** Missed: 310/402 (77) Incomplete: 92/402 (23) **Bleeding at entry (number/total (%))** Medical: 331/398 (83) Surgical: 335/402 (83) **Pain (number/total (%))** Medical: 206/398 (52) Surgical: 205/402 (51) **Inclusion criteria** Pregnancy of <13 weeks gestation, diagnosed as either: - an incomplete miscarriage (defined as areas of mixed echogenicity within the uterine cavity, with or without a disordered gestation sac) - early foetal demise (defined as a foetus >6mm crown-rump length with no heart activity on trans-vaginal		misoprostol. Women with early foetal/embryonic demise were pre-treated with a single oral dose of 200mg mifepristone, and then admitted to hospital 24-48 hours later for a single vaginal dose of 800 microgram misoprostol. A surgical evacuation of retained products of conception was offered if expulsion had not started within 8 hours of misoprostol insertion. Surgical Women were admitted for surgical suction curettage under general anaesthetic. Prophylactic antibiotics were not used. A follow-up appointment was arranged for 10-14 days after trial entry, for transvaginal ultrasound scan, full blood count, consultation with the study nurse and examination by a gynaecologist if there were symptoms of infection. Retained products of conception were diagnosed if areas of mixed echogenicity	**criteria (by 10-14 days)** Medical: 9/398 (2.3) Surgical: 12/402 (3.0) *This is the outcome used in the meta-analysis.* **c. Infection specified by criteria (by 8 weeks)** Medical: 12/398 (3) Surgical: 16/402 (4) **d. Antibiotic use for presumed infection (by 10-14 days)** Medical: 31/398 (7.8) Surgical: 34/402 (8.5) **e. Antibiotic use for presumed infection (by 8 weeks)** Medical: 43/398 (10.8) Surgical: 44/402 (10.9) **f. Vomiting and diarrhoea** The paper reports that there was no significant difference, but gives no further details. **Need for a**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	ultrasound) - early embryonic demise (defined as an intact gestation sac >20mm mean diameter with no other internal structures) **Exclusion criteria** Severe haemorrhage or pain Pyrexia >37.5 degrees Severe asthma, haemolytic disease or blood dyscrasias Current anticoagulation or systemic corticosteroid treatment Twin or higher order pregnancy Smoker aged over 35 Inability to understand written English		within the uterine cavity were seen, and a surgical curettage was offered in this case. Clinical symptoms were also considered; individual doctors in early pregnancy clinics made the decision to offer surgery in conjunction with the women. Other outcomes were assessed at 8 weeks. **Outcomes reported** **1. Need for unplanned intervention** In the paper this is reported as the number of women with an "unplanned curettage" in the surgical group, and "any curettage" in the medical group (indicated by failure of the medical management protocol, or as an emergency procedure prior to admission) within 8 weeks. **2. Incidence of side effects/complications** The primary outcome was gynaecological infection, defined as two or more of: purulent vaginal discharge, pyrexia above 38.0 degrees, tenderness over the uterus on	**blood transfusion (number of events/total (%))** Medical: 4/398 (1.0) Surgical: 0/402 (0) **Duration of bleeding/days (median (IQR))** Medical: 11 (7-15) Surgical: 8 (4-14) p=0.0004 **Pain** **a. Pain** They report no significant difference but give no further details. **b. Extra analgesia taken (number of events/total (%))** Medical: 98/398 (24.6) Surgical: 71/402 (17.7) **Unscheduled visits to a medical facility** **a. Admission (number of events/total (%))**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			abdominal examination, and a white cell count above $15x10^9$/l. The outcome is reported at both 10-14 day follow-up and 8 week follow-up. Infection specified by the prescription of antibiotics is also reported. Vomiting and diarrhoea were assessed by the medical staff **3. Need for a blood transfusion** Method of data collection not reported. **4. Duration of bleeding** Unclear at what point, and how, this was assessed. **5. Pain** Pain was assessed by the medical staff. Additional analgesia taken was used as a proxy of the need for analgesia in an outpatient setting, however the dose or method of analgesia is not reported. **5. Unscheduled visits to a medical facility** This is the number of unplanned hospital admission	Medical: 72/398 (18.1) Surgical: 32/402 (8.0) (Note: The paper also states that the number of unplanned hospital consultations (without admission) was similar in the groups, but gives no further details) **Emotional and psychological outcomes** They report that there was no differences between anxiety scores or any of the subscales of the SF-36. Raw scores are not reported.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			within the first 8 weeks after randomisation. **6. Emotional and psychological outcomes** The women completed questionnaires (SF-36 and Hospital Anxiety and Depression Scale) at 8 weeks after treatment. Method of administration of the questionnaire is not stated.		
Full citation Zhang,J., Gilles,J.M., Barnhart,K., Creinin,M.D., Westhoff,C., Frederick,M.M., National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial., A comparison of medical management with misoprostol and surgical management for early pregnancy failure, New England Journal of Medicine, 353, 761-769, 2005 **Ref Id** 65565 **Country/ies where the study was carried out**	**Sample size** N=652 **Characteristics** There were no significant differences between the two groups with regards to age, race, education level, number of previous pregnancies, planned **Age/years (mean (SD))** Medical: 29.8 (7.2) Surgical: 30.9 (7.3) **Gestational age/weeks (mean (SD))**	**Interventions** Medical management n=491 **Comparator** Surgical management n=161	**Details** This trial was conducted at 4 study sites: Columbia University, University of Pittsburgh, University of Miami and University of Pennsylvania. A sample size calculation calculated that 620 women would be needed to achieve statistical power of 80% to detect a difference of 18% between the groups, demonstrating non-inferiority. 652 women were enrolled, and suitably randomised in a 3:1 ratio of medical : surgical management. Randomisation was stratified by study site and type of pregnancy failure. Day of randomisation was considered study day 1. Medical management	**Results** **Need for unplanned intervention (number of events/total (%))** Medical: 80/488 (16.4) (in the medical group, 76 women were deemed to have a failed treatment, as defined as "need for vacuum aspiration within 30 days." However the paper also states that 4 more needed VA after 30 days, due to heavy or persistent bleeding, therefore these have also been included here) Surgical: 5/148 (3.4) (due to failure of initial	**Limitations** **Loss to follow-up and missing data** Sample sizes generally vary due to missing data and loss to follow-up. For example, for the outcome of "need for further surgery" 2 women from the medical group and 11 women from the surgical group had missing data, therefore have not been included in the population. **Definition of "sucessful" treatment** The paper had an a priori definition of success as "absence of need for vacuum

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
USA **Study type** Randomised controlled trial **Aim of the study** To assess the efficacy, safety and acceptability of misoprostol treatment **Study dates** March 2002 to March 2004 **Source of funding** National Institute of Child Health and Human Development National Institutes of Health	Medical: 7.6 (1.5) Surgical: 7.6 (1.4) **Lower abdominal pain in last 24 hours (number/total (%))** Medical: 298/491 (61%) Surgical: 86/161 (53%) **Vaginal bleeding in last 24 hours (number/total (%))** Medical: 318/491 (65%) Surgical: 101/161 (63%) **Type of pregnancy failure (number/total (%))** **Medical:** Embryonic/foetal death: 282/491 (57%) Anembryonic gestation: 179/491 (36%) Incomplete: 19/491 (4%) Inevitable: 11/491 (2%)		Four 200 microgram tablets of misoprostol were inserted into the posterior fornix through a speculum. The women returned on day 3 (range 2-5), and if expulsion was not complete (defined as visualisation of the gestational sac, or an endometrial lining greater than 30mm on TVS), a second 800 microgram dose was given. If expulsion was not complete on day 8 (range 6-10), vacuum aspiration was offered. Women returned for a follow-up visit on day 15. Surgical management Surgical management was manual vacuum aspiration in an outpatient setting at Columbia University and University of Pittsburgh (57% women), and electric vacuum aspiration in an operating room at University of Miami and University of Pennsylvania (43% women). Surgery was performed by a study investigator, or a resident physician supervised by an investigator. All patients were contacted by phone on day 8 to enquire about symptoms. Women returned to a follow-up visit on day 15 (13-18) after randomisation.	treatment) **Incidence of side effects/complications (number of events/total (%))** **a. Infection** Medical: 2/488 (0.4) Surgical: 0/148 (0) p=1.0 (All these women were hospitalised, however no maternal sepsis occurred) **b. Nausea** Medical: 250/472 (53.0) Surgical: 41/141 (29.1) p<0.001 **c. Vomiting** Medical: 96/475 (20.2) Surgical: 10/142 (7.0) p<0.001 **d. Diarrhoea** Medical: 113/473 (23.9) Surgical: 14/142 (9.9)	aspiration within 30 days of the misoprostol treatment." The paper does not strictly define success for the surgical group. **Other information** Includes missed miscarriage and incomplete miscarriage Women were randomised in a 3:1 ratio of medical : surgical management. Reason for this choice of ratio are not given, however in a later follow-up paper they report that it was to allow more precise estimates of safety and efficacy in the misoprostol group because unlike surgery, little was known about safety and efficacy of medical treatment of early pregnancy failure. **Intention-to-treat** Out of the 491 women randomised to receive misoprostol, 487 received it: - 1 was ineligible due to having received methotrexate

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Surgical: Embryonic/foetal death: 96/161 (60%) Anembryonic gestation: 56/161 (35%) Incomplete: 3/161 (2%) Inevitable: 6/161 (4%) **Inclusion criteria** Women with an anembryonic gestation or embryonic or foetal death were eligible if they had an ultrasound examination demonstrating either: - an embryonic pole or crown-rump length between 5 and 40mm without cardiac activity - an anembryonic gestational sac with a mean diameter 16-45mm - growth of gestational sac by <2mm over a 5-day period, or <3mm over a 7-day period - increase in hCG levels of <15% over a 2-day period,		Women were given ibruprofen and codeine, and a diary in which to record side effects, medication used, and emergency calls/visits to hospital. At each follow-up visit, transvaginal ultrasonography was performed, a physical exam was done, patients were interviewed and their diary pages collected. On day 15, women also completed a questionnaire on quality of life and acceptability. A telephone interview was done on day 30 (25-35) to determine any further treatment women received. Differences between groups were statistically analysed using chi-squared, Fisher's exact test or Student's t-test as appropriate. **<u>Outcomes assessed</u>** **1. Need for further surgery** Need for further surgery is not defined specifically in this paper, however they define success as "absence of the need for vacuum aspiration for any reason within 30 days."	p<0.001 **<u>Pain</u>** **a. Incidence (number of women/total (%))** Medical: 473/476 (99.4) Surgical: 134/141 (95.0) p<0.001 **b. Severity /10 (mean (SD))** Medical: 5.7 (2.4) (n=476) Surgical: 3.2 (2.4) (n=141) p<0.001 **<u>Unscheduled visits to a medical facility</u>** **a. Unscheduled visits (number of events/total (%))** Medical: 114/488 (23.4) Surgical: 25/148 (16.9) p=0.09 (Note: in the table it states that women could have multiple consultations and	prior to treatment - 2 had an expulsion before receiving misoprostol - 1 withdrew after randomisation Out of the 161 women assigned to surgery, 155 received it: - 2 were ineligible, because they did not meet the ultrasonographic criteria - 3 had an expulsion before surgery - 1 withdrew after randomisation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	with a yolk sac visualised by ultrasound examination Women with incomplete miscarriage, defined as the passage of some products of conception, with the residual anteroposterior endometrial lining exceeding 30mm on transvaginal ultrasound and a uterine size indicating <13 weeks gestation Women with inevitable miscarriage, defined as an intrauterine gestational sac of <45mm or embryonic pole of <40mm and an internal cervical os that was open to digital examination, with active vaginal bleeding **Exclusion criteria** Anaemia (haemoglobin level below 9.5g/dl) Haemodynamic instability History of clotting disorder Use of anticoagulants (not including aspirin) Allergy to prostaglandins or nonsteroidal anti-		Therefore, those who failed are likely to be the converse, i.e. those who had further surgery **2. Incidence of side effects/complications** Nausea, vomiting and diarrhoea were reported in a woman's diary within 48 hours of treatment. Infection is reported as the number of women requiring hospitalisation for endometritis. **3. Pain** Incidence and intensity were reported in women's diaries, within 48 hours of treatment. Intensity was measured on a 10-cm visual analogue scale, ranging from 0 (no pain) to 10 (worst pain ever). **4. Unscheduled visits to a medical facility** The total number of unscheduled visits to hospital was assessed at a follow-up visit, using information that women had recorded in their daily diaries. A woman could have multiple unscheduled visits. The number of admissions for haemorrage and endometritis is also	that the above relates to total visits, however in the text it refers to number of women) **b. Admission** Medical: 7/488 (1.4) (5 for haemorrhage, 2 for endometritis) Surgical: 1/148 (0.7) (1 for haemorrhage) (Note: hospitalisation for reasons other than haemorrhage or endometritis is not reported, therefore, this outcome has not been included in the meta-analysis) **<u>Measures of satisfaction</u>** **a. "Would choose again" (number of women/total (%))** Medical: 357/456 (78.3) Surgical: 112/150 (74.7) p=0.36	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	inflammatory drugs Previous surgical or medical abortion that was either self-induced or induced by other physicians in the current pregnancy		reported. **5. Satisfaction** Women completed a questionnaire on day 15, regarding quality of life and acceptability of treatment. "Would choose again" is reported as the number of women who would probably or absolutely use this treatment again.		
Full citation Chung,T.K., Lee,D.T., Cheung,L.P., Haines,C.J., Chang,A.M., Spontaneous abortion: a randomized, controlled trial comparing surgical evacuation with conservative management using misoprostol, Fertility and Sterility, 71, 1054-1059, 1999 **Ref Id** 78016 **Country/ies where the study was carried out** Hong Kong **Study type**	**Sample size** N=635 **Characteristics** **Age/years (mean (SD))** Medical: 30.8 (6.3) Surgical: 31.3 (5.9) **Gestational age/weeks (mean SD))** Medical: 10.7 (2.5) Surgical: 10.8 (2.6) **Cervical status on admission (number/total**	**Interventions** Medical management n=321 **Comparator** Surgical management n=314	**Details** A sample size calculation was done, calculating that a trial with 90% power to detect a reduction in complication rate to 2% would require a trial with 309 women in each arm. 635 women were recruited and suitably randomised to either misoprostol treatment or surgery. Medical Women were given 400 micrograms of misoprostol orally every 4 hours up to a total dose of 1200 micrograms. All cases were observed in the ward, and a TVS was performed the next day. Those with an empty uterus were discharged. Those who still had significant	**Results** **Need for unplanned intervention (number of events/total (%))** Medical: 164/321 (51.1) (159 had surgery before discharge; 3 had surgical evacuation within 2 weeks of treatment; 2 had evacuation up to 6 months after treatment) Surgical: 11/314 (3.5) (6 were within 2 weeks; 5 were within 6 months) **Incidence of side effects/complications (number of women/total**	**Limitations** **Duration of pain and bleeding** Reported as days after discharge, not total days, and standard deviations are not reported. The length of hospital stay was significantly different in the two groups, which could have had an impact on total duration of pain/bleeding. **Loss to follow up** after 2 weeks: Medical: 5/321 (1.6)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** To compare the efficacy of surgical evacuation of the uterus with medical evacuation using misoprostol in cases of spontaneous abortion **Study dates** October 1995 to January 1998 **Source of funding** Health Services Research Fund of Hong Kong	**(%))** **Medical:** Closed: 244/321 (76.0) Open: 77/321 (24.0) **Surgical:** Closed: 235/314 (74.8) Open: 79/314 (25.2) **Inclusion criteria** Clinical diagnosis of spontaneous miscarriage (made on the basis of history, examination and documentation of cervical status) TVS evidence of retained products of conception **Exclusion criteria** Choriodecidual reaction measuring <5cm^2 in transverse and 6cm^2 in the sagittal plane Severe blood loss		products of conception had surgery and were then discharged. Surgical Women were given routine "ERPC". Surgical details are not described. Before discharge, women were counselled to return to hospital if they experienced abdominal pain, discomfort, vaginal discharge, fever, general malaise or passage of any tissue mass vaginally. All patients were followed up 2-3 weeks after discharge and interviewed by a research nurse. A urinary pregnancy test was done, and if the test was positive, an assessment was made to exclude molar, ectopic, retained products of conception or continuing pregnancies. Patients were also contacted and interviewed by telephone after 6 months. Statistical tests were done, using chi-squared and t-tests.	**(%))** **a. Surgical complications** Medical: 0/321 (0) (they report that this is likely to be due to the cervical priming effect of misoprostol) Surgical: 7/314 (2.2) (6 uterine perforation; 1 cervical laceration) **b. Infection (within 2 weeks)** Medical: 9/321 (2.8) Surgical: 10/314 (3.2) *This is the outcome used for the meta-analysis.* **c. Infection (within 6 months)** Medical: 2/280 (0.7) Surgical: 2/272 (0.7) **d. Nausea**	Surgical: 2/314 (0.6) after 6 months: Medical: 41/321 (12.8%) Surgical: 42/314 (13.4%) **Population** 2 women in each group were found to have missed ectopic pregnancies, identified within 2 weeks after discharge. **Other information** Includes both incomplete and missed miscarriages (cervix could be open or closed) **Intention-to-treat (was done)** Medical: Of 321 women randomised to the protocol, 301 received it. 11 passed tissue following randomisation, 4 had side effects of misoprostol, 3 had bleeding, 1 was an inappropriate study subject, and 1 refused randomised

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Sepsis Allergy to prostaglandins or their analogues Present or past asthma Any reason, in the opinion of the attending physician, that the patient was unsuitable for misoprostol treatment		**<u>Outcomes reported</u>** **1. Need for unplanned intervention** This includes women who needed evacuation of retained products of conception, up to 6 months after treatment. It also includes women who had an emergency evacuation, following randomisation. **2. Incidence of side effects/complications** Infection is reported up to 2 weeks (pelvic), and up to 6 months (uterine). It is unclear on the time scale for the gastro-intestinal side effects, but the technical team assume they are reported in the short term. Complications at 6 months were defined as any medical complication attributable to the miscarriage and it's management. **3. Duration of bleeding** Reported as the duration of bleeding, between time of discharge and follow up appointment after two weeks.	Medical: 70/321 (21.8) Surgical: 26/314 (8.3) **e. Diarrhoea** Medical: 155/321 (48.3) Surgical: 4/314 (1.3) **<u>Duration of bleeding after discharge/days (mean)</u>** Medical: 9.1 Surgical: 9.3 p=0.48 (SD and test statistic not reported) **<u>Pain</u>** **a. Abdominal discomfort of >2 weeks (number of women/total (%))** Medical: 4/280 (1.4) Surgical: 8/272 (2.9) **b. Abdominal pain up to 6 months after discharge (number of women/total (%))**	treatment Surgical: Of 314 women randomised to surgery, 303 received it. 7 passed tissue following randomisation, 2 were inappropriate subjects, and 2 refused randomised treatment.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			4. Pain The number of women reported as having abdominal discomfort over 2 weeks, and the number having abdominal pain up to 6 months after discharge are reported. Duration of pain is reported as the duration of pelvic pain, between time of discharge and follow up appointment after two weeks. **5. Length of hospital stay** Reported in days. **6. Unscheduled visits to a medical facility** This is reported as the number of women who requested an additional check-up, up to 6 months after treatment.	Medical: 1/280 (0.4) Surgical: 5/272 (1.8) **c. Duration after discharge/days (mean)** Medical: 0.17 Surgical: 0.25 p=0.30 (SD and test statistic not reported) **Length of hospital stay/days (mean)** Medical: 2.18 Surgical: 1.78 p=0.00 (SD and test statistic not reported) **Unscheduled visits to a medical facility** **a. Visit - outpatient (number of women/total (%))** Medical: 9/280 (3.2) Surgical: 9/272 (3.3)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dao,B., Blum,J., Thieba,B., Raghavan,S., Ouedraego,M., Lankoande,J., Winikoff,B., Is misoprostol a safe, effective and acceptable alternative to manual vacuum aspiration for postabortion care? Results from a randomised trial in Burkina Faso, West Africa, BJOG: An International Journal of Obstetrics and Gynaecology, 114, 1368-1375, 2007 **Ref Id** 78041 **Country/ies where the study was carried out** Burkina Faso **Study type** Randomised controlled trial **Aim of the study** To document the effectiveness of single dose of 600 micrograms of oral misoprostol versus manual vacuum aspiration for treatment of	**Sample size** N=447 (note: 460 women were initially enrolled and randomised, but 13 were later excluded from the analysis: 12 did not meet the inclusion criteria of having an open cervical os, and 1 had incomplete records so eligibility could not be determined) **Characteristics** There were no significant differences between the two groups in age, years of education, marital status, parity, or reported previous miscarriage or induced abortion. **Induced abortion in current miscarriage (number of women/total (%))** **a. Woman's report** Medical: 23/223 (10.3) Surgical: 33/224 (14.7)	**Interventions** Medical management n=223 **Comparator** Surgical management n=224	**Details** Women were recruited from two large university hospitals - Le Centre Hospitalier National Souro Sanou in Bobo Dioulasso and Le Centre Hospitalier National Yalgado Ouedraogo in Ouagadougou. The study was designed to have 90% power to detect whether misoprostol was no more than 6.5% less effective than MVA. Recruited women were suitably randomised to medical or surgical management, stratified by study site. Eligibility criteria screened out women with very high fever or signs of severe infection, commonly associated with induced abortion. Providers were allowed to prescribe additional medications, such as antibiotics, if needed, for example to treat an infection or as prophylaxis against a future infection. Medical Women were given a single dose of 600 micrograms of oral misoprostol, which they swallowed in the presence of a study nurse.	**Results** **Need for unplanned intervention (number of events/total (%))** Medical: 12/218 (5.5) (6 were for an incomplete miscarriage at the study end, 4 were medically indicated before the study end, and 2 were the choice of the provider or woman before the study end) Surgical: 2/224 (0.9) (Both were for an incomplete miscarriage at the study end) **Incidence of side effects/complications (number of events/total (%))** **a. Nausea** Medical: 12/223 (5.4) Surgical: 2/224 (0.9) RR=6.03 (95% CI 1.36-	**Limitations** **Loss to follow-up** 5 women were lost to follow-up, all from the misoprostol arm. At last contact, they had the following diagnoses: 3 with substantial uterine debris and no sac, 1 with persistent uterine sac, and 1 with unknown clinical status. Their outcomes are reported not to have been analysed, however the n for side effects is still reported as 223. **Variable follow-up period** Women were interviewed about side effects etc when treatment was completed, not at a set time after their treatment. **Prevalence of induced abortion** This could affect the generalisability of the results to the UK population. **Anaesthesia** Proportion of surgical arm receiving verbal or local anaesthesia is not reported,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
incomplete miscarriage in a developing country setting. **Study dates** April 2004 to October 2004 **Source of funding** David and Lucile Packard Foundation	**b. Provider assessment** Medical: 27/223 (12.1) Surgical: 38/224 (17.0) **Inclusion criteria** Uterine size equivalent to a gestation of less than 12 weeks Open cervical os Past or present history of vaginal bleeding during pregnancy Ultrasound evidence of substantial uterine debris with evidence of foetal demise Living or working within the hospital's geographical area of coverage No known contraindications to misoprostol No signs of severe infection Temperature below 38 degrees		<u>Surgical</u> Women were given manual vacuum aspiration as soon as a trained provider became available. MVA was provided in the designated MVA room in the family planning ward of each hospital. Method of anaesthesia is not stated, but they state that the local standard of care is local or verbal anaesthesia. All patients were given 200mg tablets of paracetamol to manage pain, and asked to return for follow-up one week later. They were then free to leave. At the day 7 follow-up visit, miscarriage status was assessed using interview, bimanual examination and ultrasound. Women with retained products of conception could wait an additional week for the products to evacuate on their own, and if they agreed, a follow-up was scheduled for day 14. Women not wishing to wait underwent surgical evacuation using MVA. When the treatment was completed, women were interviewed to gauge acceptability of treatment. Statistical analysis was	26.62) **b. Vomiting** Medical: 5/223 (2.2) Surgical: 4/224 (1.8) RR=1.26 (0.34-4.61) **<u>Duration of bleeding/days (mean)</u>** **a. Heavy bleeding** Medical: 1.7 Surgical: 1.1 p=0.004 **b. Normal bleeding** Medical: 1.9 Surgical: 1.5 p=0.01 **c. Light bleeding** Medical: 3.1	which could have affected satisfaction measures. **Other information** Incomplete miscarriage only (had to have open cervical os and history of bleeding in current pregnancy)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	General good health **Exclusion criteria** Not stated		done using chi-square test, t-tests and ANOVA. **<u>Outcomes reported</u>** **1. Need for unplanned intervention** The number of women requiring unplanned surgery due to initial failure of treatment. **2. Incidence of side effects/complications** Collected during exit interviews conducted when treatment was completed. **3. Duration of bleeding** Collected during exit interviews conducted when treatment was completed. **4. Pain** Reported as the incidence and duration of pain or cramps. Pain level was measured on a seven point Likert scale, using a visual scale.	Surgical: 2.9 p=0.09 Note: "light bleeding" has been used in the GRADE table, because the greatest number of women experienced it, and therefore it best represents the experience of the group. However, this value under-represents total length of bleeding, because women could appear in multiple categories of bleeding and therefore have a total duration that is longer than the length of any one type of bleeding. **<u>Pain</u>** **a. Incidence (number of events/total (%))** Medical: 125/223 (56.1) Surgical: 115/224 (51.3) (note: these % do not match those quoted in the paper - they report 55.8% and 51.6%, which means they appear to have	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			5. Unscheduled visit to a medical facility Reported as the number of women who had an unscheduled visit to the hospital. **6. Measures of satisfaction** Collected during exit interviews conducted when treatment was completed. Satisfaction was measured using a five point Likert scale. It is reported as the number of women who were "very satisfied", "satisfied" or "not satisfied." For the purposes of this analysis, the technical team grouped the "very satisfied" and "satisfied" together under one heading of "satisfied." Women were also asked if they would choose the same method again.	swapped the denominators) **b. Duration/days (mean)** Medical: 1.4 Surgical: 1.3 p=0.08 **c. Severity/7 (mean)** Medical: 2.32 Surgical: 2.73 p=0.047 (no test statistic given) **Unscheduled visit to a medical facility (number of events/total (%))** **a. Visits (all, including admissions)** Medical: 13/223 (6.0) (12 before day 7, 1 after day 14. Two of these women were hospitalised, one for a blood transfusion, and one for signs of infection)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Surgical: 2/224 (0.9) (1 before day 7, and 1 at one month) p=0.006 (Note: telephone calls were more common among MVA users (3.6%) than misoprostol users (0.8%)) **b. Admissions** Medical: 2/223 (see above for reasons) Surgical: Not directly reported **Measures of satisfaction (number of women/total (%))** **a. Reported satisfaction** Medical: 210/217 (96.8) (out of these women, 33 were "very satisfied") Surgical: 215/220 (97.7) (out of these women, 17	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				were "very satisfied") **b. "Would choose again"** Medical: 205/217 (94.5) Surgical: 194/224 (86.6) RR=1.09 (95% CI 1.03-1.16) NOTE: **The best features of each mode of treatment were:** Medical: "Simple, quick and successful" (37.9%), "Saw expulsion" (21.2%) Surgical: **"**Good counselling/care" (26.5%), "Saw expulsion" (25.6%), "Simple, quick and successful" (24.6%) **The worst features of each mode of treatment were:** Medical: "No worst feature" (78.6%), "Pain" (14%) Surgical: "No worst feature" (72.6%), "Pain" (26.5%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Davis,A.R., Hendlish,S.K., Westhoff,C., Frederick,M.M., Zhang,J., Gilles,J.M., Barnhart,K., Creinin,M.D., National Institute of Child Health and Human Development Management of Early Pregnancy Failure Trial, Bleeding patterns after misoprostol vs surgical treatment of early pregnancy failure: results from a randomized trial, American Journal of Obstetrics and Gynecology, 196, 31-37, 2007 **Ref Id** 78044 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To describe and compare bleeding patterns and adverse effects that were related to bleeding after	**Sample size** N=652 (this is the number of participants in the original trial, see Zhang et al. 2005) **Characteristics** There were no significant differences between the two groups. For further details, see Zhang et al. 2005 **Inclusion criteria** See Zhang et al. 2005 **Exclusion criteria** See Zhang et al. 2005	**Interventions** Medical management n=491 (this is the number of participants in the original trial medical arm, see Zhang et al. 2005) **Comparator** Surgical management n=161 (this is the number of participants in the original trial surgical arm, see Zhang et al. 2005)	**Details** For full details of treatment and surgical methods, see Zhang et al. 2005. All participants returned for a physical exam, interview, ultrasound scan and haemoglobin count on or near day 15. At the final visit, women completed a questionnaire in which they rated the acceptability of bleeding on a scale of 1 (totally unacceptable) to 5 (totally acceptable). Patient acceptability was determined by the questionnaire. **Outcomes reported** **1. Need for a blood transfusion** The denominator is not specifically stated for this outcome. Therefore, the technical team utilised the only denominators reported in the paper. **2. Duration of bleeding** Women were asked to keep a daily diary of bleeding. Daily diary data was collapsed into 2	**Results** **Need for a blood transfusion (number of events/total (%))** Medical: 4/428 (0.9) Surgical: 0/135 (0) **Duration of any bleeding/days (median (IQR))** Medical: 12 (9-14) Surgical: 10 (7-12) **Duration of heavy bleeding/days (median (IQR))** Medical: 4 (2-6) Surgical: 1 (0-3) Note: The paper also reports that approximately 50% of women from the misoprostol group and 33% of women from surgery group report bleeding during days 15-30 after treatment (P<0.001) but no further details are given.	**Limitations** **Data collection** Missing data increased in both groups towards the end of the diary. If they stopped recording when bleeding stopped, the data is likely to overestimate the number of women experiencing bleeding. No diary data was collected after day 15. However, the interview revealed that some women had experienced continued bleeding after day 15. They found that acceptability was linked to bleeding at day 15, and therefore continued bleeding could have influenced acceptability. **Loss to follow-up** Loss to follow-up for bleeding outcomes is not directly reported. However, haemoglobin changes were recorded at day 15, for which the population size was: medical n=428, surgical n=135. This suggests that diary data for days 1-15 would be available for a similar number of women,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
medical versus surgical treatment of early pregnancy failure. **Study dates** March 2002 to March 2004 **Source of funding** National Institute of Child Health and Human Development National Institutes of Health			dichotomous variables: "any bleeding" (at least spotting) versus "no bleeding" and "heavy bleeding" (at least moderate bleeding) versus "less than heavy bleeding."		implying loss to follow-up of 63/491 (12.8%) in medical group and 26/161 (16.1%) in the surgical group. **Other information** This is secondary analysis of Zhang et al. 2005. Participants of the original trial were randomised in a 3:1 ratio.
Full citation De Jonge,E.T., Makin,J.D., Manefeldt,E., De Wet,G.H., Pattinson,R.C., Randomised clinical trial of medical evacuation and surgical curettage for incomplete miscarriage, BMJ, 311, 662-, 1995 **Ref Id** 78047 **Country/ies where the study was carried out** South Africa **Study type**	**Sample size** N=50 **Characteristics** **Age/years (median (range))** Medical: 27 (17-41) Surgical: 31 (18-42) **Parity (median (range))** Medical: 2 (0-5) Surgical: 2 (0-5) **Estimated gestation/days**	**Interventions** Medical management n=23 **Comparator** Surgical management n=27	**Details** 50 women were suitably randomised to surgical or medical management. Medical Women were given a single dose of 400 micrograms oral misoprostol. Treatment was considered successful if bleeding had reverted to a blood-stained discharge, pain had subsided, the uterus was smaller and the cervical opening had closed on repeat examination 12 hours after misoprostol administration. Pelvic ultrasonography was performed when there was uncertainty about	**Results** **Need for further intervention (number of events/total (%))** Medical: 20/23 (87) Surgical: 1/27 (3.7) p<0.00001 (The decision to proceed with surgery was made after 12 hours, however the women were observed for a median of 17 hours (range 13-23) while waiting surgery after the decision was made, during which time none had a successful	**Limitations** **Population** The inclusion criteria was an uterine size of 14 weeks or less, therefore an unknown number of women are outside the scope of the guideline. **Medical protocol** The dosage and time before judging success/failure may be inappropriate to the NHS, and hence account for the high failure rate.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** To compare medical with surgical management in terms of efficacy and morbidity **Study dates** Not stated **Source of funding** Reproductive Health Research Fund	**(median (range))** Medical: 80 (35-140) Surgical: 93 (44-161) **Inclusion criteria** History of amenorrhoea followed by abdominal cramping and vaginal bleeding Uterine size of 14 weeks or less, evaluated clinically before randomisation Dilated cervical os and palpable products of conception No foul smelling products Temperature below 37.5 degrees No excessive vaginal bleeding requiring immediate surgical evacuation Haemoglobin >90g/l after resuscitation No contraindication to		completeness. Surgical Curettages were performed twice a day. No further details are given. Chi-squared, Mann-Whitney and Wilcoxon matched pairs test were used for statistical analysis. **Outcomes reported** **1. Need for further intervention** The decision to proceed with curettage for failure of the original treatment was made 12 hours later. **2. Need for a blood transfusion** This is reported as the number of women requiring >1 unit of blood	outcome) **Need for a blood transfusion (number of events/total (%))** Medical: 7/23 (30.4) Surgical: 7/27 (25.9)	**Other information** Incomplete miscarriage only **Early cessation of trial** This trial protocol included an interim analysis of 50 patients, and the trial was stopped at this point. This also resulted in unequal size of trial arms.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	prostaglandin treatment **Exclusion criteria** Not stated				
Full citation Fang,A., Chen,Q., ZHENG,W., Li,Y., CHEN,R., Termination of Missed Abortion in A Combined Procedure: A Randomized Controlled Trial, Journal of Reproduction and Contraception, #20, 45-49, 2009 **Ref Id** 78087 **Country/ies where the study was carried out** China **Study type** Randomised controlled trial **Aim of the study** To access an ideal procedure of terminating missed miscarriage within 12 weeks of gestational	**Sample size** N=75 **Characteristics** There was no significant difference between age, parity, gravity, amenorrhea or gestational age between the groups. **Inclusion criteria** Healthy Within legal ages for participation Missed miscarriage identified via: - irregular intrauterine gestation sac in a maximum diameter of 20mm with no embryo observed - impaired uterine gestation sac development >1 week	**Interventions** Medical management n=45 (Note: in their protocol, this is split into two randomised groups with two different medical protocols - results have been pooled by the technical team) **Comparator** Surgical management n=30	**Details** Enrolled women were suitably randomised to receive either surgical management, or one of two medical protocols (the trial had 3 arms): <u>Medical</u> Women received one of the following regimens: - 0.4 mg vaginal misoprostol every 3 hours up to five doses (n=15) - 200mg oral mifepristone given 36-48 hours before 0.4mg of vaginal misoprostol every 3 hours up to five doses (n=30) <u>Surgical</u> Women received 0.4mg of vaginal misoprostol 3 hours prior to a vacuum aspiration. No follow-up is reported.	**Results** **<u>Need for unplanned intervention (number of events/total (%))</u>** Medical: 35/45 (77.8) (5 of these were reported to be emergency curettages) Surgical: 0/30 (0) **<u>Pain</u>** **a. Severity score/10 (number of women/total (%))** **Medical:** 0-3: 17/45 (37.8) 4-6: 23/45 (51.1) 7-10: 5/45 (11.1) **Surgical**	**Limitations** **<u>Intention-to-treat</u>** 30 women were initially randomised to the misoprostol only group, however 15 were excluded because they required an emergency curettage due to haemorrhage. They are not included in the population size of this study, as nothing is reported about them. **<u>Inconsistent reporting</u>** This paper reports that in the mifepristone/misoprostol group, there was 90% complete expulsion after medication. However, it also reports that 23/30 women required curettage, and that a similar proportion of women in each medical group required curettage. It is unclear what their definition of success is.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
age. **Study dates** September 1st 2005 to February 28th 2007 **Source of funding** Not stated	- intrauterine gestation sac >6mm in maximum diameter, embryo visualised without cardiac canal beating Impaired intrauterine gestation sac development, with gestational age or 84 days or less No significant pre-treatment bleeding, except occasional dotting Closed external cervical orifice before treatment Informed and agreed to accept medical and/or surgical treatment Informed and agreed to have vacuum aspiration in case of failure of medical treatment Informed and agreed to participate, capable of trial accomplishment Haemoglobin >100g/L **Exclusion criteria** Allergic to mifepristone or		**<u>Outcomes reported</u>** **1. Need for unplanned intervention** This paper reports the number of women in each medical group that required curettage. **2. Pain** Women were asked to classify their pain from 0-10, with 0 being painless and 10 being severe pain. Time of assessment is not stated. **3. Measures of satisfaction** Women were asked to rank their satisfaction level, out of "satisfied", "acceptable" or "dissatisfied".	0-3: 12/30 (40) 4-6: 15/30 (50) 7-10: 3/30 (10) **<u>Measures of satisfaction</u>** **a. Reported satisfaction (number of events/total (%))** Medical: 22/45 (48.9) Surgical: 24/30 (80) (Note: the remainder are reported to have classed it as "acceptable")	**Other information** Missed miscarriage only Women were randomised into one of three arms, however for the purposes of this review, data from the two medical arms have been pooled by the technical team. The misoprostol only group was terminated ahead of time due to poor effectiveness. No follow-up is reported, therefore the high failure rate of the medical protocol could have occurred if they only waited for the 5 doses (15 hours) before judging failure.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	misoprostol Contraindication to mifepristone (chronic adrenal failure, inherited porphyrin disease) or prostaglandin (coronary artery stenosis, glaucoma, sickle cell disease, diastolic blood pressure > 90 mmHg, systolic blood pressure < 90 mmHg, bronchial asthma) History of thrombosis or severe hepatic function impairment Prolonged remedy utility history (i.e anti-TB drugs, anti-epilepsy drugs or anti-depressive drugs) Coagulation disorder or anti-coagulate utility Relatively contraindicative to women with uterine or cervical operation history Women during breast-feeding Severe tobacco addiction (>20/day) Risk factors for other cardiovascular diseases				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Lee,D.T., Cheung,L.P., Haines,C.J., Chan,K.P., Chung,T.K., A comparison of the psychologic impact and client satisfaction of surgical treatment with medical treatment of spontaneous abortion: a randomized controlled trial, American Journal of Obstetrics and Gynecology, 185, 953-958, 2001 **Ref Id** 78251 **Country/ies where the study was carried out** Hong Kong **Study type** Randomised controlled trial **Aim of the study** To compare the psychologic impact and client satisfaction of routine surgical evacuation of the uterus with medical evacuation in the case of miscarriage.	**Sample size** N=215 **Characteristics** **Age/years (mean (SD))** 31.2 (6.0) **Number of children (mean (SD))** 0.94 (0.97) **Inclusion criteria** Clinical diagnosis of miscarriage (made on the basis of history, examination and documentation of cervical status) TVS evidence of retained products of conception **Exclusion criteria** Severe blood loss Sepsis Known allergy to prostaglandins or their	**Interventions** Medical management n=104 **Comparator** Surgical management n=111	**Details** Full details of the medical and surgical management are found in Chung et al. 1999. This paper documents data from the first part of the trial. Assessments were done at 2 weeks and 6 weeks, when women returned to the hospital. A sample size calculation was done, but not for outcomes relevant to this review. **Outcomes reported** **1. Measures of satisfaction** Satisfaction with the mode of treatment was assessed by research assistants using a semi-structured interview, including four items adapted from a Client Satisfaction Questionnaire and four items specifically for the local population. Assessment was done at 6 weeks, due to the fact that some complications take time to develop. **2. Emotional and psychological outcomes** Social perfomance schedule	**Results** **Measures of satisfaction** **a. Satisfaction score (mean (SD))** Medical: 2.75 (0.54) Surgical: 2.98 (0.44) (Note: in the medical group, women for whom misoprostol suceeded were less satisfied than women who need further surgery (p<0.001)) **b. "Would choose again" (number of women/total (%))** Medical: 56/92 (60.9) Surgical: 45/93 (48.4) (Note: in the medical group, 79% of women for whom misoprostol was successful would choose it again, whereas only 36% of women who needed further surgery would choose it again)	**Limitations** **Loss to follow-up** Medical: 104 completed social performance at 2 weeks. 92/104 (88.5%) completed satisfaction scores at 6 weeks Surgical: 111 completed social performance at 2 weeks. 93/111 (83.8) completed satisfaction scores at 6 weeks **Other information** This is a psychological analysis of some of the patients included in the Chung et al. 1999 trial. This paper examines women recruited from October 1995 to June 1996, however the main trial continued until January 1998. Satisfaction scores were reported separately for those who received misoprostol only, and those who needed later surgery. Pooled means and standard deviations were calculated by the technical team.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates October 1995 to June 1996 **Source of funding** Health Services Research Fund of Hong Kong Hospital Authority	analogues History of asthma Any reason, in the opinion of the attending physician, that the patient was unsuitable for misoprostol treatment		was assessed at 2 weeks, due to the fact that any social dysfunction associated with miscarriage is unlikely to be long-lasting. The semi-structured interview covers 8 areas of social activities, including household management, employment, child care, intimate relationship with spouse and social presentation of self, and provides a quantitative assessment. (Note: Although not indicated in the paper, research by the technical team found that a score of 0 is the best possible, illustrating no disablement. Anything over 0 indicates some degree of disablement.)	**<u>Emotional and psychological outcomes</u>** **a. Social performance schedule (mean (SD))** Medical: 0.14 (0.26) Surgical: 0.16 (0.29) p=0.93	
Full citation Shwekerela,B., Kalumuna,R., Kipingili,R., Mashaka,N., Westheimer,E., Clark,W., Winikoff,B., Misoprostol for treatment of incomplete abortion at the regional hospital level: results from Tanzania, BJOG: An International Journal of	**Sample size** N=300 **Characteristics** The two groups were not significantly different in age, education or parity. However, 67% of women in the medical group were married	**Interventions** Medical management n=150 **Comparator** Surgical management n=150	**Details** Eligible women presenting to Kagera Regional Hospital were suitably randomised to medical or surgical management. <u>Medical</u> Women received 600 micrograms of oral misoprostol	**Results** **<u>Need for unplanned intervention (number of events/total (%))</u>** Medical: 1/150 (0.7) (1 woman presented at the hospital several weeks after misoprostol treatment. Staff	**Limitations** **<u>Induced abortion rates</u>** Medical: 22-32% Surgical: 35-47% This may impact generalisability to the UK

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Obstetrics and Gynaecology, 114, 1363-1367, 2007 **Ref Id** 78461 **Country/ies where the study was carried out** Tanzania **Study type** Randomised controlled trial **Aim of the study** To investigate the safety, efficacy and acceptability of misoprostol versus manual vacuum aspiration for treatment of incomplete miscarriage **Study dates** July 2004 to April 2005 **Source of funding** Not stated	compared to 49% in the surgical group (p=0.008). **Induced abortion in current pregnancy (%)** **a. Reported by women** Medical: 22% Surgical: 35% p=0.015 **b. Suspected by staff** Medical: 32% Surgical: 47% p=0.009 **Inclusion criteria** Live and work within 1 hour of the hospital Incomplete miscarriage, judged by past or present history of bleeding in this pregnancy and cervical os open by visual/digital inspection Uterine size of no greater		in one dose. Surgical Manual vacuum aspiration, using only verbal anaesthesia (reassurance) was given. All women were observed for a maximum of three hours after treatment, and in the absence of danger signs were discharged. No admission was offered. Antibiotics were given as needed, not routinely. 17 women in the medical group and 31 in the surgical group received antibiotics on the day of their treatment. Women were requested to return to the hospital 7 days after treatment. If miscarriage was complete, women were released from the study. If miscarriage was incomplete, women were offered the choice between an additional follow-up visit in one week with no further intervention in the interim, or immediate surgical evacuation. If the miscarriage was still not complete, women underwent MVA. Routine ultrasonography was not used for initial diagnosis or determination of treatment	unaware of the study performed a routine MVA without assessing that the miscarriage was still incomplete or offering the woman a chance to let it spontaneously resolve) Surgical: 0/150 (0) **Incidence of side effects/complications (number of events/total (%))** **a. Infection** Medical: 0/150 (0) Surgical: 0/150 (0) **b. Nausea** Medical: 38/150 (25.3) Surgical: 9/150 (6) **c. Vomiting** Medical: 17/150 (11.3) Surgical: 6/150 (4)	population. **Anaesthesia** Women in the surgical group received verbal anaesthesia only, however this does not appear to have impacted satisfaction levels. **Lack of ultrasound** The study could have included women with complete miscarriages, because ultrasound was not used for diagnosis. **Other information** Incomplete miscarriage only There was no loss to follow-up. This study was conducted in a lower level facility in a developing country.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	than 12 weeks since last menstrual period Woman in good health Woman willing to return for follow-up **Exclusion criteria** Signs of severe infection: foul-smelling discharge, fever>39 degrees, or pulse >110/minute Known allergy to misoprostol		success. Chi-squared and t-tests were used to analyse differences between groups. **Outcomes reported** **1. Need for unplanned intervention** They defined "success" as complete uterine evacuation after initial treatment, with no need for a secondary surgical procedure. Therefore, those requiring unplanned interventions are those for whom treatment "failed." **2. Incidence of side effects/complications** Assessed by observation after administration of misoprostol, and at exit interview when women were asked to report any adverse effects. Pelvic infection was assessed clinically at follow-up interview, occurring at 1-2 weeks after treatment (microbiological or blood tests were not available).	**Pain** **a. Severity/7 (mean)** Medical: 3.0 Surgical: 3.5 p<0.001 (no test statistic given) **Measures of satisfaction (number of events/total (%))** **a. Reported satisfaction** Medical: 149/150 (99.3) (out of these women, 113 were "very satisfied") Surgical: 150/150 (100) (out of these women, 83 were "very satisfied") **b. "Would choose again"** Medical: 147/150 (98) Surgical: 139/150 (92.7) p=0.029 (no test statistic given)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			3. Pain Severity of pain was assessed on a Likert scale based on women choosing which of seven increasingly larger circles (depicted on a card) repreesented what they had experienced in connection with their miscarriages. **4. Measures of satisfaction** Women were to classify their satisfaction level as "very satisfied", "satisfied", "unsatisfied" or "very unsatisfied." For the purposes of this analysis, the technical team have combined "very satisfied" and "satisfied." Women were also asked if they would choose the method again.		
Full citation Smith,L.F.P., Ewings,P.D., Quinlan,C., Incidence of pregnancy after expectant, medical, or surgical management of spontaneous first trimester miscarriage: Long term follow-up of miscarriage treatment (MIST) randomised controlled trial, BMJ, 339, 910-, 2009	**Sample size** N=515 **Characteristics** Details of the characteristics of the two groups are not given. Overall data is provided, but this includes women with expectant management.	**Interventions** Medical management n=252 **Comparator** Surgical management n=263	**Details** For full details of the medical and surgical management, see Trinder et al. 2006. In 2005-07, trial participants and their GPs were sent a postal questionnaire. If question packs were returned "addressee unknown," they used the Office of National Statistics to identify the woman's current health	**Results** **Live birth rate (number of women/total (%))** Medical: 181/230 (78.7) Surgical: 192/235 (81.7)	**Limitations** **Population** Population denominators include women who did not want to conceive again, and the proportion of such women in each group was not reported. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 78470 **Country/ies where the study was carried out** UK **Study type** Randomised controlled trial **Aim of the study** To compare fertility rates after three methods of managing early miscarriage in women recruited to the MIST randomised controlled trial. **Study dates** Recruitment occurred May 1997 to December 2001. Follow-up was done in 2005-2007. **Source of funding** BMA Claire Wand Fund. Sponsorship and research governance was provided by East Somerset Research Consortium	**Inclusion criteria** See Trinder et al. 2006 **Exclusion criteria** See Trinder et al. 2006 Opting out of follow-up Original GP advised against follow-up		authority information. The health authorities were then requested to forward a pack to her GP, for subsequent forwarding. Women's GPs were also asked for details of subsequent pregnancies, but women's replies were used if there were discrepancies. Quoted denominators sometimes varied due to occasional non-response to certain questions. **<u>Outcomes reported</u>** **Live birth rate** The only outcome reported separately for the different management groups is % of women with a live birth within 5 years of the index miscarriage		This is a follow-up paper for the MIST trial (Trinder et al. 2006) Age was associated with low birth rate, however respondents and non-respondents were not significantly different in terms of age.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Graziosi,G., Bruinse,H.W., Reuwer,P.J.H., Teteringen,O., Mol,B.J.W., Fertility outcome after a randomized trial comparing curettage with misoprostol for treatment of early pregnancy failure, Human Reproduction, Vol.20, pp.1749-1750, 2005., -1750, 2005 **Ref Id** 78597 **Country/ies where the study was carried out** The Netherlands **Study type** Letter detailing long term reproductive outcomes following a randomised controlled trial (Graziosi et al. 2004) **Aim of the study** A specific aim is not stated in this letter, however the aim of the original trial was to determine the	**Sample size** N=126 **Characteristics** See Graziosi et al. 2004 **Inclusion criteria** Participation in original trial (see inclusion criteria for Graziosi et al. 2004) Attempting to conceive **Exclusion criteria** Use of assisted reproductive technology	**Interventions** Medical management n=69 (note: 37 of these needed additional curettage, which is the total number that needed additional curettage in the original group of 79) **Comparator** Surgical management n=57 (note: 2 needed recurettage)	**Details** For full details of the trial and medical/surgical interventions, see Graziosi et al. 2004. The 154 participants of the original trial were contacted by telephone at the end of 2004. 5 women could not be contacted, 8 women were excluded because they had conceived using assisted reproductive technology, and 15 women had not tried to conceive. Women were asked about time trying to conceive, and occurrence and outcomes of subsequent pregnancies. **<u>Outcomes reported</u>** **Pregnancy rate** Reported as a relative risk for conception and on-going pregnancy at 12 weeks, and cumulative conception rates (as a %) and cumulative ongoing pregnancy rates (as a %)	**Results** **<u>Pregnancy rates (relative risk (95% CI))</u>** **a. Conception** Medical: 0.98 (0.68-1.4) Surgical: 1 **b. Ongoing pregnancy at 12 weeks** Medical: 0.98 (0.66-1.5) Surgical: 1 (Note: cumulative conception rates were 94% in both groups, and cumulative ongoing pregnancy rates were 87% in both groups)	**Limitations** **<u>Lack of methodological detail</u>** This is a letter, with very few details on outcomes and methods. It is not defined which was used as the comparator for the RR, therefore the technical team made an assumption on the basis of the original trial. **<u>Outcome of pregnancy</u>** The outcome of the pregnancies is not reported, neither is the raw incidence in each group. **<u>Variable follow-up period</u>** Women were contacted in June 2003, for a trial that initially recruited November 2001 to June 2003. Therefore, the women were not contacted at a defined time after their treatment. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
effectiveness of misoprostol treatment in women with early pregnancy failure who have been managed expectantly **Study dates** Recruitment was November 2001 to June 2003. Follow-up was done at the end of 2004. **Source of funding** Not stated					This is a follow-up of Graziosi et al. 2004 This has been designated Graziosi et al. **2005b**
Full citation Graziosi,G.C., Bruinse,H.W., Reuwer,P.J., van Kessel,P.H., Westerweel,P.E., Mol,B.W., Misoprostol versus curettage in women with early pregnancy failure: impact on women's health-related quality of life. A randomized controlled trial, Human Reproduction, 20, 2340-2347, 2005 **Ref Id** 78598 **Country/ies where the**	**Sample size** N=123 **Characteristics** See Graziosi et al. 2004 **Inclusion criteria** See Graziosi et al. 2004 **Exclusion criteria** See Graziosi et al. 2004	**Interventions** Medical management n=68 **Comparator** Surgical management n=55	**Details** For details of surgical and medical management, see Graziosi et al. 2004. Questionnaires regarding quality of life and satisfaction were sent to women, to be completed at 2 weeks after treatment (they were also done at baseline, 2 days and 6 weeks, but the results are not reported here). All questionnaires were returned in sealed envelopes. Women with missing measurements were included in the analysis if data was available for at least	**Results** **<u>Measures of satisfaction (number of events/total (%))</u>** **a. Satisfaction score/4 (with recovery)** Medical: 1: 5/68 (7.4) 2: 12/68 (17.6) 3: 34/68 (50)	**Limitations** **<u>Differential loss to follow-up</u>** Medical group: 79 were initially randomised, but only 68 completed 2 week follow-up. Loss was 13.9% Surgical group: 75 were initially randomised, but only 55 completed 2 week follow-up. Loss was 26.7% **<u>Population</u>** Includes women of 6-14 weeks gestation, therefore an

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out The Netherlands **Study type** Randomised controlled trial **Aim of the study** To compare patients' health related quality of life after a misoprostol strategy to a curettage in women with early pregnancy failure, after failed expectant management. **Study dates** November 2001 to June 2003 **Source of funding** Not stated			two different time points. **<u>Outcomes reported</u>** **1. Satisfaction** Client satisfaction was measured 2 weeks after treatment, using a questionnaire derived from the Client Satisfaction Questionnaire. They assessed satisfaction with recovery after treatment and whether women would "certainly choose the same method again". Satisfaction scores range from 1 to 4, with higher scores indicating greater satisfaction. **2. Emotional and psychological outcomes** Mental health and social function are reported after randomisation, and 2 days. 2 weeks and 6 weeks after treatment, however the 2 week scores have been reported below, due to comparability with other studies. They are reported as subscales of the SF-36 scale, ranked from 1 to 100, with higher scores indicating better quality of life. Mental health is assessed as	4; 17/68 (25) Surgical: 1: 0/55 (0) 2: 10/55 (18.2) 3: 26/55 (47.3) 4: 19/55 (34.5) **b. "Would certainly choose again"** Medical: 40/68 (58.8) Surgical: 32/55 (58.2) (Note: These are the women who would "certainly" choose it again. 8/68 and 1/55 "would not" choose it again, and the remainder "might" choose it. In the misoprostol group, the decision to choose again was significantly lower in those for whom misoprostol had failed ($p<0.01$)) **<u>Emotional and psychological outcomes</u>**	unknown proportion are outside of the exact scope of the guideline. **<u>Availability of misoprostol</u>** Misoprostol was only available for women in the trial, therefore, women who did not want to participate were always treated with curettage. **Other information** **<u>Expectant management</u>** Women had already had a week of expectant management This paper has been designated Graziosi et al. **2005a**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			psychological distress and well-being, and the mean reference value for the general population is 78. Social functioning refers to limitations in common social activities resulting from health problems. Anxiety was measured using the State-Trait Anxiety Index at 2 weeks after treatment. Stait anxiety is reported here, which corresponds to momentarily experienced anxiety (trait anxiety is considered a personality trait). Scores range from 20 to 80, with higher scores indicating more anxiety. The reference value quoted for normal women is 38. (Note: pain is also reported as a component of the SF-36 scale, however it has been reported elsewhere for the same study in Graziosi et al. 2004)	**at 2 weeks after treatment (mean (SD))** **a. Mental health/100** Medical: 75 (17) Surgical: 78 (15) (Note: at 2 days after treatment, scores were Medical: 62 (17) and Surgical: 68 (21)) **b. Social function/100** Medical: 78 (24) Surgical: 80 (19) (Note: at 2 days after treatment, scores were Medical: 62 (24) and Surgical: 65 (25)) **c. Anxiety (range 20-80)** Medical: 33 (9) Surgical: 38 (10) (Note: at 2 daya after treatment, scores were Medical: 36 (10) and Surgical: 34 (7))	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Graziosi,G.C.M., Mol,B.W.J., Reuwer,P.J.H., Drogtrop,A., Bruinse,H.W., Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: A randomized trial, Human Reproduction, #19, 1894-1899, 2004 **Ref Id** 78599 **Country/ies where the study was carried out** The Netherlands **Study type** Randomised controlled trial **Aim of the study** To determine the effectiveness of misoprostol treatment in women with early pregnancy failure who have been managed expectantly **Study dates**	**Sample size** N=154 **Characteristics** **Age/years (mean (SD))** Medical: 32.5 (4.8) Surgical: 32.1 (4.1) **Gestational age/weeks (mean (SD))** Medical: 10.2 (1.8) Surgical: 10.1 (1.8) **Duration of expectant management/days (mean (SD))** Medical: 11.4 (7.4) Surgical: 10.1 (4.1) **Clinical symptoms (number (% bleeding))** Medical: 27/79 (34) Surgical: 21/75 (28)	**Interventions** Medical management n=79 **Comparator** Surgical management n=75	**Details** The study was performed in three teaching hospitals. Of 241 eligible women, 87 declined to participate, resulting in 154 participants. This fit the requirements of the sample size calculation, which calculated that 150 participants would be needed to detect a difference of 15% efficacy with 80% power. Women were suitably randomised, and randomisation was stratified for previous vaginal birth, duration of amenorrhoea (<10 or >10 weeks) and participating centre. Medical Misoprostol was given in an out-patient setting. It consisted of four tablets of 200 microgram misoprostol placed in the posterior fornix using a speculum. The effect was evaluated 24 hours after the dose, and in the presence of residual conception products, a second 800 microgram dose was administered vaginally. The patients were then assessed a further 23 hours later.	**Results** **Need for unplanned intervention (number of events/total (%))** Medical: 37/79 (46.8) (12 were emergency curettage; 20 were curettage following failure of 2 doses of misoprostol; 3 were curettage due to persistent bleeding; 2 were protocol violations because they took place after only 1 dose of misoprostol) Surgical: 6/75 (8) (2 were emergency curettage before planned surgery; 3 were repeat curettages; 1 was a hysteroscopic resection needed as a result of interuterine synechia) **Incidence of side effects/complications (number of events/total (%))** **a. Surgical complications**	**Limitations** **Population** Includes women of 6-14 weeks gestation, therefore an unknown proportion are outside of the exact scope of the guideline. **Availability of misoprostol** Misoprostol was only available for women in the trial, therefore, women who did not want to participate were always treated with curettage. **Other information** Missed miscarriage only (excludes incomplete) **Expectant management** Women had already had a week of expectant management, apart from two who were randomised after 5 and 6 days. **Time to evacuation** The authors state that the time to complete evacuation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
November 2001 to June 2003 **Source of funding** Not stated	**Nulliparous (number (%))** Medical: 33/79 (42) Surgical: 36/75 (48) **Previous miscarriage (number (%))** Medical: 15/79 (19) Surgical: 10/75 (13) **Inclusion criteria** Aged 18-45 Diagnosis of early pregnancy failure of 6-14 weeks gestation Having been managed expectantly for at least a week **Exclusion criteria** Incomplete miscarriage Haemodynamic instability History of caesarean section Known uterine anomalies		Misoprostol was considered to have failed when abnormal bleeding and signs of retained products of conception (i.e. a focal hyperechoic intrauterine mass with an anterior-posterior diameter over 15mm at sonography) were found. In the absence of complete evacuation after >3 days following first dose, curettage was performed. Surgical Curettage consisted of evacuation of the uterus under suction curettage under general anaesthesia in a day care setting, within a week of randomisation. It was considered to have failed when intervention was needed because of abnormal bleeding and signs of retained products of conception visible at sonography. In the curettage group, only patients with clinical symptoms suggesting incomplete miscarriage were given an ultrasound. **Outcomes reported** **1. Need for unplanned**	Medical: 0/79 (0) Surgical: 3/75 (4) (1 uterine perforation managed expectantly; 1 haemorrhage requiring uterotonic agents and transfusion; 1 case of amenorrhoea due to intrauterine synechia) **b. Nausea** Medical: 11/79 (13.9) Surgical: 0/75 (0) **c. Diarrhoea** Medical: 21/79 (26.6) Surgical: 0/75 (0) (Note: the authors state that the nausea and diarrhoea were not severe) **Need for a blood transfusion (number of events/total (%))**	was not decreased in women treated with misoprostol, compared with those treated with surgery, This was a result of the failure rate, and delayed diagnosis of incomplete miscarriage.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Multiple pregnancies Infection Suspicion of extra-uterine pregnancy Coagulopathies Allergy to misoprostol Severe pulmonary disease Congenital or acquired heart disease Liver disease Glaucoma Sickle cell disease Prolonged use of corticosteroids Adrenal gland insufficiency		**intervention** Includes emergency curettage, repeat curettage, curettage due to failure of medical protocol, and any further surgery required to deal with complications. **2. Incidence of side effects/complications** Patients were given a questionnaire after 2 days and 2 weeks, regarding side effects. Complications were defined as infection, need for transfusion and surgical complications like perforation and surgical tear. **3. Need for a blood transfusion** Included in reporting of complications, as described above **4. Duration of bleeding** Patients were given a questionnaire after 2 days and 2 weeks, regarding bleeding. **5. Pain** Patients were given a	Medical: 0/79 (0) Surgical: 1/75 (1.3) **Duration of bleeding/days (mean (SD))** Medical: 10.4 (5.6) Surgical: 8.7 (5.1) p=0.12 **Pain** **a. Severity/10 (mean (SD))** Medical: 5 (3) Surgical: 3 (2.4) p<0.001	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			questionnaire after 2 days and 2 weeks. Visual analogue score was used to rank severity of pain from 0 (no pain) to 10 (severe pain). It is not clear which results are reported, or whether scores were combined.		
Full citation Dabash,R., Ramadan,M.C., Darwish,E., Hassanein,N., Blum,J., Winikoff,B., A randomized controlled trial of 400-mug sublingual misoprostol versus manual vacuum aspiration for the treatment of incomplete abortion in two Egyptian hospitals, International Journal of Gynaecology and Obstetrics, 111, 131-135, 2010 **Ref Id** 81158 **Country/ies where the study was carried out** Egypt **Study type** Randomised controlled trial **Aim of the study**	**Sample size** N=697 **Characteristics** The women were not statistically different in terms of age, marital status, education, parity, previous miscarriage, previous induced abortion or haemoglobin levels. Provider's suspected that 2.0% women in the medical group and 2.3% of women in the surgical group had interfered with their current pregnancy. **Inclusion criteria** Incomplete miscarriage, defined as an open cervical os confirmed by clinical examination with either: - past or present history of	**Interventions** Medical management n=349 **Comparator** Surgical management n=348	**Details** A sample size calculation calculated that 668 women were needed to detect a one-sided difference of 4% or more in efficacy. Women presenting at two large tertiary hospitals (El Galaa Teaching Hospital, Cairo and Shatby Maternity Hospital, Alexandria) were suitably randomised to medical or surgical management. Medical Women received two 200 microgram misoprostol tablets to hold under the tongue for 20 minutes, after which time they were instructed to swallow any remnants. Discharge was at the provider's discretion, generally within 1 hour. Surgical Women underwent manual vacuum aspiration. Pain management depended on	**Results** **Need for unplanned intervention (number of events/total (%))** Medical: 6/348 (1.7) (2 due to persistent heavy bleeding, 3 with evidence of retained products of conception at follow-up, and 1 woman who underwent surgery a few hours after misoprostol (due to light-moderate bleeding) by a provider unfamiliar with the method and study protocol) Surgical: 1/347 (0.3) (1 woman underwent a second evacuation at a private clinic following persistent pain and bleeding) **Incidence of side effects/complications (number of events/total**	**Limitations** **Anaesthesia** The type of anaesthesia women received during manual vacuum aspiration was as follows: Sedative (diazepam): 75% Verbal/none: 26% General: 7% Local: <1% This could have impacted satisfaction levels. **Loss to follow-up** 1 patient from each group was lost for the primary outcome of efficacy (i.e. need for unplanned intervention). 21/349 (6.0%) were lost from the medical group and 32/348 (9.2%) from the surgical group for reporting of adverse effects, pain and bleeding.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare the safety, efficacy and acceptability of 400 microgram sublingual misoprostol with that of manual vacuum aspiration in two Egyptian hospitals. **Study dates** February 7th 2007 to October 28th 2008 **Source of funding** David and Lucille Packard Foundation	vaginal bleeding - evidence of retained products of conception if ultrasound was performed Maximum uterine size of 12 weeks of gestation At least 21 years old Live or work within 1 hour of the hospital Agreed to provide contact information and return for follow-up **Exclusion criteria** Known allergy to prostaglandins Symptoms of possible ectopic pregnancy Haemodynamic instability Signs of infection requiring immediate intervention		provider preference, and ranged from verbal anaesthesia only to general anaesthesia. Discharge was variable and dependent on hospital procedure. Antibiotics were only prescribed if there were signs of infection. Women in both groups were provided with 500-mg paracetamol to take as needed. All women were scheduled for a 1-week follow-up visit and given a study card to record adverse effects. Women with a closed cervical os and no signs of incomplete miscarriage were deemed to have been successful and were discharged. Women with signs of RPOC and no complications were given the option of waiting an additional week before surgical evacuation. If miscarriage was still not complete 1 week later, women underwent immediate surgery. Women who failed to return for follow-up were contacted by telephone to reschedule. If they were contactable but unwilling or unable to return, they provided most of their follow-up information by telephone.	**(%))** **a. Nausea** Medical: 132/327 (40.4) Surgical: 83/316 (26.3) **b. Vomiting** Medical: 32/327 (9.8) Surgical: 17/316 (5.4) **Need for a blood transfusion (number of events/total (%))** Medical: 0/348 Surgical: 0/347 **Duration of bleeding/days (mean)** **a. Heavy** Medical: 1.13 Surgical: 1.40 p=0.54 **b. Normal** Medical: 2.26 Surgical: 1.52 p<0.01	**Other information** incomplete miscarriage only

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Chi-squared or t-tests were used, as appropriate, to analyse outcomes. **<u>Outcomes reported</u>** **1. Need for unplanned intervention** The number of women with RPOC requiring further surgery. **2. Incidence of side effects/complications** Self-reported on a study card at home, and brought to 1-week follow-up visit. **3. Need for a blood transfusion** Data was collected on study forms by trained physicians, nurses and social workers. **4. Duration of bleeding** Assessed at 1-week follow-up, and classed as heavy, normal or light compared to normal periods.	**c. Light** Medical: 3.23 Surgical: 2.73 p<0.01 Note: "light bleeding" has been used in the GRADE table, because the greatest number of women experienced it, and therefore it best represents the experience of the group. However, this value under-represents total length of bleeding, because women could appear in multiple categories of bleeding and therefore have a total duration that is longer than the length of any one type of bleeding. **<u>Pain</u>** **a. Incidence (number of events/total (%))** Medical: 287/327 (87.8) Surgical: 240/316 (75.9) **b. Duration/days (mean)** Medical: 2.63	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			5. Pain Reported as the incidence/duration of pain or cramps. **6. Unscheduled visit to a medical facility** Method of assessment not reported, neither is it reported if the women were hospitalised, they simply refer to a "visit." **7. Measures of satisfaction** Women were asked whether they were satisfied, and whether they would choose the method again.	Surgical: 2.63 p=0.98 **<u>Unscheduled visit to a medical facility</u>** **a. Visits (number of events/total (%))** Medical: 10/348 (2.9) Surgical: 1/347 (0.3) (All visits were before day 7; reasons for the visit, and whether the women were admitted are not reported) **<u>Measures of satisfaction (number of events/total (%))</u>** **a. Reported satisfaction** Medical: 337/348 (96.8) Surgical: 341/347 (98.3) RR=0.99 (95% CI 0.96-1.01) **b. "Would choose again"** Medical: 285/348 (81.9) Surgical: 218/347 (62.8)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RR=1.30 (95% CI 1.19-1.43) NOTE: **The best features of the methods were as follows:** Medical: "Avoids surgery/hospitalisation" (90.5%), "Avoids anaesthesia" (36.3%) Surgical: "Fast" (50.7%), "Avoids surgery/hospitalisation" (30.1%) **The worst features of the methods were as follows:** Medical: "Pain" (33.9%), "Other adverse effects" (20.9%) Surgical: "Invasive/complicated" (69.9%), Pain (15.9%)	
Full citation Hinshaw,H.K.S., Medical management of miscarriage, Problems in early pregnancy - advances in diagnosis and management, 1997., p 284	**Sample size** N=437 (Note: The randomised portion of the trial comprised 200 women. A further 237 women participated, however	**Interventions** Medical management n=186 (of which 100 were randomised to	**Details** 237 women had a preference for one method of management, and were given their preferred method. A further 200 women were randomised to either medical or surgical management	**Results** **<u>Measures of satisfaction</u>** **a. "Would choose again" (%)** Randomised to medical: 85	**Limitations** **<u>Randomisation</u>** Method of randomisation not stated

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
- 295 **Ref Id** 81179 **Country/ies where the study was carried out** UK **Study type** Partially randomised trial (included primarily for qualitative data about preference for one mode of management) **Aim of the study** To compare the efficacy of the new medical methods with the gold standard of surgical uterine evacuation **Study dates** Not stated **Source of funding** Scottish Office Home and Health Department	they were not prepared to be randomised and were allocated to their chosen imanagement method) **Characteristics** **Study arms (number of women/total (%))** Preferred medical: 86/437 (19.7) Preferred surgical: 151/437 (34.6) Randomised to medical: 100/437 (22.9) Randomised to surgical: 100/437 (22.9) There were no differences in physical, reproductive or demographic characteristics between the four study arms. **Inclusion criteria** Not stated **Exclusion criteria** Not stated	medical management) **Comparator** Surgical management n=251 (of which 100 were randomised to surgical management)	(method of randomisation not stated). Medical Women with an intact intrauterine sac (missed miscarriage or anembryonic pregnancy) were given 200 mg of mifepristone. Three sequential doses of oral misoprostol were given 2 hours apart (400/600/400 micrograms). Women with an incomplete miscarriage were given 400 micrograms of oral misoprostol, and then 200 micrograms two hours later. Surgical Surgical uterine evacuation was done under general anaesthesia, using suction curettage in cases of women with an intact intrauterine sac. Women attended for a review appointment a median of 15 days later (399 women attended, a 91.3% response rate). Complete uterine evacuation was confirmed using clinical history and examination, without arranging routine ultrasonography.	Randomised to surgical: 99 Chose medical: 85 Chose surgical: 98 (Note: Loss to follow-up was not reported for each group individually, therefore denominators are unknown and raw numbers cannot be calculated) Overall (including randomised and non-randomised participants), the acceptability was lower for medical methods (p<0.001). However, this was not the case for women with incomplete miscarriage, or women with missed abortion/anembryonic pregnancies of <71 day gestation. Generally, the authors felt that the symptomatology associated with medical evacuation affected how women perceived the overall acceptability of the methods **Reasons for preference** 54.2% of women had a preference for one method. **Prefer medical (number of**	**Loss to follow-up** 38/437 (8.7%) did not return for follow-up visit. Therefore, the denominator is unknown for satisfaction measures. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			General practioners were sent a questionnaire eight weeks after the miscarriage, to record any complications not reported by the patients. **<u>Outcomes reported</u>** **1. Satisfaction** Women were asked whether they would choose the same method again in the future. The time of the assessment is not stated, however it is likely to have been at the follow-up appointment. The outcome is reported as a % of women in each group, both randomised and non-randomised. **2. Reasons for preference for one method** Women who refused to be randomised were asked to give reasons for their choice. **3. Psychological dysfunction** This was measured using the HAD scale, at the time of miscarriage and at 2 week follow-up, however randomised and non-randomised cohorts	**women/total (%))** Avoidance of general anaesthetic or surgery: 48/84 (57.1) More natural/in control: 30/84 (35.7) **Prefer surgical (number of women/total (%))** Timescale: 106/147 (72.1) Issues of awareness etc: 63/147 (42.9) Avoidance of pain/bleeding: 60/147 (40.8) Method more effective: 19/147 (12.9) **<u>Psychological dysfunction</u>** The authors report an average "borderline raised" level of anxiety at the time of miscarriage, with no differences between medical and surgical groups (combined randomised and non-	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			were not reported separately. The majority of the outcomes reported in the paper, including efficacy measures, are not reported here, because they report medical vs. surgical only, without separating non-randomised and randomised cohorts.	randomised). At discharge, heavy smokers or women with a history of psychiatric or psychological dysfunction tended to have higher HAD scores, and the authors speculate that these women may need special support. Levels had returned to normal for most women by the 2-weeks review, with those reporting excessive tiredness or pain more likely to have a high maintained score.	
Full citation Tam,W.H., Tsui,M.H., Lok,I.H., Yip,S.K., Yuen,P.M., Chung,T.K., Long-term reproductive outcome subsequent to medical versus surgical treatment for miscarriage, Human Reproduction, 20, 3355-3359, 2005 **Ref Id** 81253 **Country/ies where the study was carried out**	**Sample size** N=261 **Characteristics** **Age/years (mean (range))** Medical: 30 (25-33) Surgical: 30 (26-33) **Number of previous miscarriages (number (%))** **Medical:**	**Interventions** Medical management n=131 **Comparator** Surgical management n=130	**Details** For details of the surgical and medical management, see Chung et al. 1999. Trial participants were followed up prospectively by telephone interview at a median (range) of 6 (4-9) years. 423 women could be contacted, but 4 declined to be interviwed. 261 of these women reported attempting to have become pregnant since the treatment of the index miscarriage, therefore form the population for this study. A structured questionnaire was used to	**Results** **Pregnancy rates** **a. Conception rate (number of events/total (%))** Medical: 128/131 (97.7) Surgical: 127/130 (97.7) p=0.99 **b. Live birth rate (number of events/total (%))** Medical: 109/131 (83.2) Surgical: 112/130 (86.2)	**Limitations** **Loss to follow-up** Loss to follow up was 38.3% of original trial participants. Respondents available for follow-up were significantly older than those not available, and may have had different reproductive outcomes. **Generalisability of population** The authors state that this cohort may have a lower

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Hong Kong **Study type** Randomised controlled trial **Aim of the study** To evaluate and compare long term fertility and pregnancy outcomes following medical or surgical evacuation for the treatment of miscarriage. **Study dates** Recruitment was from October 1995 to January 1998. **Source of funding** Not stated in this paper, but the original trial, Chung et al. 1999, was funded by a grant from Health Services Research Fund of Hong Kong	0: 89 (67.9) 1: 33 (25.2) >2: 9 (6.9) **Surgical:** 0: 90 (69.2) 1: 30 (23.1) <2: 10 (7.7) **<u>Previous treatment complications (number (%))</u>** **Medical:** Uterine perforation: 0 (0) PID: 4 (3.1) **Surgical:** Uterine perforation: 2 (1.5) PID: 2 (1.5) There were no significant differences between age, number of previous live births, termination of pregnancies, miscarriages and methods of contraception		conduct an interview on desire to become pregnant, contraceptive history, history of infertility, assisted reproduction, and outcomes of pregnancies immediately after the index miscarriage. **<u>Outcomes reported</u>** **1. Pregnancy rates** The outcome measure was dichotomous as either "pregnant" or "not pregnant" achieved by natural conception over the defined period. The number of women with live births were also reported. If the pregnancy was achieved using any infertility treatments, it was excluded from analysis.	(note: these % do not match those reported in the paper, because they report number of live births as a % of total births, not women)	fecundity than the general population, due to the number of previous miscarriages and terminations. **Other information** This is a follow-up paper to Chung et al. 1999

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	used. **Inclusion criteria** Participation in the original trial (Chung et al. 1999) Desire to get pregnant **Exclusion criteria** Previous miscarriage Molar pregnancy Known history of infertility Sterilisation during last miscarriage				
Full citation Montesinos,R., Durocher,J., Leon,W., Arellano,M., Pena,M., Pinto,E., Winikoff,B., Oral misoprostol for the management of incomplete abortion in Ecuador, International Journal of Gynaecology and Obstetrics, 115, 135-139, 2011 **Ref Id** 154641	**Sample size** N = 242 **Characteristics** Women in the misoprostol group were significantly younger than those in the surgical group. Apart from that, there were no significant differences in the arms with respect to education, parity, marital status, pretreatment haemoglobin and previous	**Interventions** Medical management (n = 122) **Comparator** Surgical management (n = 120)	**Details** The study was conducted in a large public tertiary level maternity hospital and a small private secondary-level clinic. Women presenting with complications of miscarriage were screened by study physicians. Those meeting the inclusion criteria had their incomplete miscarriage verified by ultrasound. Any eligible women were counselled by hospital staff and informed consent was obtained. Any women who did not wish to	**Results** <u>Need for an unplanned intervention (n/total (%))*</u> Medical: 6/116 (5.7) Surgical: 0/97 (0) * this is as reported in the paper, and does not include the women lost to follow-up. 1 was for an incomplete abortion at study end, 2 were medically indicated before the study end, and 3 was for provider or woman choice.	**Limitations** **<u>Induced abortion</u>** 3/122 (2.5%) in the medical arm and 4/120 (3.3%) of women in the surgical arm reported that their current abortion was induced. The providers had suspicion that the woman had interfered in the pregnancy for 5 (4.1%) of the medical arm and 6 (5.0%) of the surgical arm. **<u>Loss to follow-up</u>**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Ecuador **Study type** Randomised controlled trial **Aim of the study** To assess the feasibility of introducing misoprostol for the treatment of incomplete miscarriage **Study dates** November 2006 to November 2007 **Source of funding** Grant from the David and Lucille Packard Foundation	miscarriage/abortion. **Inclusion criteria** Open cervix Vaginal bleeding during the current pregnancy Uterine size of 12 weeks or less **Exclusion criteria** Empty gestational sac (missed miscarriage) Ectopic pregnancy Complete miscarriage Known allergies to prostaglandins Signs of severe infection or ill health Younger than 14 years old Lived or worked more than 1 hour from the study site Unwilling to provide contact information for follow-up		participate were given standard surgical care. Consenting women were randomised using a computer generated random sequence in blocks of 10, stratified by site. The randomisation scheme generated sequentially numbered sealed opaque envelopes that revealed treatment allocation on opening. Treatment allocation was concealed from providers and participants until after the clinical diagnosis was confirmed and informed consent was gained. Women received their assigned method of management on the day of enrolment. <u>Medical</u> Women assigned to the medical arm swallowed three misoprostol tables (200 micrograms each) in the presence of study staff <u>Surgical</u> Women assigned to the surgical arm received a manual vacuum aspiration (MVA) according to the standard of care at the site, which consisted of general anaesthesia at the hospital and local anaesthesia at the clinic.	<u>Adverse effects (number/total (%))</u> a. Nausea Medical: 5/106 (4.7) Surgical: 0/97 (0) b. Vomiting Medical: 2/106 (1.9) Surgical: 0/97 (0) c. Fever Medical: 3/106 (2.8) Surgical: 1/97 (1.0) d. Shivering/chills Medical: 1/106 (0.9) Surgical: 2/97 (2.1) e. Other adverse effects Medical: 5/106 (4.7) Surgical: 1/97 (1.0) (Note: these were reported to include migraine, diarrhoea, dizziness and painful urination) **<u>Measures of pain</u>** a. Incidence Medical: 67/106 (63.2) Surgical: 44/97 (45.4)	39/242 (16%) of women did not return for their follow-up visit and were excluded from the analysis. This was 16 (13%) women from the medical arm and 23 (19%) women from the surgical arm. **<u>Ultrasound confirmation</u>** In the private clinic, ultrasound was more frequently used for women treated with misoprostol than it was for those treated with MVA($p < 0.0001$). In the public hospital, more women in the medical arm received ultrasound but the difference was not significant ($p = 0.079$) **Other information** Incomplete miscarriage only

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			Antibiotics were not routinely given and all participants were offered prescriptions for ibuprofen to manage their pain at home if needed. All patients remained at the study for 1-3 hours. Before discharge, women were counselled on the expected side effects and scheduled a follow-up appointment. Women were requested to record adverse effects in a standardised register that they took home with them. Providers were able to intervene surgically at any time if it was medically necessary or the women requested it. Women were scheduled to return at 1 week for an evaluation. If there was evidence of substantial retained products of conception, the woman was offered an immediate surgical evacuation or to wait another week to see if the products would be expelled. There was no option for repeat misoprostol treatment. Complete uterine evacuation was determined by ultrasound and/or clinical exam. The women were asked to detail any adverse effects experienced and to discuss	b. Duration/days (mean) Medical: 2.5 Surgical: 2.6 (p = 0.739) Note: the authors additionally report that most women reported their severity of pain as a 2/7, which was similar for both groups. **Duration of bleeding/days (mean)** a. Heavy bleeding Medical: 1.9 Surgical: 2.5 (p = 0.456) b. Normal bleeding Medical: 2.3 Surgical: 1.5 (p = 0.030) c. Light bleeding Medical: 3.4 Surgical: 3.0 (p = 0.223) **Measures of satisfaction (number/total (%))** **a. Overall satisfaction level**	

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			their symptoms. Women with no further signs and symptoms, confirmed with a bimanual exam were discharged after an exit interview. At follow-up, women received a semi-structured interview about their experience. The study had originally aimed to enrol 500 women within a year; however during the time frame, only half that number were enrolled. The trial was therefore stopped after a year and analysis was conducted on the number of cases available. Analysis was done using chi-squared or Fisher exact test for categorical variables, and using a t-test for continuous variables. $p \leq 0.05$ was considered significant. <u>Outcomes reported</u> 1. Need for further intervention: the number of women requiring a surgical completion 2. Adverse effects: incidence of nausea, vomiting, fever and shivering/chills were assessed through a combination of the exit interview and the registry that women filled in at home 3. Pain: assessed using a 7	- Very satisfied Medical: 50/106 (47.2) Surgical: 39/97 (40.2) - Satisfied Medical: 52/106 (49.1) Surgical: 55/97 (56.7) - Unsatisfied Medical: 4/106 (3.8) Surgical: 3/97 (3.1) **<u>b. Would choose same method again</u>** Medical: 99/106 (93.4) Surgical: 85/97 (87.6) The reported best features of medical management were avoid surgery (44%), avoid anaesthesia (43%), rapid effective method (26%) and no pain (21%). The reported best features of surgery were no pain (57%), few adverse effects/complications (23%) and good hospital care (21%).	

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			point visual analogue scale; incidence and duration are also reported 4. Bleeding: number of days with heavy bleeding (> menstruation), normal bleeding (= menstruation) and light bleeding (< menstruation) are reported 5. Satisfaction: overall satisfaction was assessed using a 4-point Likert scale; women were also asked if they would choose the same treatment again		
Full citation Taylor,J., Diop,A., Blum,J., Dolo,O., Winikoff,B., Oral misoprostol as an alternative to surgical management for incomplete abortion in Ghana, International Journal of Gynaecology and Obstetrics, 112, 40-44, 2011 **Ref Id** 154665 **Country/ies where the study was carried out** Ghana	**Sample size** N = 230 **Characteristics** There were no statistically significant differences between the two arms with regards to age, years of education, parity, previous miscarriage and previous induced abortion. **Inclusion criteria** Incomplete miscarriage, defined as: - open cervical os - uterine size equivalent to less than 12 weeks	**Interventions** Medical management (n = 113) **Comparator** Surgical management (n = 119)	**Details** A power calculation based on 98% efficacy of MVA and 80% power with an alpha of 0.05 calculated that 95 women were needed per study arm. During the study period, 230 women meeting the inclusion criteria were recruited. All women would have received MVA under local or verbal anaesthesia if misoprostol had not been available. Ultrasound confirmation of pregnancy status was not required; however providers could use ultrasound if there was any doubt about the diagnosis of incomplete miscarriage. Providers were allowed to prescribe antibiotics to treat	**Results** **<u>Need for further intervention (n/total (%))</u>** Medical: 2/113 (1.8) Surgical: 1/116 (0.9) (Note: The woman from the MVA arm underwent a repeat surgery to treat ongoing heavy bleeding after 3 days. 1 woman from the medical arm had retained products at her first follow-up visit and underwent an MVA. The other woman made an unscheduled visit after 6 days, reporting cramping and abdominal pain, and was found to have a	**Limitations** **<u>Induced abortion</u>** Providers believed that the abortion was induced for 9.2% of women in the medical arm and 12.1% of the surgical arm. (out of 76 women for whom data is reported, 13 women stated that the abortion was induced) **<u>Missing data</u>** There is varying amount of missing data for bleeding in the misoprostol arm which is not accounted for by the loss to follow-up.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised controlled trial **Aim of the study** To investigate whether oral misoprostol (600 micrograms) is an effective alternative to surgical management of an incomplete miscarriage (using manual vacuum aspiration [MVA]) **Study dates** July 16th 2004 to July 20th 2005 **Source of funding** Fred H. Bixby Foundation David and Lucille Packard Foundation	- past or present history of bleeding in the current pregnancy and/or ultrasound evidence of substantial uterine debris with evidence of fetal demise Living or working within the hospital's geographic area of coverage No known contraindications to misoprostol No signs of severe infection or temperature about 38 degrees General good health **Exclusion criteria**		infection or as prophylaxis. All study personnel were trained for 2 days regrading the interventions and the trial protocol. A pilot study of 10 women was conducted to ensure that staff were comfortable with the protocol. Any eligible women were counselled about the trial by nurses and midwives. Those that consented were randomised using a computer generated random number sequence. Allocation was concealed from providers and participants until after consent had been given, after which time the next sequentially numbered envelope was opened. **Medical** Women assigned to the medical group swallowed 600 micrograms if misoprostol in the presence of a study nurse. **Surgical** Women allocated to the surgical arm received a standard surgical evacuation using MVA. All women received paracetamol for pain	ruptured ectopic for which she had a laparotomy and blood transfusion) **Incidence of adverse effects/complications (n/total (%))** a. Nausea Medical: 7/93 (7.5) Surgical: 5/112 (4.5) b. Vomiting Medical: 5/93 (5.4) Surgical: 4/112 (3.6) c. Fever Medical: 16/93 (17.2) Surgical: 9/112 (8.0) d. Chills Medical: 10/93 (10.8) Surgical: 4/112 (3.6) **Duration of bleeding (mean)** Medical: 2.86 Surgical: 1.64 (p = 0.001) **Measures of pain** a. Incidence of pain/cramps Medical: 83/93 (89.2) Surgical: 103/112 (92.0)	**Anaesthesia** The proportion of women in the surgical arm not receiving anaesthesia is not reported, which could have affected pain and satisfaction measures and limited the applicability to the UK setting **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			management, were counselled about adverse effects, and were scheduled to return to the hospital for follow-up care 1 week later. They were also told that they could return to the hospital or contact the study providers at any time with additional questions or concerns. At the follow-up visit, the status of the women was assessed via a clinical examination, including an interview and a bimanual examination. Any women with substantial retained products (by clinical judgement and/or ultrasound) were given the option to wait an additional week, in which case another appointment was booked for day 14. Women not wishing to wait underwent immediate surgical completion with MVA. At day 14, any remaining women with retained products underwent surgery. Upon completion of treatment, women were interviewed to gauge the acceptability of the treatment. 230 were enrolled and randomised; however initial data was only available for 229 and then 11 women were lost to follow-up (5 from medical arm and 6 from surgical arm). The authors report that every	b. Duration/days (mean) Medical: 1.44 Surgical: 1.34 (p = 0.44) **Measures of satisfaction (n/total (%))** a. Overall satisfaction - Very satisfied Medical: 47/108 (44.3) Surgical: 9/110 (8.2) - Satisfied Medical: 56/108 (52.8) Surgical: 99/110 (90.0) - Unsatisfied or very unsatisfied Medical: 3/108 (2.8) Surgical: 2/110 (1.8) b. Would choose again Medical: 102/108 (95.3) Surgical: 39/110 (35.5) **Best and worst features of the methods (summary)** 64% of women in the medical arm and 77% of women in the surgical arm said that the best feature of the method was that it was simple, quick, convenient. The worst features of the	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			attempt was made to contact them. **<u>Outcomes reported</u>** 1. Need for further intervention: MVA or other surgical intervention 2. Incidence of adverse effects: assessed at exit interview 3. Bleeding: assessed at exit interview 4. Pain: assessed using a 7 point Likert scale 5. Satisfaction: assessed using a 5 point Likert scale	medical method were bleeding (26%) and pain (20%). The worst features of the surgical arm were the pain (64%), lack of confidentiality (18%) and lack of anaesthesia or pain medication (15%).	

What is the most appropriate dose of misoprostol and mifepristone to provide for managing miscarriage?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bagratee,J.S., Khullar,V., Regan,L., Moodley,J., Kagoro,H., A randomized controlled trial comparing medical and expectant management of first trimester miscarriage, Human Reproduction, 19, 266-271, 2004 **Ref Id** 65131 **Country/ies where the study was carried out** United Kingdom **Study type** Randomised controlled trial **Aim of the study** To determine whether medical management using vaginal misoprostol is superior to expectant management in	**Sample size** N=104 **Characteristics** Age/years (mean (SD)) Misoprostol: 33.2 (6.9) Placebo: 30.9 (6.3) (p=0.079) Gestational age/days (mean (SD)) Misoprostol: 73.8 (9.9) Placebo: 73.0 (11.6) (NS) Previous miscarriage (%) Misoprostol: 23.1 Placebo: 26.9 (NS) Previous abortion (%) Misoprostol: 19.2 Placebo: 30.8 (NS) Vaginal bleeding (%) Misoprostol: 67.3	**Interventions** 600 micrograms of vaginal misoprostol (repeat after 24 hours if needed) (n=52) Placebo placed vaginally (repeat after 24 hours if needed) (n=52)	**Details** All women with an incomplete miscarriage or early pregnancy < 13 weeks gestation that presented to the Early Pregnancy Assessment Unit (EPAU) of St Mary's Hospital, London, during the study period were assessed for eligibility. Of 131 eligible women, 12 elected to have surgery, 8 elected to have expectant management and 7 elected to have medical management. Therefore, 104 women were randomised. Incomplete miscarriage was diagnosed when there was a history of passage of tissue and/or blood, and was confirmed by a transvaginal ultrasound scan identifying heterogeneous material in the uterine cavity with an endometrial thickness of >15 mm. Early pregnancy failure was diagnosed when clinical examination showed a closed cervical os, and ultrasound confirmed either	**Results** Treatment success (number/total (%)) a. In women with incomplete miscarriage Misoprostol: 7/7 (100) Placebo: 12/14 (85.7) b. In women with early pregnancy failure Misoprostol: 39/45 (86.7) Placebo: 11/38 (28.9) c. Overall Misoprostol: 46/52 (88.5) Placebo: 23/52 (44.2) Need for further intervention (number/total (%)) a. In women with incomplete miscarriage Misoprostol: 0/7 (0) Placebo: 2/14 (14.3) b. In women with early pregnancy failure Misoprostol: 6/45 (13.3) Placebo: 27/38 (71.1)	**Limitations** For each outcome apart from success and need for further intervention, data is not reported separately for women with incomplete miscarriages and early pregnancy failures. **Other information** 600 VAGINAL MISOPROSTOL VS. PLACEBO EARLY PREGNANCY FAILURE + INCOMPLETE MISCARRIAGE Blinding was done. There was no loss to follow-up. Treatment doses (number/total (%)) Misoprostol - 1 dose: 17/52 (32.7) - 2 doses: 35/52 (67.3) Placebo - 1 dose: 3/52 (57.7) - 2 doses: 49/52 (94.2) Day of success (number/total (%)) Misoprostol - Day 1: 17/52 (32.7)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
reducing the need for surgical evacuation of retained products of conception. **Study dates** August 2001 to March 2002 **Source of funding** Not reported	Placebo: 75.0 (NS) Type of miscarriage (n (%)) Misoprostol: - Early pregnancy failure: 45 (86.5) - Incomplete miscarriage: 7 (13.5) Placebo: - Early pregnancy failure: 38 (73.1) - Incomplete miscarriage: 14 (26.9) **Inclusion criteria** Spontaneous incomplete miscarriage or early pregnancy failure Up to 13 weeks gestation **Exclusion criteria** Complete miscarriage (as assessed by endometrial thickness of ≤ 15 mm on transvaginal ultrasound) Fever (> 37.5ºC)		an intact gestational sac of > 20 mm in diameter with no visible embryonic pole (anembryonic), or an intrauterine gestation with an embryo of crown-rump length > 5 mm without heart pulsations. Symptomatic and asymptomatic miscarriages were differentiated by the presence or absence of vaginal bleeding. Sample size calculation The required sample size was based on improving the success rate of 70% with expectant management to 95% with misoprostol. A trial with 90% power and an alpha of 0.05 required a sample of 96 women. Randomisation Randomisation of 104 women was carried out by allocation of women to either misoprostol or placebo. Three misoprostol or placebo tablets were placed in each of two small envelopes and sealed. The small envelopes were then placed in consecutively numbered large envelopes	c. Overall Misoprostol: 6/52 (11.5) (Note: 5 incomplete, 1 with no products passed) Placebo: 29/52 (55.8) (Note: 6 incomplete, 23 with no products passed) Duration of bleeding/days (mean (SD)) Misoprostol: 11.65 (4.4) Placebo: 10.88 (4.78) Mean difference (95% CI): 0.77 (-1.02, 2.56) Adverse effects (number/total (%)) a. Nausea Misoprostol: 18/52 (34.6) Placebo: 16/52 (30.8) b. Vomiting Misoprostol: 8/52 (15.4) Placebo: 7/52 (13.5) c. Diarrhoea Misoprostol: 11/52 (21.1) Placebo: 11/52 (21.1) d. Pelvic inflammatory disease Misoprostol: 1/52 (1.9)	- Day 2: 21/35 (60) - Day 7: 8/14 (57.1) Placebo - Day 1: 3/52 (5.8) - Day 2: 4/49 (8.2) - Day 7: 16/45 (35.6)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Haemoglobin < 10 g/dl Contraindication to prostaglandin therapy (asthma, hypertension, glaucoma, mitral stenosis) Excessive bleeding requiring emergency surgery		according to randomisation schedule, and sealed by staff not involved with the study. <u>Treatment protocol</u> Followed informed consent, women received their allocated treatment of either 3 x 200 micrograms of misoprostol or 3 placebo tablets, placed in the posterior fornix of the vagina by a doctor or nurse in the EPAU. Both the women and the investigators were blinded to treatment allocation. Baseline haemoglobin and white cell count were obtained, and Rhesus negative women received anti-D immunoprophylaxis. Paracetamol with codeine was prescribed for pain and they were provided with telephone numbers to contact a doctor if necessary. All women attended for speculum and bimanual examinations, and ultrasound, the next day (day 1). Women diagnosed with a complete miscarriage were discharged with follow-up booked for 14	Placebo: 0/52 (0) <u>Pain severity: VAS score/10 (mean (SD))</u> Misoprostol: 6.0 (2.7) Placebo: 5.4 (2.7) Mean difference (95% CI): 0.57 (-0.49, 1.63) <u>Satisfaction</u> <u>a. VAS score/10 (mean (SD))</u> Misoprostol: 8.9 (1.3) Placebo: 8.7 (1.5) <u>b. Would choose again (number/total (%))</u> Misoprostol: 48/52 (92.3) Placebo: 38/52 (73.1) Mean difference (95% CI): 0.25 (-0.30, 0.80)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			days time. The remaining women had a second dose of their allocated treatment, and were seen the next day (day 2). Women for whom treatment was not successful by day 2 were asked to return on day 7, and if miscarriage was not complete, were scheduled for a surgical evacuation in theatre. all women scheduled for evacuation had their surgery performed as day cases. Follow-up All women in the study were seen 14 days after the diagnosis of complete miscarriage or the performance of a surgical evacuation. They were assessed for signs of bleeding, pain and infection, and had repeat full blood counts and serum hCG measurements. If hCG was > 20 IU, patients were seen weekly until a negative results of < 20 IU. A questionnaire, including visual analogue scales, was used to assess the severity of pain and the satisfaction of the treatment. Outcomes reported		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			1. Success rate: reported as complete miscarriage without surgical evacuation by day 7 2. Need for further intervention: the need and reason for a surgical evacuation 3. Duration of bleeding: assessed at 14 day follow-up 4. Adverse effects: incidence of pelvic inflammatory disease, nausea, diarrhoea and vomiting 5. Severity of pain: assessed using visual analogue scales at follow-up appointment 6. Satisfaction: assessed using questionnaire		
Full citation Creinin,M.D., Moyer,R., Guido,R., Misoprostol for medical evacuation of early pregnancy failure, Obstetrics and Gynecology, 89, 768-772, 1997 **Ref Id**	**Sample size** N=20 **Characteristics** **Age/years** Oral: 26.3 (7.0) Vaginal: 29.8 (8.0)	**Interventions** 400 micrograms of oral misoprostol 800 micrograms of vaginal misoprostol	**Details** Eligible women were identified, and a history, physical examination, baseline haemoglobin and blood type were taken. Women meeting the inclusion criteria were recruited and suitably randomised. Neither the clinician or patient were	**Results** **Treatment success (number/total (%))** Oral: 3/12 (25) Vaginal: 7/8 (87.5) (p=0.01) **Need for further intervention**	**Limitations** **Ineligible participants** On review, it was discovered that 2 patients in the oral arm did not meet the ultrasound criteria for early pregnancy failure. One passed the pregnancy with a single dose, and the other was a treatment failure. However, even if they are excluded, the difference in the success rate is

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
65195 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial (pilot) **Aim of the study** To determine whether misoprostol 400 micrograms orally or 800 micrograms vaginally will cause complete uterine evacuation in women with early pregnancy failure. **Study dates** Not reported **Source of funding** Magee Women's Health Foundation	**Gravidity (mean (SD))** Oral: 3.8 (2.9) Vaginal: 3.3 (2.1) **Parity (mean (SD))** Oral: 1.4 (1.7) Vaginal: 0.8 (0.9) **Prior elective abortion (number/total (%))** Oral: 6/12 (50) Vaginal: 3/8 (37.5) **Prior miscarriage (number/total (%))** Oral: 6/12 (50) Vaginal: 4/8 (50) There were no significant differences in age, race or obstetric history. **Inclusion criteria** Healthy English speaking Diagnosis of early		blinded to treatment allocation. **Treatment protocol** Women received one of two treatment regimens: - 400 micrograms of oral misoprostol (repeat dose after 24 hours if needed) - 800 micrograms of vaginal misoprostol (repeat dose after 24 hours if needed) Subjects in the oral arm swallowed misoprostol in the presence of a member of the research staff. Those in the vaginal arm had four 200 micrograms tablets of misoprostol administered vaginally. Participants were asked to keep a symptom log, describing side effects and pain medication use. All patients received - a packet of eight 600-mg ibuprofen tablets with instructions to take as needed for abdominal pain - a prescription for 20 tablets of acetaminophen with codeine (300mg/30mg) - an instruction sheet with contact details for a	The authors state that "no woman required a suction curettage because of incomplete passage of the uterine tissue." However, considering their trial protocol and success rates, it is unclear whether women may have had curettage for other reasons (i.e. no passage of tissue). Therefore, this outcome has not been included in the GRADE table. **Duration of vaginal bleeding (mean (SD))** (Note: the following only includes successfully treated patients) **a. Vaginal bleeding** Oral: NR Vaginal: 2.3 (1.4) **b. Spotting** Oral: NR Vaginal:7.8 (3.8) **c. Any bleeding** Oral: NR Vaginal: 10.0 (2.8) **Adverse effects of treatment**	still significant (p=0.015). **Lack of blinding** Blinding was not done. This would not have been possible for the participants, or those administering the misoprostol, but could have been achieved for those assessing outcomes. **Small sample size** N=20, and for some outcomes there is missing data which reduces sample size further. **Other information** EARLY EMBRYONIC/FETAL DEMISE ORAL vs. VAGINAL **Point of expulsion** **Oral arm:** One subject expelled tissue after one dose, one after the repeat dose, and one passed some tissue after the first dose but had tissue in the os that was withdrawn using ring forceps on day 2 **Vaginal arm:** Five subjects expelled uterine contents after one dose, and two subjects after the second dose.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	pregnancy failure, based on ultrasound demonstration of one of the following: - Embryonic pole 5-14 mm with no embryonic cardiac activity - Irregular intrauterine gestational sac with mean sac diameter of 16 mm or greater and no embryonic pole - Abnormal growth on ultrasound over a minimum of 1 week - Yolk sac present with an abnormal increase in hCG (50% or less) over 48 hours, and an initial value less than 2000 IU/l At least 18 years old Vaginal bleeding no more than spotting (not requiring more than one sanitary towel a day) Gestational age of 8 weeks of less by ultrasound or physical examination Closed cervical os on bimanual pelvic		physician Participants returned the next day (approximately 24 hours later), when a history of events was obtained and an ultrasound was performed. If the gestational sac was absent, the woman was scheduled to return in 2 weeks for a follow-up evaluation. If the gestational sac was still present, the misoprostol dose was repeated and the subject returned the following day (study day 3). If the gestational sac was still present on day 3, the woman was offered suction curettage. Treatment was considered successful if uterine contents were expelled within 24 hours of the initial or repeat dose. **Follow-up** At the follow-up visit, women were asked about the severity of their pain using a 10 point visual analogue scale. A haemoglobin and urine pregnancy test were also performed. If the pregnancy test was negative, the study was complete. If it was positive and bleeding was	**(number of women/total (%))** **a. Any side effect** Oral: 8/12 (66.7) Vaginal: 7/8 (87.5) (Note: the one in the vaginal arm with no side effects was the treatment failure) **b. Nausea** Oral: 6/12 (50) Vaginal: 5/8 (62.5) **c. Vomiting** Oral: 3/12 (25) Vaginal: 1/8 (12.5) **d. Diarrhoea** Oral: 5/12 (41.7) Vaginal: 3/8 (37.5) **Measures of pain** **a. Severity of pain/10 (mean (SD))** Oral: 4.0 (3.6) Vaginal: 5.9 (2.7) (p=0.33) (Note: data were not available for 1 woman in each arm)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	examination Haemoglobin of 10mg/dl or more Willingness and ability to sign informed consent Willingness to abstain from intercourse for the first 3 days of the study and comply with visit schedule Adequate venous access for phlebotomy Easy access to a telephone **Exclusion criteria** History of inflammatory bowel disease Intolerance or allergy to misoprostol		no longer occurring, hCG levels were obtained and followed weekly until levels were below 10 IU/l. All patients with ultrasound findings demonstrating no yolk sac or embryonic pole on day 2 or 3 had serum hCG evaluation, due to the possibility of ectopic pregnancy. If hCG had not declined by 50% compared to baseline, passage of the pregnancy was not considered complete, and hCG was done at 1-2 day intervals. If hCG plateaued or the patient's condition indicated, a suction curettage or treatment for ectopic pregnancy was done. **Outcomes reported** **1. Successful expulsion**: Uterine contents expelled within 24 hours of misoprostol administration (initial or repeat dose) **2. Duration of vaginal bleeding:** Reported only for those who were treated successfully **3. Side effects:**		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Participants were asked to keep a symptom log, describing side effects and pain medication use **4. Pain:** The maximal amount of pain was assessed using a visual analogue scale, consisting of a 10 mm line with "no pain" at one end and "severe pain" at the other end.		
Full citation Kovavisarach,E., Jamnansiri,C., Intravaginal misoprostol 600 microg and 800 microg for the treatment of early pregnancy failure, International Journal of Gynaecology and Obstetrics, 90, 208-212, 2005 **Ref Id** 65332 **Country/ies where the study was carried out** Thailand **Study type** Randomised controlled	**Sample size** N=114 **Characteristics** The authors report that characteristics such as maternal age, gravidity, parity, pregnancy duration, prior miscarriage, prior elective abortion and body mass index were similar between the two arms. No further details are given. **Inclusion criteria** Pregnancy duration up to 12 weeks	**Interventions** 600 micrograms of vaginal misoprostol (n=57) 800 micrograms of vaginal misoprostol (n=57)	**Details** 114 women meeting the inclusion criteria were recruited during the study period. There were no withdrawals. After informed consent was obtained, their complete medical history was taken and a physical examination confirmed their eligibility. A complete blood count was performed for each woman and a coagulation profile was obtained at study entry in missed miscarriage cases. If the blood test results were normal, women were suitably randomised to one of two treatment regimens. The allocations had been placed in opaque envelopes by a nurse not involved in any other part of the study process. All other staff and	**Results** **<u>Expulsion rate within 24 hours of misoprostol treatment (number/total (%))</u>** **<u>a. Complete expulsion</u>** **600:** 26/57 (45.6) **800:** 39/57 (68.4) (p=0.03) **<u>b. Incomplete expulsion</u>** **600:** 24/57 (42.1) **800:** 16/57 (28.1) **<u>c. No expulsion</u>** **600:** 7/57 (12.3) **800:** 2/57 (3.5) (Note: the authors report that the rate of any expulsion (complete/incomplete) was 96.5% in the 800µg arm, and	**Limitations** No obvious serious limitations **Other information** EARLY FETAL/EMBRYONIC DEMISE ONLY (those with an open os are excluded) VAGINAL DOSAGE COMPARISON: 600 vs. 800 Blinding was done. **<u>Time to expulsion/hours (mean (SD))</u>** **600:** 15.00 (5.7) **800:** 12.95 (6.18) (NS, p-value not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trial **Aim of the study** To determine the effectiveness and side effects of 600 and 800 micrograms of intravaginal misoprostol in obtaining complete miscarriage in cases of early pregnancy failure **Study dates** November 25th 2002 to July 31st 2003 **Source of funding** Not reported	Ultrasound diagnosis of early pregnancy failure, defined as one of: - An intrauterine gestational sac with a mean diameter of at least 25 mm and no visible embryonic pole - An embryonic pole of 5-14 mm with no cardiac activity - Abnormal growth or persistent absence of fetal cardiac activity on a second scan 7-10 days later **Exclusion criteria** Open endocervical os Medical and obstetric complications Known allergy to prostaglandins		patients were blinded to the regimen allocation. **Treatment protocol** Group 1 (600 micrograms) received three 200 microgram tablets of misoprostol and 1 tablet of placebo. Group 2 (800 micrograms) received four 200 microgram tablets of misoprostol. All tablets were placed in the posterior vaginal fornix. The women then remained in a semi-prone position for 30 minutes, and remained in the observation room for 24 hours. Vital signs, presence of uterine bleeding and conception products, and side effects such as fever, lower abdominal pain, nausea, vomiting and diarrhoea were recorded by the nurses and physician on call. Pager and telephone numbers were given to the nurse in the observation room for immediate consultation with the physician if needed. Emergency dilatation and curettage (D&C) was arranged when excessive vaginal bleeding,	87.7% in the 600µg arm) **Adverse effects within 24 hours of treatment (number of women/total (%)** **a. Nausea** **600:** 2/57 (3.5) **800:** 7/57 (12.3) (p=0.08) **b. Diarrhoea** **600:** 0/57 (0) **800:** 2/57 (3.5) (p=0.15) **c. Vomiting** **600:** 0/57 (0) **800:** 0/57 (0) **d. Fever** **600:** 10/57 (17.5) **800:** 16/57 (28.1) (p=0.18) **Pain: Incidence of lower abdominal pain (number of women/total (%))** **600:** 30/57 (52.6) **800:** 42/57 (73.7) (p=0.20)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			incomplete miscarriage or severe abdominal pain occurred. The decision to perform an emergency D&C was made by the physician on call based on clinical judgement. These physicians were blinded to the patient's treatment dose. A single investigator performed a vaginal ultrasound evaluation on all women who had not received a curettage in the last 24 hours. If the gestation sac or products of conception (defined as an hyperechoic or a mixed hyper/hypoechoic region of any thickness in the uterine cavity) were still present after 24 hours, a D&C was performed. If complete miscarriage had occurred, the women were discharged from hospital. All women were scheduled to return for a follow-up evaluation 1 week later. Treatment was considered successful if the uterine contents were completely expelled within 24 hours of the initial drug administration, with no need		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			for uterine curettage. **Outcomes reported** **1. Expulsion rate:** The authors report the rates of complete, incomplete and no miscarriage within 24 hours of misoprostol administration. **2. Adverse effects:** The incidence of fever, nausea, diarrhoea and vomiting within 24 hours of treatment are reported. This was recorded by the nurses and physicians. **3. Pain:** The incidence of lower abdominal pain within 24 hours of treatment are reported, as recorded by nurses and physicians. **Analysis** The results of a small pilot study of 20 women in each arm and a power calculation resulted in a target sample size of 50 in each arm. 10% was added to compensate for withdrawals or loss to follow-up and resulted in 57 participants in each arm. The data were analysed using chi-squared		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			test, Fisher's exact test and t-tests as appropriate. p<0.05 was considered statistically significant.		
Full citation Kushwah,B., Singh,A., Sublingual versus oral misoprostol for uterine evacuation following early pregnancy failure, International Journal of Gynaecology and Obstetrics, 106, 43-45, 2009 **Ref Id** 65336 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy of misoprostol administered sublingually or orally for uterine evacuation after	**Sample size** N=100 **Characteristics** **Age/years (mean (SD))** Sublingual: 26.6 (4.4) Oral: 24.6 (3.8) **Parity (mean (SD))** Sublingual: 2.1 (0.9) Oral: 2.1 (0.9) **Gestation/days (mean (SD))** Sublingual: 57.7 (7.8) Oral: 59.9 (9.0) (Note: only 1 woman, from the oral arm, had gestation of over 80 days) **Type of pregnancy (number/total (%))** Sublingual: - Anembryonic: 23/50 (46)	**Interventions** 200mg of oral mifepristone + 600 micrograms sublingual misoprostol (n=50) 200mg of oral mifepristone + 600 micrograms of oral misoprostol (n=50)	**Details** This trial was conducted at the prenatal clinic of the Department of Obstetrics and Gynaecology of Sucheta Kriplani Hospital, Delhi, India. All participants had early pregnancy failure confirmed by ultrasound between the 7th and 14th week of gestation. Eligible participants gave consent and were randomised using computer generated random numbers. **Treatment protocol** After assessment of blood haemoglobin, serum bilirubin and urea, and urine albumin and sugar concentrations, women received one of the following: - 200mg of mifepristone given orally, following by 600 micrograms of misoprostol sublingually - 200mg of mifepristone given orally, following by 600 micrograms of	**Results** **Successful uterine evacuation (number of women/total (%))** Sublingual: 46/50 (92) Oral: 42/50 (84) **Adverse effects of treatment (number of women/total (%))** **a. Nausea** Sublingual: 17/50 (34) Oral: 26/50 (52) (Note: 1 woman from each arm required medication) **b. Vomiting** Sublingual: 11/50 (22) Oral: 22/50 (44) (Note: 3 women from the oral arm required medication) **c. Diarrhoea** Sublingual: 24/50 (48) Oral: 28/50 (56) (Note: 5 women in each arm had more than 4 episodes and required medication) **d. Fever: any**	**Limitations** **Point of assessment of outcomes** The point at which adverse effects, pain and satisfaction were assessed is not reported. **Lack of blinding** Blinding is not reported. **Other information** MISSED MISCARRIAGE/ANEMBRYONIC PREGNANCIES ONLY ORAL VS. SUBLINGUAL (BOTH WITH MIFEPRISTONE) **Induction to evacuation interval/hours (mean (SD))** Sublingual: 46 (4.5) Oral: 9.4 (5.6) (Note: this only includes women for whom evacuation was successful) It is not reported how many women required the supplemental doses of misoprostol.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
early pregnancy failure. **Study dates** April 2003 to March 2004 **Source of funding** Not reported	- Missed miscarriage: 27/50 (54) Oral: - Anembryonic: 34/50 (68) - Missed miscarriage: 16/50 (32) **Inclusion criteria** Gestational sac of 25 mm or larger with no embryo present (anembryonic gestation) Presence of a fetal pole without cardiac pulsations (missed miscarriage) **Exclusion criteria** Vaginal bleeding Any evidence of infection History of allergy to misoprostol Major medical problems		misoprostol orally The women in the sublingual group were instructed to place the three 200 microgram tablets under their tongue, and were not allowed to eat or drink for 20 minutes to allow the tablets to dissolve completely. Women in the oral group were instructed to swallow the three tablets with water. Blood pressure, pulse rate and body temperature were recorded hourly. Whenever women expelled products of conception or bled vaginally, they were given a vaginal examination to assess the degree of expulsion, which was then determined to be complete on ultrasound. Evacuation was considered complete when the woman had no active bleeding, had a closed cervical os, and had an empty uterine cavity on ultrasound examination. Evacuation was considered incomplete when active vaginal bleeding continued, the cervical os remained open, and products of conception were visible on ultrasound. In this case, women underwent surgical	Sublingual: 10/50 (20) Oral: 26/50 (52) **e. Fever: ≥37.8ºC** Sublingual: 0 Oral: 4/50 (8) **Measures of pain (number/total (%))** **a. Incidence of pain requiring no analgesia** Sublingual: 14/50 (28) Oral: 26/50 (52) **b. Incidence of pain requiring analgesia** Sublingual: 9/50 (18) Oral: 18/50 (36) **c. Incidence of pain: total** Sublingual: 23/50 (46) Oral: 44/50 (88) **Reported satisfaction (number/total (%))** Sublingual: 46/50 (92) Oral: 36/50 (72)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			evacuation under paracervical block. Women who did not expel products of conception within 12 hours of the first dose of misoprostol were given up to 3 supplemental doses of 400 micrograms at three hour intervals (sublingually or orally depending on their allocation). Those who received the maximum misoprostol allocation and did not expel products of conception within 4 hours of taking the last 400 microgram dose underwent surgical evacuation under intravenous sedation and paracervical block. After complete uterine evacuation, whether medical or surgical, the women were kept under observation for 6 hours and then discharged. They returned 7 days later for an assessment of haemoglobin level, and had a routine check-up 2 weeks after discharge. **<u>Outcomes reported</u>** **1. Successful uterine evacuation:** not directly defined, but see criteria for		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			complete evacuation above. **2. Adverse effects of treatment:** The incidence of nausea, vomiting, diarrhoea (≤4 episodes and >4 episodes), and fever (both above and below 37.8°C) are reported. It is unclear at what point these outcomes were assessed. **3. Measures of pain:** The incidence of abdominal pain requiring no analgesia and requiring analgesia are reported (along with the % of women who had no abdominal pain). It is unclear at what point this outcome was assessed. **4. Satisfaction:** The proportion of women reporting being satisfied (phrased as a yes or no question) is reported. **Analysis** The chi-squared test, Fishers exact test and t-test were used where appropriate. $p<0.05$ was considered significant. The mean difference in induction-evacuation time was used to calculate that a sample size of 100 women		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			would have 80% power.		
Full citation Lelaidier,C., Baton-Saint-Mleux,C., Fernandez,H., Bourget,P., Frydman,R., Mifepristone (RU 486) induces embryo expulsion in first trimester non-developing pregnancies: a prospective randomized trial, Human Reproduction, 8, 492-495, 1993 **Ref Id** 65346 **Country/ies where the study was carried out** France **Study type** Randomised controlled trial **Aim of the study** To investigate whether	**Sample size** N=46 **Characteristics** Age/years (mean (SD)): 31.3 (4) Gestational age/weeks (mean (range)): 11 (6.6 - 14) **Inclusion criteria** Evidence of a non-developing intrauterine pregnancy at two successive ultrasound examinations at least 7 days apart, of which at least one was performed at the study centre Absence of bleeding No sign of any uterine contraction **Exclusion criteria** Not reported	**Interventions** 600 mg of Mifepristone (n=23) Placebo (n=23)	**Details** Over a period of 6 months, 64 women were referred to the study hospital with the diagnosis of missed miscarriage or blighted ovum. 50 were eligible (see inclusion criteria), of which 4 refused to participate, leaving a study population of N=46. This was a randomised double blind trial. Tablets were supplied by the pharmacological unit following randomisation by the method of permutation blocks (blocks of four). Treatment was started in the morning under the supervision of the clinician, with women receiving either: - 600 mg of mifepristone (in three tablets) - placebo (three tablets) The external appearance of the placebo was similar to that of the mifepristone, and the authors report that both the patients and clinicians were blinded to the treatment. Patients were	**Results** Natural expulsion of products (number/total (%)) Mifepristone: 19/23 (82.6) Placebo: 2/23 (8.7) Need for further intervention (number/total (%)) Mifepristone: 6/23 (26.1) (Note: 4 for treatment failure and 2 for frank haemorrhage on days 2 and 3 respectively) Placebo: 19/21 (90.5) Adverse effects: incidence of clinical endometritis (number/total (%)) Mifepristone: 1/23 (4.3) Placebo: 1/21 (4.8) (NS) Pain: incidence (number/total (%)) Mifepristone: 12/23 (52.2) Placebo: 5/21 (23.8) (p=0.08)	**Limitations** Small sample size (N=46) Baseline characteristics not reported separately for each arm of the trial 2/23 women in the placebo arm were not included in the analysis because they received advice from clinicians resulting in regular dilatation and aspiration. The technical team have included them in the denominator for natural expulsion, in order that estimates are conservative. **Other information** MIFEPRISTONE VS. PLACEBO MISSED MISCARRIAGE/BLIGHTED OVUM POPULATION Day of expulsion (number expelling on each day/total that ever had expulsion (%)) - Day 2 Mifepristone: 2/19 (10.5) placebo: 0/2 (0) - Day 3 Mifepristone: 7/19 (36.8) Placebo: 0/2 (0)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
mifepristone without associated prostaglandin treatment could hasten embryo expulsion in non-developing first trimester pregnancies with no clinical sign of miscarriage **Study dates** Not reported, but it was a 6 month period **Source of funding** Not reported			then discharged and instructed to seek medical advice in the case of severe pain or heavy bleeding. They were also asked to maintain a diary documenting vaginal bleeding, uterine contraction, passage of tissue, and any side effects. <u>Follow-up</u> On day 5, a repeat ultrasound was performed to assess the uterine cavity. If this revealed failed expulsion, aspiration under local or general anaesthesia was performed on the same day. hCG measurements and progesterone measurements were taken on day 1 and day 5, regardless of expulsion. <u>Outcomes reported</u> 1. Natural expulsion: 2. Need for further intervention: need for a D&C is reported 3. Adverse effects: incidence of endometritis, defined as fever of at least 38ºC, is reported		- Day 4 Mifepristone: 5/19 (26.3) Placebo: 1/2 (50) - Day 5 Mifepristone: 5/19 (26.3) Placebo: 1/2 (50)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			4. Pain: incidence of pain is reported, as documented in women's diaries Analysis Student's t-test and chi-squared tests were used for analysis. A p-value of <0.05 was considered statistically significant.		
Full citation Stockheim,D., Machtinger,R., Wiser,A., Dulitzky,M., Soriano,D., Goldenberg,M., Schiff,E., Seidman,D.S., A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure, Fertility and Sterility, 86, 956-960, 2006 **Ref Id** 65505 **Country/ies where the**	**Sample size** N=115 **Characteristics** **Age/years (mean (SD), range)** Mf + Ms: 32 (6), 20-43 Ms only: 32 (6), 20-44 **CRL/mm (mean (SD))** Mf + Ms: 49 (7) Ms only: 48 (8) **Nulliparous (%)** Mf + Ms: 24.6 Ms only: 25.8 **Parity (mean (SD), range)**	**Interventions** Mf + Ms: 600mg of oral mifepristone, and then after 48 hours, two 400 microgram doses of oral misoprostol, three hours apart (n=58) Ms only: Two 400 microgram doses of oral misoprostol, three hours apart, and then after 48 hours, the same dosage again (n=57)	**Details** 115 women with a diagnosis of blighted ovum or missed miscarriage (and meeting the inclusion criteria) were suitably randomised. Neither the patient or the treating physicians were blinded to the treatment allocation. **Treatment protocol** The regimens were as follows: **Mf + Ms:** Patients received 600mg of oral mifepristone and were discharged after 2 hours of observation **Ms only:** Patients received two 400 microgram doses of oral misoprostol, three	**Results** **Treatment success (number/total (%))** Mf + Ms: 38/58 (65.5) Ms only: 42/57 (73.7) (Note: 2 patients from Mf+Ms and 9 patients from Ms only had success after the first medication round) **Need for further intervention and reasons (number/total (%))** **Mf + Ms: 20/58 (34.5)** - Persistent gestational sac: 6/20 - Emergency due to bleeding from incomplete miscarriage: 3/20 - Other complications: emergency due to fever and bleeding: 1/20 - Suspected RPOC after menstruation: 10/20 (of which 8	**Limitations** No obvious serious limitations Note: Participants were not blinded to their treatment allocation; however the staff responsible for assessing the results of transvaginal scan (and hence need for curettage) were blinded and therefore this study has not been downgraded. **Other information** EARLY FETAL/EMBRYONIC DEMISE MIFEPRISTONE + MISOPROSTOL vs. MISOPROSTOL ONLY

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Israel **Study type** Randomised controlled trial **Aim of the study** To compare the outcome of medical treatment of early pregnancy failure with misoprostol (Ms) alone or following mifepristone (Mf) pre-treatment. **Study dates** July 2001 to December 2002 **Source of funding** Not reported	Mf + Ms: 1.7 (1.8), 0-10 Ms only: 1.4 (1.8), 0-10 **Previous miscarriage (%)** Mf + Ms: 31 Ms only: 30.6 **Previous induced abortion (%)** Mf + Ms: 13 Ms only: 12.9 **Type of miscarriage (%)** **Missed miscarriage** Mf + Ms: 85.2 Ms only: 79 **Blighted ovum** Mf + Ms: 14.8 Ms only: 21 **Inclusion criteria** Blighted ovum or missed miscarriage diagnosed using transvaginal ultrasound: - No fetal heart beat in a fetus with CRL > 5		hours apart, for a total of 800 micrograms. They were observed for 6 hours after the first dose. **Both arms:** Patients from both arms were requested to return after 48 hours, when they all received 800 micrograms of oral misoprostol, divided into two equal doses three hours apart. Any women who had significant vaginal bleeding underwent a transvaginal ultrasound, and misoprostol was not given to anyone with an empty uterine cavity (n=2 in Mf + Ms arm, n=9 in Ms only arm). Women were discharged within 6 hours of the first misoprostol dose, depending on the severity of bleeding and pain. Patients were advised to return to the hospital if they experienced significant bleeding, severe pain or fever. All Rh- women were given anti-D. **Follow-up** If women did not bleed within 48 hours of	were hysteroscopies and 2 were curettage) **Ms only: 15/57 (26.3)** - Persistent gestational sac: 10/15 - Emergency due to bleeding from incomplete miscarriage: 1/15 - Other complications: emergency due to pain: 1/15 - Suspected RPOC after menstruation: 3/15 (of which 2 were hysteroscopies and 1 was curettage) **Adverse effects of treatment (number of women/total (%))** In their discussion, the authors also state that women did not experience side effects; however no details of how this was assessed are reported.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	mm - A smaller fetus with no appearance of a heartbeat after a 1 week follow-up - Empty gestational sac with a proven gestational age of at least 6 weeks Crown-rump length compatible with < 9 weeks gestation Agreeing to sign informed consent Aged 20-45 Haemoglobin level at least 8.0 g/dL No significant vaginal bleeding **Exclusion criteria** Incomplete miscarriage Inevitable miscarriage (products of gestation bulging from the cervix) Suspicion of extrauterine		completion of the treatment, they were requested to return for a transvaginal scan. If a gestational sac was still present, surgical evacuation was performed. 10-14 days after treatment, women were invited for a clinical interview and a transvaginal scan. A well-defined endometrial line, with a maximum thickness of < 15mm, combined with the absence of vaginal bleeding, was defined as a complete miscarriage. In the absence of any other clinical complaint, these patients were discharged. Women with suspected RPOC (anteroposterior diameter > 15mm or presence of blood vessels in the suspicious tissue) were invited for a follow-up clinical and ultrasound exam after their first period. Women with suspected RPOC after menstruation underwent diagnostic and, if necessary, operative hysteroscopy. RPOC were suspected based on ultrasound images or complaints of prolonged bleeding from patients. The physicians performing		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	pregnancy CRL compatible with > 9 weeks gestation Drug or alcohol abuse, as reported by the patient Abnormal complete blood counts routinely obtained		the vaginal scan to determine the need for surgery were blinded to treatment allocation. **Outcomes reported** **1. Treatment success:** Defined as no need for surgical intervention **2. Need for further intervention:** Need for either emergency curettage, or surgery for failure of medical protocol. **Analysis** Fisher's exact test, t-tests and Mann-Whitney tests were used as appropriate.		
Full citation Tang,O.S., Lau,W.N., Ng,E.H., Lee,S.W., Ho,P.C., A prospective randomized study to compare the use of repeated doses of vaginal with sublingual misoprostol in the management of first trimester silent miscarriages, Human Reproduction, 18, 176-181, 2003	**Sample size** N=80 **Characteristics** **Age/years (mean (SD))** Sublingual: 32.3 (7.3) Vaginal: 33.6 (6.0) **Weight/kg (mean**	**Interventions** 600 micrograms of sublingual misoprostol, every 3 hours up to a maximum of three doses (n=40) 600 micrograms of vaginal misoprostol, every 3 hours up to a maximum of three doses (n=40)	**Details** A total of 80 women with a diagnosis of first trimester silent miscarriage (see inclusion criteria) were recruited. An ultrasound was performed to confirm the diagnosis. Women were randomised using computer-generated random numbers. **Treatment protocol**	**Results** **Clinical outcome (number/total (%))** **a. Complete miscarriage** Sublingual: 35/40 (87.5) Vaginal: 35/40 (87.5) **b. Incomplete miscarriage** Sublingual: 4/40 (10) Vaginal: 3/40 (7.5)	**Limitations** **Blinding** Blinding is not reported - this would be impossible for the participants, however could have been achieved for those assessing outcomes. **Missing data** Unclear why not all the participants responded to some of the acceptability questions.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 65516 **Country/ies where the study was carried out** Hong Kong **Study type** Randomised controlled trial **Aim of the study** To compare repeated doses of sublingual with vaginal misoprostol in the medical management of first trimester miscarriages. **Study dates** Not reported **Source of funding** Not reported	**(SD))** Sublingual: 54.1 (9.7) Vaginal: 53.0 (7.1) **Height/cm (mean (SD))** Sublingual: 158.8 (6.8) Vaginal: 158.2 (5.2) **Gestational age/days (mean (SD))** Sublingual: 74.6 (13.1) Vaginal: 75.9 (15.6) **Previous live birth (number/total (%))** Sublingual: 18/40 (45) Vaginal: 22/40 (55) **Previous miscarriages (number/total (%))** Sublingual: 13/40 (32.5) Vaginal: 6/40 (15) **Previous induced abortion**		Women were randomised to one of two treatment regimens: - 600 micrograms misoprostol sublingually, every 3 hours up to a maximum of three doses - 600 micrograms misoprostol vaginally, every 3 hours up to a maximum of three doses The sublingual group were instructed to put the tablets under their tongues themselves. They were not allowed any food or drink for 20 minutes to allow complete dissolution of the tablets. In the vaginal group, the research nurses was responsible for putting the three misoprostol tablets into the vaginal fornix. Blood pressure, pulse rate and side effects (including pain) were recorded every hour, and body temperature was recorded every 3 hours. Oral or parenteral analgesic was given if the women complained of severe pain. Women were discharged after the completion of the course of misoprostol if	**c. Silent miscarriage** Sublingual: 0/40 (0) Vaginal: 1/40 (2.5) **d. Undetermined** Sublingual: 1/40 (2.5) Vaginal: 1/40 (2.5) (Note: these women did not return on day 43 so their outcome could not be assessed) **Need for further intervention (number of women/total (%))** Sublingual: 4/39 (10.3) Vaginal: 4/39 (10.3) (Note: 1 woman, from the vaginal arm, had surgery on day 7 for silent miscarriage. The other seven women had surgery in other facilities because of persistent vaginal bleeding) **Duration of vaginal bleeding/days (median (range))** Sublingual: 12.5 (4 - 36) Vaginal: 12.0 (5 - 79) (NS) **Adverse effects of treatment (number of women/total (%))** **a. Nausea**	**Other information** EARLY FETAL/EMBRYONIC DEMISE ONLY VAGINAL vs. SUBLINGUAL **Interval between misoprostol administration and start of bleeding/hours (median)** Sublingual: 2.5 Vaginal: 3.0 **Interval between misoprostol administration and expulsion/hours (median)** Sublingual: 9.5 Vaginal: 13.5 (NS)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(number/total (%)) Sublingual: 9/40 (22.5) Vaginal: 10/40 (25) There were no significant differences between the two groups. **Inclusion criteria** First trimester silent miscarriage, defined as: - intrauterine gestational sac with mean sac diameter of ≥ 2 cm without a fetal pole - presence of fetal pole with no cardiac pulsation - gestational sac < 2 cm with no interval growth or persistent absence of fetal cardiac activity on rescanning 7 - 10 days later < 13 weeks gestation **Exclusion criteria**		there was no heavy bleeding and they were not in pain. The women were asked to inform the nurse when they passed any products at the hospital, and were given a bottle of formalin to collect any products passed at home. The products were sent for histological confirmation. Emergency surgical evacuation was performed if the blood loss or abdominal pain was uncontrolled. **Follow-up** The outcome of the treatment was assessed on day 7 after misoprostol. A transvaginal ultrasound was done. Surgical evacuation was performed if a gestational sac was still present, or if there was a significant amount of products of conception in the uterus combined with heavy vaginal bleeding. If the ultrasound showed complete or incomplete miscarriage without heavy vaginal bleeding, no action was taken. The amount of bleeding was monitored, and women were asked to return on day 43 to ascertain bleeding patterns	Sublingual: 24/40 (60) Vaginal: 20/40 (50) **b. Vomiting** Sublingual: 7/40 (17.5) Vaginal: 9/40 (22.5) **c. Diarrhoea** Sublingual: 28/40 (70) Vaginal: 11/40 (27.5) (p<0.005) **d. Fever** Sublingual: 23/40 (57.5) Vaginal: 19/40 (47.5) **e. Chills** Sublingual: 6/40 (15) Vaginal: 3/40 (7.5) **f. Dizziness** Sublingual: 16/40 (40) Vaginal: 10/40 (25) **g. Fatigue** Sublingual: 26/40 (65) Vaginal: 16/40 (40) (p=0.043) **h. Headache** Sublingual: 18/40 (45)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Complete miscarriage Incomplete miscarriage		and return of menstruation. **<u>Outcomes reported</u>** **1. Complete miscarriage:** The outcome of treatment was classified as complete miscarriage if surgical evacuation was not required up to the time of return to normal menstruation. **2. Need for further intervention** **3. Duration of bleeding:** Assessed on day 43 **4. Adverse effects:** Recorded during treatment. Fever was defined as a highest temperature of at least 38ºC. **5. Pain:** Recorded during treatment. Degree of pain was assessed using a questionnaire. **6. Satisfaction:** Assessed by questionnaires on days 7 and 43. Unclear which results are reported, or whether they were combined.	Vaginal: 12/40 (30) **<u>Measures of pain (number of women/total (%))</u>** **<u>a. Incidence of lower abdominal pain</u>** Sublingual: 40/40 (100) Vaginal: 40/40 (100) **<u>b. Degree of pain</u>** **- Severe, not tolerable** Sublingual: 6/40 (15) Vaginal: 8/40 (20) **- Tolerable** Sublingual: 24/40 (60) Vaginal: 22/40 (55) **- Expected** Sublingual: 5/40 (12.5) Vaginal: 4/40 (10) **- Little pain** Sublingual: 3/40 (7.5) Vaginal: 6/40 (15) **- No pain at all** Sublingual: 2/40 (5) Vaginal: 0/40 (0) **<u>Measures of satisfaction (number of women/total (%))</u>** **<u>a. Would recommend treatment to others</u>**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Analysis Data were analysed using Student's t-test, Mann-Whitney, chi-squared and Fisher's exact test as appropriate.	Sublingual: 36/38 (94.7) Vaginal: 33/39 (84.6) **b. Treatment preferred if given the opportunity to choose again** **- Surgery:** Sublingual: 7/38 (18.4) Vaginal:10/39 (25.6) **- Vaginal misoprostol:** Sublingual: 2/38 (5.3) Vaginal: 27/39 (69.2) **- Sublingual misoprostol:** Sublingual: 29/38 (76.3) Vaginal: 1/39 (2.6) **- Vaginal or sublingual misoprostol:** Sublingual: 0/38 (0) Vaginal: 1/39 (2.6) **c. Overall comments about treatment** **- Excellent** Sublingual: 4/38 (10.5) Vaginal: 3/39 (7.7) **- Satisfactory** Sublingual: 26/38 (68.4) Vaginal: 28/39 (71.8) **- Fair** Sublingual: 6/38 (15.8) Vaginal: 5/39 (12.8) **- Not satisfactory**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Sublingual: 2/38 (5.3) Vaginal: 3/39 (7.7) (Note: Not all participants gave answers to these questions - the denominators stated above refer to those who answered, not total participants as calculated in the paper)	
Full citation Tang,O.S., Ong,C.Y., Tse,K.Y., Ng,E.H., Lee,S.W., Ho,P.C., A randomized trial to compare the use of sublingual misoprostol with or without an additional 1 week course for the management of first trimester silent miscarriage, Human Reproduction, 21, 189-192, 2006 **Ref Id** 65517 **Country/ies where the study was carried out** Hong Kong **Study type** Randomised controlled	**Sample size** N=180 **Characteristics** There were no significant differences between the two arms. **Age/years (mean (SD))** **600 micrograms:** 31.7 (6.7) **Extended course:** 32.1 (6.3) **Weight/kg (mean (SD))** **600 micrograms:** 53.2 (7.4) **Extended course:** 54.3 (7.8) **Height/cm (mean**	**Interventions** **600 group:** 600 micrograms of sublingual misoprostol every 3 hours up to a maximum of 3 doses (n=90) **Extended course group:** 600 micrograms of sublingual misoprostol every 3 hours up to a maximum of 3 doses, plus an extended course of 400 micrograms of sublingual misoprostol daily for a further week (n=90)	**Details** Women with a diagnosis of first trimester miscarriage were recruited. An ultrasound examination was performed to confirm the diagnosis of silent miscarriage (see inclusion criteria). 206 women with a silent miscarriage were screened, however 12 refused trial entry because they preferred the surgical method, 8 passed products of conception before the treatment was started, and 6 had other medical problems and did not meet the inclusion criteria. Therefore, 180 eligible women were randomised to one of two regimens, using computer generated random numbers. Blinding was not done - participants and investigators were aware of treatment allocation.	**Results** **Clinical outcome (number/total (%))** **a. Complete miscarriage** **600:** 83/90 (92.2) **Extended course:** 84/90 (93.3) **b. Incomplete miscarriage** **600:** 0/90 (0) **Extended course:** 4/90 (4.4) **c. Silent miscarriage** **600:** 5/90 (5.6) **Extended course:** 1/90 (1.1) **d. Undetermined** **600:** 2/90 (2.2) (Note: One patient passed tissue on day 1, but an ultrasound on day 9 showed incomplete miscarriage, and she	**Limitations** **Lack of blinding** Neither participants or physicians were blinded **Missing data** The denominators for the days 2 - 9 adverse effects are not stated, however in order to get the % that the authors have reported, the denominators have to be 86 in each arm. Loss to follow-up at day 9 is reported as n=1 in the text, therefore this missing data is unexplained. **Other information** EARLY EMBRYONIC/FETAL DEMISE SUBLINGUAL DOSAGE COMPARISON: 600µg vs. 600µg + extended course **Interval between misoprostol and**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trial **Aim of the study** To investigate whether the addition of an extended one week course of sublingual misoprostol can improve the success rate of medical management and shorten the duration of vaginal bleeding after miscarriage. **Study dates** July 2002 to January 2004 **Source of funding** The Committee on Research and Conference Grants of the University of Hong Kong	**(SD))** **600 micrograms:** 159.0 (3.8) **Extended course:** 158.5 (5.6) **Gestational age/days (mean (SD))** **600 micrograms:** 50.1 (9.6) **Extended course**: 50.6 (10.0) **Previous live birth (number/total (%))** **600 micrograms:** 53/90 (58.9) **Extended course:** 64/90 (71.1) **Previous miscarriage (number/total (%))** **600 micrograms:** 20/90 (22.2) **Extended course:** 21/90 (23.3) **Previous induced abortion (number/total (%))**		**Treatment protocols** Participants received one of two regimens: - 600 micrograms of sublingual misoprostol every 3 hours up to a maximum of 3 doses (day 1) - 600 micrograms of sublingual misoprostol every 3 hours up to a maximum of 3 doses, plus an extended course of 400 micrograms of sublingual misoprostol daily for a further week (days 2-8) Women were instructed by the study investigator to put the three tablets of misoprostol under their tongue themselves. They were not allowed any food or drink for the next 20 minutes to allow complete dissolution of the tablets. The blood pressure, pulse rate and side-effects were recorded every hour and the body temperature was recorded every 3 hours. Oral or parenteral analgesic was given if the women complained of severe pain. The women were asked to	did not return on day 43. The other did not pass any tissue on day 1, and did not return on day 9.) **Extended course:** 1/90 (1.1) (Note: This patient did not pass any tissue on day 1, then an ultrasound on day 9 showed incomplete miscarriage and she did not return on day 43.) **Duration of vaginal bleeding/days (median (range))** **600:** 11.5 (5-35) **Extended course:** 11.0 (6-42) (NS) **Adverse effects of treatment (number of women/total (%))** **a. Nausea: day 1** **600:** 38/90 (42.2) **Extended course:** 45/90 (p=0.26) **b. Nausea: days 2-9** **600:** 13/86 (15.1) **Extended course:** 18/86 (20.9) (p=0.32) **c. Vomiting: day 1**	**passage of products of conception / hours (median (range))** **600:** 10.1 (2.8-139.5) **Extended course:** 9.2 (2-128) (NS)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	600 micrograms: 23/90 (25.6) **Extended course:** 24/90 (26.7) **Inclusion criteria** < 13 weeks gestation Diagnosis of silent miscarriage, based on: - Intrauterine gestational sac with a mean sac diameter of ≥ 2 cm without a fetal pole - Presence of a fetal pole with no cardiac pulsation - Gestational sac diameter < 2 cm with no interval growth or persistent absence of fetal cardiac pulsation on rescanning 7-10 days later **Exclusion criteria** Incomplete miscarriage		inform the nurse when they passed any tissue at the hospital and they were given a bottle with formalin to collect any tissue passed at home. The tissue was sent for histological confirmation. The women were discharged after completion of the course of misoprostol if they were not experiencing heavy vaginal bleeding or pain. Women in group 2 were given tablets of 400 micrograms of misoprostol to be taken daily at home starting from day 2 of the study. Emergency surgical evacuation was carried out if the blood loss or abdominal pain was uncontrolled. All the women were asked to use barrier method for contraception if necessary. **Follow up** The outcome of the study was assessed on day 9. A transvaginal ultrasound examination of the pelvis was performed. Surgical evacuation was done if a gestational sac was still present or if there was	**600:** 13/90 (14.4) **Extended course:** 14/90 (15.6) (p=0.81) **d. Vomiting: days 2-9** **600:** 1/86 (1.2) **Extended course:** 5/86 (5.8) (p=0.10) **e. Diarrhoea: day 1** **600:** 61/90 (67.8) **Extended course:** 63/90 (70) (p=0.66) **f. Diarrhoea: days 2-9** **600:** 19/86 (22.1) **Extended course:** 38/86 (44.2) (p=0.002) **g. Fever: day 1** **600:** 52/90 (57.8) **Extended course:** 55/90 (61.1) (p=0.65) **h. Fever: days 2-9** **600:** 0/86 (0) **Extended course:** 0/86 (0) (p=1.0) **i. Chills and rigor: day 1**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			significant amount of products of conception in the uterus together with clinical evidence of heavy vaginal bleeding. Otherwise, the amount of bleeding was monitored and the woman was asked to come back on day 43 for the assessment of bleeding pattern and return of menstruation. The outcome of treatment was classified as complete miscarriage if surgical evacuation was not required. **Outcomes reported** **1. Clinical outcome:** Complete miscarriage rate is reported as the number of women for whom surgical evacuation was not required. Incomplete miscarriage, silent miscarriage and undetermined rates are also reported. **2. Duration of vaginal bleeding:** Appears to have been assessed on day 43 after treatment. **3. Adverse effects of treatment:** Incidences on day 1, and days 2-9 are	**600:** 10/90 (11.1) **Extended course:** 13/90 (14.4) (p=0.49) **j. Chills and rigor: days 2-9** **600:** 0/86 (0) **Extended course:** 0/86 (0) (p=1.0) **k. Headache: day 1** **600:** 19/90 (21.1) **Extended course:** 25/90 (27.8) (p=0.28) **l. Headache: days 2-9** **600:** 30/86 (34.9) **Extended course:** 30/86 (34.9) (p=1.0) **m. Breast tenderness: day 1** **600:** 14/90 (15.6) **Extended course:** 10/90 (11.1) (p=0.40) **n. Breast tenderness: days 2-9** **600:** 20/86 (23.3) **Extended course:** 10/86 (11.6) (p=0.044) (Note: the authors also report that no serious complications	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			reported. Diarrhoea is defined as more than three episodes. Fever is defined as a highest temperature of at lest 38ºC. **4. Measures of pain:** The incidence of lower abdominal pain on day 1, and days 2-9 is reported. **Analysis** Student's t-test, Mann–Whitney U-test , χ^2-test and the Fisher exact test were used for analysis, as appropriate.The difference in complete miscarriage rate was used to calculate the sample size required. According to the previous studies, the use of this regimen of sublingual misoprostol without an extended course would achieve a complete miscarriage rate of 87.5%. The use of an extended course of misoprostol would be considered superior if it could achieve a complete miscarriage rate of 97.5%. A sample size of 90 in each group gave 80% power in detecting a difference of 10% in complete miscarriage rate with an alpha of 0.05.	occurred) **Measures of pain** **a. Incidence of lower abdominal pain: day 1** **600:** 88/90 (97.8) **Extended course:** 88/90 (97.8) (p=1.0) **b. Incidence of lower abdominal pain: days 2-9** **600:** 66/86 (76.7) **Extended course:** 74/86 (86.0) (p=0.12)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ngoc,N.T., Blum,J., Westheimer,E., Quan,T.T., Winikoff,B., Medical treatment of missed abortion using misoprostol, International Journal of Gynaecology and Obstetrics, 87, 138-142, 2004 **Ref Id** 69531 **Country/ies where the study was carried out** Vietnam **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy of two routes of misoprostol administration (oral and vaginal) for the treatment of missed miscarriage. **Study dates**	**Sample size** N=200 **Characteristics** Age/years (range): 19 - 45 Education/years (mean): 8 Nulliparous (%): 30 No prior elective abortions (%): 65 The authors give no further details, but report that there were no significant differences between the two groups, confirming that randomisation was effective. **Inclusion criteria** First trimester, missed miscarriage, defined as: - ultrasound evidence of an intact gestational sac - no evidence of fetal cardiac activity (6	**Interventions** 800 micrograms of oral misoprostol (n = 101) 800 micrograms of vaginal misoprostol (n = 99)	**Details** Recruitment for this study occurred at Hung Vuong Hospital, a premier research and referral facility in Ho Chi Minh City, Vietnam. During the study period, 200 women with confirmed first trimester missed miscarriage consented to participate and were randomised to one of two treatment regimens. All women would have been advised to have a surgical evacuation under general anaesthesia as part of the normal standard of care. **Treatment protocol** Women were randomised to receive either: - Four 200 micrograms tablets of misoprostol orally - Four 200 micrograms tablets of misoprostol vaginally Every woman self-administered their misoprostol in the presence of a study investigator. Neither the investigator or the patient was blinded to	**Results** **Treatment success (number/total (%))** Oral: 89/101 (88.1) Vaginal: 91/99 (91.9) **Need for further intervention (number/total (%))** **a. Total** Oral: 11/100 (11) Vaginal: 7/98 (7.1) (NS) **b. Medically indicated before study end** Oral: 5/100 (5) (Note: 3 were for haemostatic control, 1 for incomplete miscarriage, and 1 for an unspecified reason) Vaginal: 2/98 (2.0) (Note: reasons not stated) (NS) **c. Intervention at patient request** Oral: 6/100 (6) Vaginal: 5/98 (5.1) (NS)	**Limitations** **Lack of blinding** Blinding the patient would have been difficult (although not impossible), however those assessing outcomes such as treatment success and need for further intervention could have been blinded to treatment allocation. **Misdiagnoses** Two women with an invasive choriocarcinoma and a cervical pregnancy were included after being incorrectly diagnosed with a missed miscarriage. This particularly affects the outcome of hospitalisation. **Other information** EARLY EMBRYONIC/FETAL DEMISE ONLY ORAL vs. VAGINAL **Time to expulsion/hours (mean)** Oral: 21.0 Vaginal: 13.5 (p=0.04)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
January to August 2003 **Source of funding** David and Lucille Packard Foundation	weeks after last menstrual period) - closed cervical os - history of no or minimal bleeding No known contraindications to misoprostol General good health Willingness to attend a follow-up visit **Exclusion criteria** See above		treatment allocation. **Follow-up** All women were given a follow-up appointment two days later, at which time miscarriage status was evaluated using ultrasound. If substantial debris remained in the uterus, women were given the option to return 5 days later (one week after misoprostol administration) to allow additional time for complete expulsion. If women did not wish to wait, they were given a surgical evacuation. If, at the second follow-up visit, miscarriage was not complete, a surgical evacuation was performed. All women were advised that they could return to the hospital at any time if complications or questions arose, and that they could request a surgical completion at any point. Data was collected to record clinical outcome, any additional interventions, acceptability and side effects. Women were asked to keep a diary of side effects, including pain.	**Admission to hospital (number/total (%))** Oral: 0/100 (0) Vaginal: 2/98 (2.0) (Note: 1 was due to a suspected molar pregnancy following failure of the initial treatment. She was subsequently discovered to have an invasive choriocarcinoma, requiring a hysterectomy. The other woman required a blood transfusion after uncontrolled bleeding due to a cervical pregnancy. Therefore, these women were incorrectly diagnosed with a missed miscarriage. The analysis was performed both with and without these women without a significant change in results.) **Duration of bleeding/days (mean)** (Note: n=95 in each arm for this outcome) **a. All bleeding** Oral: 2.87 Vaginal: 2.69 (NS)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			<u>Outcomes reported</u> **1. Treatment success:** Complete uterine evacuation without the need for surgical evacuation **2. Need for further intervention:** Medically indicated surgical evacuation and evacuations at the patient's request are reported. **3. Hospitalisation** **4. Duration of bleeding:** The duration of heavy bleeding (more than a period), normal bleeding (like a period), and light bleeding (less than a period) are reported. **5. Adverse effects of treatment:** The incidence of diarrhoea, fever/chills, and vomiting is reported. This was self reported by the women, using a diary. **6. Measures of pain:** The incidence of pain/cramps is self reported, as with adverse effects. **7. Measures of**	**<u>b. Heavy bleeding</u>** Oral: 0.89 Vaginal: 0.90 (NS) **<u>c. Normal bleeding</u>** Oral: 1.29 Vaginal: 1.09 (NS) **<u>d. Light bleeding</u>** Oral: 0.73 Vaginal: 0.73 (NS) **<u>Adverse effects of treatment (number of women/total (%))</u>** **<u>a. Vomiting</u>** Oral: 4/95 (4.2) Vaginal: 14/95 (14.7) (p=0.023) **<u>b. Diarrhoea</u>** Oral: 24/95 (25.3) Vaginal: 23/95 (24.2) (NS) **<u>c. Fever/chills</u>** Oral: 7/95 (7.4) Vaginal: 7/95 (7.4)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			satisfaction: The number of women reporting being satisfied or very satisfied with their allocated method was assessed at follow-up, and women were also asked to describe the best and worst features of their allocated method. **Analysis** Data was analysed using frequencies, cross-tabulations, chi-squared tests and t-tests where appropriate. Differences were considered to be statistically significant if $p<0.05$. Two women in the vaginal group and one in the oral group were lost to follow-up; however one woman in the vaginal group was later reached by telephone. Analysis is based on the 198 women for whom follow-up information was available.	(NS) **Measures of pain: Incidence of pain/cramps (number of women/total (%))** Oral: 84/95 (88.4) Vaginal: 85/95 (89.5) (NS) **Measures of satisfaction** **a. Satisfied or very satisfied with the method (number of women/total (%))** Oral: 86/100 (86.0) Vaginal: 88/98 (89.8) **b. Would choose the method again (%)** Oral: 85.0 Vaginal: 92.9 (NS) **c. Would recommend the method to a friend (%)** Oral: 83.0 Vaginal: 90.8	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Blanchard,K., Taneepanichskul,S., Kiriwat,O., Sirimai,K., Svirirojana,N., Mavimbela,N., Winikoff,B., Two regimens of misoprostol for treatment of incomplete abortion, Obstetrics and Gynecology, 103, 860-865, 2004 **Ref Id** 77948 **Country/ies where the study was carried out** Thailand **Study type** Randomised controlled trial **Aim of the study** To evaluate two misoprostol regimens and estimate whether they were effective in treating incomplete miscarriage	**Sample size** N=169 **Characteristics** **Study site (number/total (%))** **Study site A:** 68/169 (40.2) **Study site B:** 101/169 (59.8) Note: The following characteristics are reported split by study site, and by the arm that participants were randomised **Age/years (mean)** **Study site A:** 28.9 **Study site B:** 27.7 p=0.26 **Single dose:** 28.6 **Double dose:** 27.7 p=0.41 **Education level/years (mean)** **Study site A:** 7.3 **Study site B:** 9.3	**Interventions** Single dose of 600 microgram, oral misoprostol (n=86) Double dose (4 hours apart) of 600 microgram, oral misoprostol (total dose of 1200µg) (n=83)	**Details** Women meeting the inclusion criteria that presented at 2 teaching hospitals in Bangkok (Chulalongkorn Hospital and Siriraj Hospital) were enrolled. A total of 169 women were enrolled, however 1 woman at site A and 2 women at site B were lost to follow-up. After signing an informed consent form, women were randomised using a pseudo-random number generator and opaque envelopes that contained details of the allocated regimen. Neither the provider nor the woman was blinded to the treatment regimen. **Treatment protocol** Women were randomised to receive either: - A single, oral dose of 600 microgram misoprostol - Two oral doses of 600 microgram misoprostol, with 4 hours between doses The decision of whether or not to admit the woman to	**Results** **Complete miscarriage (number/total (%))** **Single dose:** 57/86 (66.3) **Double dose:** 58/83 (69.9) **Need for further intervention (number/total (%))** **a. Medically necessary** **Single dose:** 22/85 (25.9) **Double dose:** 18/81 (22.2) **b. Intervention at patient request** **Single dose:** 4/85 (4.7) **Double dose:** 0/81 (0) **c. Intervention because of provider preference** **Single dose:** 0/85 (0) **Double dose:** 1/81 (1.2) **d. Intervention for other reasons** **Single dose:** 2/85 (2.4) **Double dose:** 4/81 (4.9) (Note: 1 woman from the single dose arm and 2 from the double dose arm had unknown outcomes, and therefore have	**Limitations** **Lack of blinding** Neither participants or providers were blinded to treatment allocation. **Point of assessment of outcomes** Not reported how and when satisfaction was assessed **Other information** INCOMPLETE MISCARRIAGE ONLY ORAL DOSAGE COMPARISON - 600 micrograms vs. 2 x 600 micrograms (4 hours apart) **Misoprostol taken as scheduled (number/total (%))** **Study site A:** 64/68 (94.1) **Study site B:** 101/101 (100) (p=0.02) **Single dose:** 84/86 (97.7) **Double dose:** 81/83 (97.6) (p=1.00) **Decision to take second dose at home** 68/83 (81.9%) women randomised to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates September 2000 to April 2002 **Source of funding** Not reported	p<0.01 **Single dose:** 8.5 **Double dose:** 8.5 p=0.98 **Nulliparous (number/total (%))** **Study site A:** 22/68 (32.4) **Study site B:** 52/101 (51.5) p=0.02 **Single dose:** 34/86 (39.5) **Double dose:** 40/83 (48.2) p=0.33 **Time since last menstrual period/days (mean)** **Study site A:** 88.9 **Study site B:** 92.8 p=0.52 **Single dose:** 89.5 **Double dose:** 93.5 p=0.50 (Note: 9 women at site A, 3 women at site B, 2 women in single-dose group,		hospital was made at the discretion of the local investigator. However, investigators were encouraged to admit the initial cases if they were concerned about the tolerability of the regimen. At site A, hospital admission was the standard of care for the treatment of incomplete miscarriage, therefore a larger proportion of women were admitted. Each woman received 500-mg tablets of paracetamol and was instructed to take 2 tablets every 6 hours to manage pain. **Follow-up** Women were asked to return to the clinic 2 days after misoprostol administration for their initial follow-up visit. The outcome was assessed by ultrasound examination. If the miscarriage was not complete, women were given the option of waiting an additional 5 days (1 week from initial treatment) to see if the miscarriage would become complete without further intervention. If miscarriage was not complete after 1 week, or	not been included in the denominator for need for further intervention) **Duration of bleeding/days (mean)** **a. Heavy bleeding** **Single dose:** 1.31 **Double dose:** 1.63 (p=0.21) **b. Normal bleeding** **Single dose:** 2.86 **Double dose:** 2.76 (p=0.79) **c. Spotting** **Single dose:** 2.94 **Double dose:** 2.88 (p=0.89) **Adverse effects of treatment** **a. Nausea: incidence (number of women/total (%))** **Single dose:** 15/86 (17.4) **Double dose:** 18/83 (21.7) (p=0.62) **b. Nausea: duration/days (mean)**	the double-dose regimen chose to take the second dose of misoprostol at home. This was 19/32 (59.4%) at site A and 49/51 (96.1) at site B (p<0.01). **Differences between study sites** Rates of complete miscarriage were higher at site B (85.1%) than site A (42.6%). Site A had higher rates of medically necessary interventions and slightly higher rates of intervention at patient request. The regimens were better accepted overall at site B. More women at site A reported heavy bleeding, normal bleeding, nausea and pain.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	and 10 women in double-dose group had missing LMP data. Where women knew the month but not date, the 15th was assigned) **Previous induced abortion (number/total (%))** **Study site A:** 13/68 (19.1) **Study site B:** 13/101 (12.9) p=0.37 **Single dose:** 13/86 (15.1) **Double dose:** 13/83 (15.7) p=0.91 **Previous miscarriage (number/total (%))** **Study site A:** 15/68 (22.1) **Study site B:** 76/101 (75.2) p<0.01 **Single dose:** 49/86 (57.0) **Double dose:** 42/83 (50.6)		the woman refused an extension, a surgical evacuation was performed according to the standard practise at the hospital. (Note: 59% of women chose to wait for the further 5 days) **Outcomes reported** **1. Complete miscarriage:** assessed by ultrasound examination as described above **2. Need for further intervention:** criteria, or reasons, for further intervention are reported. **3. Duration of bleeding:** Heavy bleeding is defined as heavier than that of a normal period. **4. Adverse effects:** Self-reported nausea, vomiting and fever/chills using diary of side effects **5. Pain:** Measured using a visual analogue scale of 7 circles, with the smallest indicating no pain and the largest indicating the worst pain women had ever	**Single dose:** 1.40 **Double dose:** 1.72 (p=0.51) **c. Vomiting: incidence (number of women/total (%))** **Single dose:** 6/86 (7.0) **Double dose:** 7/83 (8.4) (p=0.95) **d. Vomiting: duration/days (mean)** **Single dose:** 1.17 **Double dose:** 1.00 (p=0.36) **e. Fever/chills: incidence (number of women/total (%))** **Single dose:** 12/86 (14.0) **Double dose:** 10/83 (12.1) (p=0.89) **f. Fever/chills: duration/days (mean)** **Single dose:** 1.00 **Double dose:** 2.30 (p=0.10) **Measures of pain:** **a. Pain/cramps: incidence (number of women/total (%))** **Single dose:** 57/86 (66.3) **Double dose:** 63/83 (75.9)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	p=0.50 **Inclusion criteria** Women with signs of incomplete miscarriage, with ultrasound findings consistent with first trimester miscarriage, who would have been advised to have a surgical evacuation In good general health Agree to return for follow-up and complete a diary of side effects Good access to emergency care facilities **Exclusion criteria** Known allergy to misoprostol		experienced. **6. Satisfaction:** Not reported how and when this was assessed **Analysis** A sample size calculation was performed, and the authors aimed to enrol 100 women in each arm to give 80% power to detect a difference of 20% between the two groups. Chi-squared test, Fisher's exact test, sample t-tests and Mann-Whitney tests were used to compare variables where appropriate. A p-value of <0.05 was considered statistically significant.	(p=0.23) **b. Pain level/7 (mean)** **Single dose:** 3.65 (n=85) **Double dose:** 4.09 (n=81) (p=0.20) (Note: The assessment of pain level does not include the 3 women lost to follow-up) **Measures of satisfaction (number of women/total (%))** **a. Satisfied or very satisfied with treatment** **Single dose:** 68/85 (80.0) **Double dose:** 63/81 (77.8) (p=0.87) **b. Would choose this method again** **Single dose:** 74/85 (87.1) **Double dose:** 71/81 (87.7) (p=0.91) **c. Would recommend this method to a friend** **Single dose:** 79/85 (92.9) **Double dose:** 71/81 (87.7) (p=0.37) (Note: the 3 women lost to follow-up are not included in the	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				satisfaction outcomes)	
Full citation Ngoc,N.T.N., Blum,J., Durocher,J., Quan,T.T., Winikoff,B., A randomized controlled study comparing 600 versus 1,200 microg oral misoprostol for medical management of incomplete abortion, Contraception, 72, 438-442, 2005 **Ref Id** 78319 **Country/ies where the study was carried out** Vietnam **Study type** Randomised controlled trial **Aim of the study** To document the effectiveness of 600 micrograms vs. 1200 micrograms of oral misoprostol as a non-surgical treatment for	**Sample size** N=300 (Note: 5 were lost to follow-up, and their data has been excluded from all analyses, therefore reported population is N=295) **Characteristics** **Age/years (mean (range))** **Single dose:** 28.5 (18-48) **Double dose:** 28.6 (18-46) **Education/years (mean)** **Single dose:** 8.0 **Double dose:** 7.7 **Gestational age/weeks (mean)** **Single dose:** 8.0 **Double dose:** 8.3	**Interventions** Single dose of 600 microgram oral misoprostol (n=150) Double dose (4 hours apart) of 600 microgram oral misoprostol (total dose of 1200 micrograms) (n=150)	**Details** During the study period, 300 women presenting with diagnosed incomplete miscarriage (see inclusion criteria) were recruited at a large tertiary facility in Ho Chi Minh City. Ultrasound was only used for diagnosis when there was a suspicion that the uterus had been emptied (i.e. when the choriodecidual reaction in the uterine cavity measured <11 mm). If products of conception were seen or felt at the external os, ultrasound was not performed. All these women would have received surgical evacuation using aspiration, with or without anaesthesia, if misoprostol had not been available. Eligible women who gave informed consent were randomised using a computer generated random sequence in envelopes (not reported if they were opaque). **Treatment protocol** Women were randomised to one of two treatment	**Results** **Success rate (number/total (%))** **Single dose:** 142/150 (94.7) **Double dose:** 137/150 (91.3) **Need for further intervention (number/total (%))** **a. Due to incomplete miscarriage at study end** **Single dose:** 4/149 (2.7) **Double dose:** 4/146 (2.7) (NS) **b. Medically indicated surgical intervention before study end** **Single dose:** 3/149 (2.0) **Double dose:** 4/146 (2.7) (NS) (Note: 6 were medically indicated for haemostatic control and 1 was given on day 3 when the woman presented with signs of infection) **c. Surgical completion for provider preference before**	**Limitations** **Lack of blinding** Blinding is not reported in this study. **Missing data** Loss to follow-up was 1/150 (0.7%) in the single dose arm and 4/150 (2.7%) in the double dose arm (NS). Apart from the loss to follow-up they reported, there is missing data for 1 participant in the double dose group for the outcomes of adverse effects, pain and satisfaction (n=145). This omission is not explained. **Other information** INCOMPLETE MISCARRIAGE ONLY ORAL DOSAGE COMPARISON: 600 micrograms vs. 2 x 600 micrograms (4 hours apart) **Time to expulsion** 60% of the women had completed their miscarriages by study day 3. The remaining women with successful treatment had completed it by study day 7. At the follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
incomplete miscarriage **Study dates** May 2002 to January 2003 **Source of funding** David and Lucille Packard Foundation	**Parity (mean)** **Single dose:** 1.4 **Double dose:** 1.3 **Primigravida (number/total (%))** **Single dose:** 57/149 (38.3) **Double dose:** 51/146 (34.9) **Number of previous elective abortions (mean (range))** **Single dose:** 0.52 (0-5) **Double dose:** 0.44 (0-6) **Number of previous miscarriages (mean (range))** **Single dose:** 0.16 (0-3) **Double dose:** 0.12 (0-2) The authors report that there were no significant differences in the characteristics of the two study		protocols: - A single dose of 600 microgram oral misoprostol - Two 600 microgram doses of oral misoprostol 4 hours apart, for a total of 1200 micrograms All women swallowed their misoprostol in the presence of study staff at the hospital. Women in the repeated dose group were asked to remain in the hospital for their second dose. All women were released shortly after misoprostol administration. Women were given eight 500mg paracetamol tablets to manage any pain, counselled about the side effects of misoprostol, and scheduled to return for follow-up care 2 days later. Women were also asked to complete a diary card to record any side effects and use of pain medication. They were told that they could return to the hospital or contact the study providers at any time if they had additional questions or concerns. **Follow-up** At the follow-up visit, each	**study end** **Single dose:** 0/149 (0) **Double dose:** 1/146 (0.7) (NS) (Note: this woman was given surgical completion after the provider suspected an intracervical polyp on follow-up examination) **Duration of bleeding/days (mean (SD))** **a. Any bleeding** **Single dose:** 4.1 (2.3) **Double dose:** 3.7 (2.3) (NS) **b. Heavy bleeding** **Single dose:** 0.8 (0.8) **Double dose:** 0.8 (0.7) (NS) **c. Normal bleeding** **Single dose:** 1.2 (0.9) **Double dose:** 1.2 (1.2) (NS) **d. Light bleeding** **Single dose:** 2.1 (2.1)	visit, women were asked if they had observed the expulsion. 85.2% in the single dose group and 80.0% in the double dose group had observed the expulsion (note: women who reported having observed the expulsion were more likely to indicate that they were satisfied with the method, p<0.001). The mean time (in hours) to expulsion was: **Single dose:** 13.6 **Double dose:** 14.0 (NS)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	groups. **Inclusion criteria** Women with incomplete miscarriage, diagnosed using the following criteria: - Transvaginal ultrasound evidence of substantial debris in the uterus (echogenic mass >12 mm) - Past or present history of vaginal bleeding during pregnancy - Open cervical os, with or without products of conception present in the cervical or vaginal canal Aged 18 years or older Living or working within 1 hour of the study hospital No known contraindication to misoprostol		woman's miscarriage status was assessed. Women with retained products in the cervix (i.e. intrauterine echoic mass > 12 mm, dilated cervix and/or heavy bleeding on study day 3) were offered the option of waiting an additional week to see if these products would evacuate on their own. If they agreed, they were given a second follow-up appointment on study day 7 after initial treatment. Women who did not want to wait were given an immediate surgical completion. All women with retained products on study day 7 were given surgery. Upon completion of treatment, women were interviewed to gauge the acceptability of the treatment. **Outcomes assessed** **1. Success rate:** The primary outcome for this study was complete uterine evacuation without recourse to surgical intervention at any point for any reason during the study period. **2. Surgical intervention before study end:** They	**Double dose:** 1.8 (2.1) (NS) **Adverse effects of treatment (number of women/total (%))** **a. Nausea** **Single dose:** 33/149 (22.1) **Double dose:** 19/145 (13.1) (p=0.04) **b. Vomiting** **Single dose:** 19/149 (12.8) **Double dose:** 17/145 (11.7) (NS) **c. Diarrhoea** **Single dose:** 51/149 (34.2) **Double dose:** 68/145 (46.7) (p=0.03) **d. Fever/chills** **Single dose:** 15/149 (10.1) **Double dose:** 12/145 (8.3) (NS) (Note: they report that there were no serious complications or adverse effects reported by any of the participants in the study)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	General good health **Exclusion criteria** Not reported (but those lost to follow-up were excluded from all analyses)		report the incidence of medically indicated surgery, and surgery due to provider preference **3. Duration of bleeding:** They report duration of heavy bleeding (more than a period), normal bleeding (like a period) and light bleeding (less than a period). **4. Adverse effects:** Incidence of nausea, vomiting, diarrhoea and fever/chills. Information was collected using the diary card which was reviewed at the exit interview. **5. Measures of pain:** Incidence of pain/cramps was collected using the diary card which was reviewed at the exit interview. Pain level was measured on a seven point scale. **6. Measures of satisfaction:** Overall satisfaction (very satisfied, satisfied, neutral, unsatisfied), whether the woman would choose the method again, and whether she would recommend it to	**Measures of pain** **a. Incidence of pain/cramps (number of women/total (%))** **Single dose:** 125/149 (83.9) **Double dose:** 120/145 (82.8) (NS) **b. Pain level/7 (mean)** **Single dose:** 3.7 **Double dose:** 3.6 (NS) **Measures of satisfaction (number of women/total (%))** **a. Satisfied or very satisfied with treatment** **Single dose:** 143/149 (96.0) **Double dose:** 136/145 (93.8) (Note: 4/149 (2.7%) in the single dose group and 3/145 (2.1%) in the double dose group were unsatisfied. The remainder were neutral) **b. Would choose method again** **Single dose:** 139/149 (93.3) **Double dose:** 129/145 (89.0)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			a friend were assessed in an exit interview. The best and worst features of the methods were also assessed. **Analysis** 5 women (1 from single dose group and 4 from the double dose group) were lost to follow-up. Every effort was made to contact them by home visits and phone calls; however this was unsuccessful and their outcomes are unknown. They have been excluded from all analyses. Data entry and analysis were conducted using SPSS. Chi-squared and t-tests were used as appropriate, and $p<0.05$ was considered statistically significant.	**c. Would recommend method to a friend** **Single dose:** 144/149 (96.6) **Double dose:** 135/145 (93.1) **Best features of the methods (number/total (%))** **a. Successful, feels good after** **Single dose:** 84/149 (57.1) **Double dose:** 70/145 (48.6) **b. Does not affect health** **Single dose:** 57/149 (38.8) **Double dose:** 49/145 (34.0) **c. Perceived better method** **Single dose:** 18/149 (12.2) **Double dose:** 24/145 (16.7) **d. Avoid curettage** **Single dose:** 5/149 (3.4) **Double dose**: 7/145 (4.9) **e. Fewer side effects** **Single dose:** 7/149 (4.8) **Double dose:** 5/145 (3.5)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				f. Others **Single dose:** 1/49 (1.0) **Double dose:** 4/145 (2.8) **g. Don't know** **Single dose:** 9/149 (6.1) **Double dose:** 11/145 (7.6) **Worst features of the methods (number/total (%))** **a. None** **Single dose:** 122/149 (82.4) **Double dose:** 118/145 (82.0) **b. Pain, body aches** **Single dose:** 12/149 (8.1) **Double dose:** 14/145 (9.7) **c. Diarrhoea, vomiting** **Single dose:** 6/149 (4.1) **Double dose:** 4/145 (2.8) **d. Too time consuming** **Single dose:** 6/149 (4.1) **Double dose:** 5/145 (3.5) **e. Bleeding**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Single dose: 4/149 (2.7) **Double dose:** 6/145 (4.2) **f. Weakness, fatigue** **Single dose:** 5/149 (3.4) **Double dose:** 5/145 (3.5) **g. Anxious, worried** **Single dose:** 1/149 (1.0) **Double dose:** 1/145 (1.0) **h. Other reason** **Single dose:** 2/149 (1.4) **Double dose:** 0/145 (0)	
Full citation Rita, Gupta,S., Kumar,S., A randomised comparison of oral and vaginal misoprostol for medical management of first trimester missed abortion, JK Science, 8, 35-38, 2006 **Ref Id** 78403 **Country/ies where the study was carried out**	**Sample size** N=100 **Characteristics** **Age/years (number of women/total (%))** **15-20** Oral: 9/50 (18) Vaginal: 8/50 (16) **21-25** Oral: 25/50 (50) Vaginal: 21/50 (42) **26-30** Oral: 14/50 (28)	**Interventions** 400 micrograms of oral misoprostol, repeated every three hours up to a maximum of 3 doses (n=50) 600 micrograms of vaginal misoprostol, with a second dose after 4 hours (n=50)	**Details** This study was conducted in the Department of Obstetrics and Gynaecology of SMGS Hospital, Government Medical College, Jammu. All women satisfying the inclusion criteria underwent transvaginal ultrasound to confirm the diagnosis, after a thorough physical and systemic examination. 100 women consented to participate and were randomised (using permuted block method).	**Results** **Treatment success (number/total (%))** Oral: 18/50 (36) Vaginal: 40/50 (80) **Need for further intervention (number/total (%))** Oral: 32/50 (64) Vaginal: 10/50 (20) **Adverse effects of treatment (number/total (%))** **a. Nausea**	**Limitations** **Definition of outcomes** Unclear how and when "severe pain" and adverse effects were judged. **Blinding** There is no reported blinding. It would have been difficult to blind the participants, however the physicians assessing the treatment success and need for further intervention could have been blinded to treatment allocation. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
India **Study type** Randomised controlled trial **Aim of the study** To compare the safety and efficacy of oral versus vaginal misoprostol for medical management of missed miscarriage. **Study dates** 2002 to 2003 **Source of funding** Not reported	Vaginal: 17/50 (34) **31-35** Oral: 2/50 (4) Vaginal: 4/50 (8) (p=0.87) **Gravidity (number of women/total (%))** **1** Oral: 21/50 (42) Vaginal: 19/50 (38) **2** Oral: 8/50 (16) Vaginal: 15/50 (30) **3** Oral: 12/50 (24) Vaginal: 8/50 (16) **4** Oral: 9/50 (18) Vaginal: 8/50 (16) (p=0.37) **Residence (number of women/total (%))** **Urban** Oral: 32/50 (64) Vaginal: 29/50 (58) **Rural** Oral: 18/50 (36) Vaginal: 21/50 (42)		**Treatment protocol** Women received one of two regimens: - 400 micrograms given orally, and repeated every 4 hours up to a maximum of three doses - 600 micrograms inserted into the posterior vaginal fornix, with a second dose repeated after 4 hours Over the next 10-12 hours, complete, incomplete, or no expulsion was documented by transvaginal ultrasound. The absence of an echogenic structure measuring less 15 mm in diameter suggested complete miscarriage. Nothing was given by mouth except medication for pain relief until complete expulsion or surgical evacuation. Information was obtained regarding side effects. Rh- women were given anti D immunoglobulin. Surgical evacuation was performed in the case of heavy vaginal bleeding, or when transvaginal ultrasound did not document complete	Oral: 25/50 (50) Vaginal: 20/50 (40) **b. Vomiting** Oral: 6/50 (12) Vaginal: 3/50 (6) **c. Diarrhoea** Oral: 5/50 (10) Vaginal: 5/50 (10) **d. Hyperpyrexia** Oral: 2/50 (4) Vaginal: 2/50 (4) **Measures of pain: incidence of severe pain (number/total (%))** Oral: 8/50 (16) Vaginal: 5/50 (10)	EARLY EMBRYONIC/FETAL DEMISE ONLY ORAL vs. VAGINAL **Number of doses required in successfully treated patients (number/total (%))** **Oral (n=18)** **1:** 3/18 (16.7) **2:** 6/18 (33.3) **3:** 9/18 (50) **Vaginal (n=40)** **1:** 9/40 (22.5) **2:** 31/40 (77.5) **Time interval between first dose and expulsion/hours (mean (SD))** Oral: 9.83 (2.09) Vaginal: 8.15 (2.85) (p=0.01)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(p=0.53) **Period of gestation/weeks (number of women/total (%))** **6-8** Oral: 9/50 (18) Vaginal: 7/50 (14) **8-10** Oral: 10/50 (20) Vaginal: 10/50 (20) **10-12** Oral: 18/50 (36) Vaginal: 15/50 (30) **12-13** Oral: 13/50 (26) Vaginal: 18/50 (36) (p=0.89) **Inclusion criteria** Gestation less than 13 weeks Haemodynamically stable Haemoglobin more than 10gm%		expulsion after 10-12 hours. **Outcomes reported** **1. Treatment success:** Defined as complete, drug induced expulsion of the products of conception **2. Need for further intervention:** The number of women requiring surgical evacuation **3. Adverse effects of treatment:** Incidence of nausea, vomiting, diarrhoea and hyperpyrexia are reported. **4. Pain:** Incidence of severe pain is reported; however it is unclear what criteria was used to judge severity.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Closed cervical os Axillary temperature of < 37.5ºC **Exclusion criteria** History of inflammatory bowel disease Allergy to misoprostol				
Full citation Shah,N., Azam,S.I., Khan,N.H., Sublingual versus vaginal misoprostol in the management of missed miscarriage, Journal of the Pakistan Medical Association, 60, 113-116, 2010 **Ref Id** 78450 **Country/ies where the study was carried out** Pakistan **Study type** Randomised controlled	**Sample size** N=50 **Characteristics** **Age/years (mean (SD))** Sublingual: 26.2 (4.2) Vaginal: 26.4 (4.4) (p=0.870) **Parity (median (range))** Sublingual: 2 (0-5) Vaginal: 2 (0-5) (p=0.845) **Gestational age/weeks (mean (SD))**	**Interventions** 400 micrograms of sublingual misoprostol, every three hours up to a maximum of 5 doses (n=25) 400 micrograms of vaginal misoprostol, every three hours up to a maximum of 5 doses (n=25) (Note: those with a gestational age and uterine size of more than 12 weeks were given 200 micrograms of misoprostol instead, in both arms)	**Details** This is a prospective open-labelled trial conducted in the Department of Obstetrics and Gynaecology at Civil Hospital, Karachi. A total of 50 women diagnosed with a missed miscarriage were admitted from the out-patient clinic after doing a pelvic examination and gaining informed consent. Women were randomised using consecutive sealed envelopes. **Treatment protocol** Women received one of two regimens: - 400 micrograms of sublingual misoprostol, every three hours up to a	**Results** **Complete miscarriage rate (number/total (%))** **a. In those ≤ 12 weeks** Sublingual: 11/22 (50) Vaginal: 10/19 (52.6) (p=0.557) **b. In those > 12 weeks** Sublingual: 2/3 (66.7) Vaginal: 2/6 (33.3) (p=0.404) **c. All women** Sublingual: 13/25 (52.0) Vaginal: 12/25 (48.0) (p=0.571) **Need for further intervention**	**Limitations** **Blinding** Blinding was not done. Blinding the participants would have been difficult (although not impossible), however they could have blinded the physicians judging treatment success and need for further intervention. **Indirectness of population** For need for further intervention, adverse effects, and satisfaction, the population includes women with gestational ages that are outside the scope of the guideline. **Small sample size** N=50

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trial **Aim of the study** To compare the efficacy of sublingual and vaginal misoprostol in the medical management of missed miscarriage. **Study dates** Not reported **Source of funding** Not reported	Sublingual: 10.1 (2.62) Vaginal: 10.6 (2.92) (p=0.480) (Note: 22/25 in the sublingual arm and 19/25 in the vaginal arm had a gestational age of less than or equal to 12 weeks, and hence constitute the main population of interest for this review question) **Uterine size/weeks (range)** Sublingual: 8-16 Vaginal: 8-18 (p=0.952) **Inclusion criteria** Ultrasound diagnosis of missed miscarriage < 20 weeks gestation **Exclusion criteria** Incomplete miscarriage Retained products of conception Previous caesarean		maximum of 5 doses - 400 micrograms of vaginal misoprostol, every three hours up to a maximum of 5 doses However, patients with a gestational age of more than 12 weeks, whose uterine size was also more than 12 weeks, were given 200 micrograms instead of 400 micrograms in both sublingual and vaginal groups. Patients were monitored by the duty doctor for blood pressure, pulse, temperature, lower abdominal pain or bleeding, and the development of any side effects. Women were told to inform the duty doctor if they experienced pain, bleeding, passed the gestational sac, or developed any side effects like fever or shivering. Two tablets of oral paracetamol were given if women complained of severe lower abdominal pain. Information regarding age, parity, gestational age, uterine size, ultrasound diagnosis, number of doses, induction interval, side	**(number/total (%))** Sublingual: 11/25 (44.0) Vaginal: 13/25 (52.0) (Note: 1 further woman in the sublingual group had an incomplete miscarriage - it is not reported whether she had a surgical evacuation) **Adverse effects of treatment (number/total (%))** **a. Any side effects** Sublingual: 18/25 (72.0) Vaginal: 5/25 (20.0) (p<0.001) **b. Nausea** Sublingual: 5/25 (20.0) Vaginal: 1/25 (4.0) (p=0.094) **c. Unpleasant taste** Sublingual: 15/25 (60.0) Vaginal: 1/25 (4.0) (p<0.001) **d. Shivering** Sublingual: 6/25 (24.0) Vaginal: 4/25 (16.0)} (p=0.362)	**Other information** EARLY EMBRYONIC/FETAL DEMISE SUBLINGUAL vs. VAGINAL **Interval between misoprostol and expulsion/hours (mean (SD))** Sublingual: 13.07 (5.63) Vaginal: 13.29 (5.63) (NS)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	section scars		effects and treatment success were recorded on structured proformas. Women who expelled the sac were sent for ultrasound to exclude the possibility of RPOC. Those who failed to miscarry after 5 doses of misoprostol, and those who had incomplete miscarriage were sent for surgical evacuation under general anaesthesia on the next day. They were discharged 6 hours after the evacuation. Patients were not called for any follow-up visit. **Outcomes reported** **1. Complete miscarriage rate:** This is split by those with a pregnancy of less than or equal to 12 weeks, and those with a pregnancy of more than 12 weeks. **2. Need for further intervention** **3. Adverse effects of treatment:** The incidence of any side effects, nausea, unpleasant taste and shivering are reported. **4. Satisfaction:** Assessed	**Satisfaction (%)** Sublingual: 52 Vaginal: 48 (NS) (Note: the authors report that this closely followed the success rate of the regimen)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			by verbally asking patients whether they were satisfied, dissatisfied or neutral with regards to their treatment regimen.		
Full citation Tanha,F.D., Feizi,M., Shariat,M., Sublingual versus vaginal misoprostol for the management of missed abortion, Journal of Obstetrics and Gynaecology Research, 36, 525-532, 2010 **Ref Id** 78505 **Country/ies where the study was carried out** Iran **Study type** Randomised controlled trial **Aim of the study** To evaluate the efficacy of two routes of misoprostol administration (sublingual and	**Sample size** N=220 **Characteristics** **Age/years** Vaginal: 29.1 Sublingual: 28.5 (p=0.516) **Gestational age/weeks** Vaginal: 10.8 Sublingual: 10.6 (p=0.655) **Gravidity** Vaginal: 2.87 Sublingual: 2.85 (p=0.926) **Parity** Vaginal: 0.44 Sublingual: 0.23 (p=0.013) **Previous**	**Interventions** 400 micrograms of vaginal misoprostol every 6 hours (n=110) 400 micrograms of sublingual misoprostol every 6 hours (n=110)	**Details** Recruitment for this trial took place at Mirza Kochak Khan Hospital, a premier research and referral facility in Tehran. An ultrasound examination was performed on all women to confirm the diagnosis of first trimester silent miscarriage (see inclusion criteria). All eligible women were suitably randomised to one of two treatment regimens. Neither the clinician or the patient were blinded to treatment allocation. **Treatment protocols** Women received one of two treatment regimens: - 400 micrograms of vaginal misoprostol every 6 hours - 400 micrograms of sublingual misoprostol every 6 hours The research resident was responsible for administration of the vaginal misoprostol, placing the	**Results** **Complete evacuation (number/total (%))** Vaginal: 51/110 (46.4) Sublingual: 93/110 (84.5) RR (95% CI): 0.54 (0.442-0.681) (p<0.0001) **Need for further intervention (number/total (%))** Vaginal: 59/110 (53.6) (Note: 15 due to persistent gestational sac after 2 days; 44 due to incomplete miscarriage. Histology from 3 of the patients showed a partial mole) Sublingual: 17/110 (Note: 5 due to persistent gestational sac after 2 days; 12 due to incomplete miscarriage. Histology from 2 of the patients showed a partial mole and complete hydatiditiform mole) RR (95% CI): 3.471 (2.168-5.555) (p<0.0001)	**Limitations** **Dosage** The trial protocol does not state whether there was a maximum number of tablets that a woman could receive. The mean number of tablets was 4.45 in the vaginal group and 4.85 in the sublingual group (p=0.211). **Lack of blinding** Those assessing treatment outcome were not blinded to treatment allocation. **Misdiagnosis** 5 of the participants were later diagnosed as having a partial or complete mole (however, this represents only 2.3% of the study population) **Other information** EARLY FETAL/EMBRYONIC DEMISE VAGINAL vs. SUBLINGUAL

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
vaginal) for the treatment of missed miscarriage. **Study dates** January 2005 to February 2007 **Source of funding** Not reported	**miscarriage** Vaginal: 0.60 Sublingual: 0.71 (p=0.528) **Live children** Vaginal: 0.84 Sublingual: 0.96 (p=0.535) (Note: it is not reported what these statistics represent, although the technical team hypothesise that they represent means) **Inclusion criteria** Silent miscarriage, defined as: - intrauterine gestational sac with a mean sac diameter of at least 2 cm without a fetal pole - presence of a fetal pole with no cardiac activity - gestational sac < 2 cm with no interval growth, or persistent absence of fetal cardiac pulsation on rescanning 7-10 days		tablet into the posterior fornix. Women in the sublingual group were instructed to place the misoprostol tablet under their tongues themselves. They were not allowed any food or drink for the next 20 minutes to allow complete dissolution of the tablet. All women were admitted to the hospital, and a follow-up appointment was conducted at the hospital for 1-2 days later. Miscarriage status was determined at that point using ultrasound. If substantial debris (anteroposterior diameter > 15 mm on transvaginal scan) remained in the uterus, women were given a dilatation and curettage. **Outcomes reported** **1. Success rate:** Defined as the passage of products of conception without needing vacuum aspiration or dilatation and curettage. This was assessed at the follow-up appointment 1-2 days after treatment. **2. Need for further intervention:** The number	**Adverse effects of treatment (number of women/total (%))** **a. Vomiting** Vaginal: 13/110 (11.8) Sublingual: 22/110 (20) RR (95% CI): 0.591 (0.255-1.128) (p=0.140) **b. Diarrhoea** Vaginal: 40/110 (36.4) Sublingual: 76/110 (69.1) RR (95% CI): 0.526 (0.399-0.694) (p<0.0001) **c. Fever** Vaginal: 4/110 (3.6) Sublingual: 26/110 (23.6) RR (95% CI): 0.154 (0.056-0.426) (p<0.0001) **Measures of pain (number of women/total (%))** **a. Cramp pain** Vaginal: 62/110 (56.4) Sublingual: 94/110 (85.5) RR (95% CI): 0.660 (0.550-	COMPARISON **Time to expulsion/hours (mean)** Vaginal: 19.86 Sublingual: 9.53 (p=0.000)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	later < 13 weeks gestation No known contraindications to misoprostol General good health No vaginal bleeding **Exclusion criteria** Incomplete miscarriage Inevitable miscarriage (products of gestation bulging from the cervix) Suspicion of an extra-uterine pregnancy Drug or alcohol abuse as reported by the woman Abnormal blood count tests obtained routinely		of women requiring surgery, and reasons for the intervention are reported. **3. Adverse effects of treatment:** This is reported by the women for the period from 1 hour to 24 hours after every administration of misoprostol, up to the first follow-up visit. Fever is defined as an oral temperature of at least 37.8°C. **4. Measures of pain:** The incidence of cramping pain and severe pain are reported by the women for the period from 1 hour to 24 hours after every administration of misoprostol, up to the first follow-up visit. **5. Measures of satisfaction:** Assessed by questionnaire at follow-up **Analysis** Data were analysed using chi squared, t-tests, and risk ratios where appropriate. A p-value < 0.05 was considered significant.	0.791) (p<0.0001) **b. Severe pain** Vaginal: 42/110 (38.2) Sublingual: 77/110 (70) RR (95% CI): 0.859 (0.713-1.036) (p=0.091) **Measures of satisfaction (%)** **a. Reported being satisfied with treatment** Vaginal: 53.6 Sublingual: 93.6 (p=0.001) **b. Would recommend method to others** Vaginal: 53.6 Sublingual: 84.5 (p=0.004) (Note: satisfaction was also related to success of treatment)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wood,S.L., Brain,P.H., Medical management of missed abortion: a randomized clinical trial.[Erratum appears in Obstet Gynecol 2002 Jul;100(1):175 Note: Dosage error in published abstract; MEDLINE/PubMed abstract corrected], Obstetrics and Gynecology, 99, 563-566, 2002 **Ref Id** 78565 **Country/ies where the study was carried out** Canada **Study type** Randomised controlled trial **Aim of the study** To estimate the efficacy of vaginal misoprostol for medical management of missed miscarriage	**Sample size** N=50 **Characteristics** Age/years (mean (SD)) Misoprostol: 32 (5.0) Placebo: 33 (3.9) Gestational age/weeks (mean (SD)) Misoprostol: 11.4 (2.2) Placebo: 11.7 (2.7) Diameter of gestational sac/mm (mean (SD)) Misoprostol: 3.8 (1.6) Placebo: 3.6 (1.5) **Inclusion criteria** Ultrasound diagnosis of a non-viable pregnancy, defined as one of the following: - embryo greater than 7 mm with no embryonic cardiac activity - irregular gestational	**Interventions** 800 micrograms of misoprostol vaginally (repeat after 24 hours if needed) (n=25) Placebo (repeat after 24 hours if needed) (n=25)	**Details** Eligible women (see inclusion criteria) gave informed consent, and then were randomly allocated to receive either 800 micrograms of misoprostol vaginally or placebo. Randomisation was achieved using a computer generated random number list, and pharmacy staff placed either placebo or misoprostol into numbered envelopes. The investigators were not aware of the randomisation schedule. Because the tablets were not identical, additional precautions were taken to maintain allocation concealment. After the clinical assessment, the study nurse placed the pills in an opaque vaginal introducer, which the physician then used to insert the tablets. The women were provided with acetaminophen and combined acetaminophen/codeine tablets for analgesia. They were instructed to use one or two of these tablets every 4 hours as needed. Subjects were also asked to complete a patient	**Results** Complete miscarriage (number/total (%)) Misoprostol: 20/25 (80) Placebo: 4/25 (16) (p < 0.001) Need for a D&C (number/total (%)) Misoprostol: 7/25 (28) Placebo: 21/25 (84) (p < 0.001) Adverse effects: gastrointestinal side effects (number/total (%)) Misoprostol: 1/25 (4) Placebo: NR Satisfaction (number/total (%)) a. Agree/strongly agree that they would choose again Misoprostol: 19/21 (90.5) Placebo: NR b. Agree/strongly agree that they would recommend to a friend Misoprostol: 18/21 (85.7) Placebo: NR	**Limitations** 4/25 (16%) women did not return their questionnaires for the satisfaction outcomes. Adverse effects and satisfaction are only reported for one arm of the trial Small sample size (N=50) **Other information** 800 MICROGRAMS VAGINAL MISOPROSTOL VS. PLACEBO EARLY FETAL/EMBRYONIC DEMISE ONLY Blinding was done.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates February 1999 to April 2000 **Source of funding** Office of the Associate Dean of Research, Faculty of Medicine, University of Calgary	sac with mean sac diameter greater then 16 mm - gestational sac greater than 15 mm with no visible fetal pole Closed internal os **Exclusion criteria** Active vaginal bleeding (note: those with light spotting, without cramping, were eligible) Cramping Dilatation of the internal os Non-viable embryo that measured greater than a 12 week size		satisfaction questionnaire and a symptom log. An information sheet was provided with instructions to return to the hospital if heavy bleeding occurred. Heavy bleeding was defined as saturating more than one heavy pad every hour for more than two hours, or more than one heavy pad per 30 minutes for more than an hour. A container was provided for any products of conception that the subjects were able to retrieve. Baseline haemoglobin and hCG levels were obtained. The serum hCG was repeated at 48 hours and the haemoglobin at 1 week. <u>Follow-up</u> Follow-up was arranged at 24 hours, 48 hours, and at 1 week. Speculum and bimanual examinations were performed at each visit, and any tissue passed by subjects was examined. If complete miscarriage was not suspected after 24 hours, the medication was repeated. At 48 hours if there had been no response to the medication or an incomplete miscarriage was		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			suspected, the subjects were offered a D&C. Transvaginal ultrasound was used in cases of suspected incomplete miscarriage, as appropriate. An ultrasound finding of a focal hyperechoic intrauterine mass was considered sufficient for diagnosis of incomplete miscarriage. All subjects with a clinically suspected complete miscarriage were instructed to have a urine hCG test after 4 weeks. Pathology reports for all tissue submitted for examinations were reviewed. The subjects were also asked to complete a post-treatment questionnaire. <u>Outcomes reported</u> 1. Complete miscarriage: defined as either the expulsion of the products of conception without D&C with a negative follow-up urine hCG test at 4 weeks, OR the absence of products of conception in the surgical specimen from D&C in subjects who had suspected incomplete miscarriage		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			2. Need for further intervention: the rates of dilation and curettage are reported 3. Adverse effects: gastrointestinal side effects are reported in the misoprostol arm only 4. Satisfaction: Patient satisfaction was assessed by asking the women to rate their degree of agree with the following statements: - I would recommend the treatment with the vaginal tablets to a friend or family member who had a missed miscarriage - I would try treatment with the vaginal tablets again if I had another missed miscarriage. The subjects indicated their agreement on a five-point scale: strongly disagree, disagree, neutral, agree or strongly agree		
Full citation Ayudhaya,O.P.N., Herabutya,Y., Chanrachakul,B., Ayuthaya,N.I.N., Prasertsawat,P., A comparison of the efficacy of sublingual	**Sample size** N=138 (however 2 participants were later excluded)	**Interventions** 400 micrograms of misoprostol orally every 4 hours, up to a maximum of 6 doses (n=68) 400 micrograms of	**Details** 138 women with a diagnosis of early pregnancy failure who presented to the Department of Obstetrics and Gynaecology at Ramathibodi Hospital,	**Results** **<u>Clinical outcome of treatment (number/total (%))</u>** **<u>a. Complete miscarriage</u>** Oral: 17/66 (25.8) Sublingual: 15/70 (21.4)	**Limitations** **<u>Blinding</u>** Blinding is not reported. It would have been difficult to blind the participants (although not impossible); however those assessing the outcome of the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and oral misoprostol 400 microgram in the management of early pregnancy failure: A randomized controlled trial, Journal of the Medical Association of Thailand, 89, S5-S10, 2006 **Ref Id** 78585 **Country/ies where the study was carried out** Thailand **Study type** Randomised controlled trial **Aim of the study** To compare repeated doses of sublingual with oral misoprostol in the medical management of early pregnancy failure. **Study dates** November 2004 to December 2005	**Characteristics** **Age/years (mean (SD))** Oral: 32.0 (5.8) Sublingual: 33.4 (6.2) (NS) **Gestational age/weeks (mean (SD))** Oral: 10.7 (1.5) Sublingual: 11.0 (1.4) (NS) **Nulliparous (number/total (%))** Oral: 31/68 (45.6) Sublingual: 27/70 (38.6) (NS) **Inclusion criteria** Diagnosis of early pregnancy failure, defined as one of the following: - Intrauterine gestational sac with mean sac diameter of >2 cm without a fetal pole (blighted ovum) - Presence of a fetal pole without cardiac	misoprostol sublingually every 4 hours, up to a maximum of 6 doses (n=70)	Bangkok, were recruited. An ultrasound examination was performed in all cases to confirm the diagnosis. Women were randomised using computer generated random numbers. However, 2 women from the oral group were excluded for having an incomplete medical record. **Treatment protocol** Women received one of two treatments: - 400 micrograms of misoprostol orally every 4 hours, up to a maximum of 6 doses - 400 micrograms of misoprostol sublingually every 4 hours, up to a maximum of 6 doses Women in the sublingual group had two tablets placed under the tongue by a nurse. They were not allowed to eat for 20 minutes, to allow complete dissolution. A nurse was also responsible for oral administration to the patients. Patients were allowed 30 ml of water to drink, then misoprostol was given the same way every 4 hours until products of	(NS) **b.Incomplete miscarriage** Oral: 23/66 (34.8) Sublingual: 27/70 (38.6) (NS) **c. Medical failure** Oral: 26/66 (39.4) Sublingual: 28/70 (40.0) (NS) **Adverse effects of treatment (number of women/total (%))** **a. Nausea/vomiting** Oral: 3/66 (4.5) Sublingual: 2/70 (2.9) **b. Diarrhoea** Oral: 7/66 (10.6) Sublingual: 6/70 (8.6) **c. Fever** Oral: 2/66 (3.0) Sublingual: 15/70 (21.4) **d. Chills** Oral: 0/66 (0)	treatment could have been blinded to allocation. **Other information** EARLY EMBRYONIC/FETAL DEMISE ORAL vs. SUBLINGUAL **Induction to expulsion interval/hours (mean (SD))** Oral: 10.7 (6.6) Sublingual: 8.7 (5.4) **Total dosage received/micrograms (mean (SD))** Oral: 1706 (90.1) Sublingual: 1640 (83.0) (NS)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	pulsations - Gestational sac diameter <2cm with no interval growth or a persistent absence of fetal cardiac pulsation on re-scanning after 7-10 days Gestational age of 7-12 weeks **Exclusion criteria** Abnormal vaginal bleeding Severe abdominal pain		conception were detected. The blood pressure, pulse rate, and body temperature were recorded every 4 hours. Adverse effects including abdominal pain, diarrhoea, nausea, vomiting, chills and headache were recorded. If patients complained of severe pain, they were given two oral tablets of 500mg paracetamol. Parenteral pethidine was given if the pain persisted. If body temperature was > 38ºC, two tablets were also provided every 4 hours. If patients passed products of conception or experienced vaginal bleeding, they were told to inform the nurses who could then notify the attending doctor. The doctor determined if the miscarriage was complete by performing a vaginal examination. Complete miscarriage was defined as no active bleeding, closed cervical os and endometrial thickness < 1 cm. Incomplete miscarriage was defined as active vaginal bleeding or open cervical os and endometrial thickness >	Sublingual: 4/70 (5.7) (Note: these % have been calculated by the technical team and differ slightly from those reported in the paper, because the authors calculated % using 68 women in the oral arm, despite reporting excluding them, and excluding them for other outcomes. The authors also report that no serious complications occurred in either group.) **Measures of pain: abdominal pain (number of women/total (%))** Oral: 40/66 (60.6) Sublingual: 47/70 (67.1)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			1 cm. Those with incomplete miscarriage underwent emergency surgical evacuation under local anaesthesia. Medical failure was defined as the patients who received 6 doses and did not pass products of conception. These patients were scheduled for surgical evacuation the following morning. The products of conception were sent for histological diagnosis. All patients had a follow-up appointment two weeks after discharge. **Outcomes reported** **1. Clinical outcomes:** Complete miscarriage, incomplete miscarriage, and medical failure within 24 hours. **2. Adverse effects:** Nausea or vomiting, diarrhoea, fever and chills are reported. **3. Abdominal pain**		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Lister,M.S., Shaffer,L.E., Bell,J.G., Lutter,K.Q., Moorma,K.H., Randomized, double-blind, placebo-controlled trial of vaginal misoprostol for management of early pregnancy failures, American Journal of Obstetrics and Gynecology, 193, 1338-1343, 2005 **Ref Id** 78608 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To determine whether misoprostol medical management of early pregnancy failures is more effective than	**Sample size** N=36 **Characteristics** Age/years (mean) Misoprostol: 33.7 Placebo: 34.4 (p=0.706) Gestational age/weeks (mean) Misoprostol: 8.7 Placebo: 9.5 (p=0.079) Ultrasound criteria (n (%)) a. Embryonic pole/no cardiac activity Misoprostol: 12 (66.7) Placebo: 6 (37.5) b. Irregular intrauterine gestational sac/no embryonic pole Misoprostol: 10 (55.6) Placebo: 10 (62.5) c. Abnormal growth on ultrasound	**Interventions** 800 micrograms of vaginal misoprostol (repeat after 24 hours if needed) (n=19) Placebo (repeat after 24 hours if needed) (n=17)	**Details** Women presenting to the Riverside Methodist Hospital in Columbus, Ohio, with early pregnancy failure were eligible if they met the inclusion criteria. Patients provided informed consent and enrolled within 14 days after diagnosis. Randomisation was blocked and stratified by physician office and timing of treatment in relation to diagnosis. The study epidemiologist generated the allocation sequence. It was anticipated that some patients would need time to accept their diagnosis and consider participation in the study. Patients who enrolled some time after diagnosis might have uterine environments more favourable to medical expulsion of contents. The diagnosis date was defined as the date that the management options were first reviewed with patient. Of the 36 women enrolled, 1 was removed by her physician on day 2 without completing the protocol, and 1 was excluded for failure to meet the early pregnancy failure criteria.	**Results** Treatment success (number/total (%)) Misoprostol: 15/19 (78.9) Placebo: 2/17 (11.8) Need for further intervention (number/total (%)) Misoprostol: 3/18 (16.7) (Note: 1 patient was re-treated with misoprostol and had complete expulsion at 32 days; 2 patients had D&Cs at 9 and 19 days after treatment) Placebo: 13/16 (81.1) (Note: 11 elected to receive misoprostol and 2 had a D&C. A further 1 patient had expectant management, but this has not been reported here) Unplanned visit to medical facility (number/total (%)) Misoprostol: 0/18 Placebo: 3/16 (18.8) (Note: 1 patient was seen for vaginal bleeding after 4 days and had products removed from the cervical os, and was given Methergine; 1 patient was seen for pain requiring IV analgesics after expulsion of uterine	**Limitations** Following randomisation, 2 women withdrew (1 from each arm). 1 did not complete the protocol and 1 did not meet the criteria for early pregnancy failure. The technical team have included them in the denominator for the outcome of treatment success only, in order that the estimate is as conservative as possible. For the outcomes of pain severity 2/18 (11.1%) of women from the misoprostol arm have missing data. For the outcome of satisfaction, 1/16 (6.3) women from the placebo arm and 3/18 (16.7%) from the misoprostol arm had no data available. Small sample size (N=36) **Other information** 800 MICROGRAMS VAGINAL MISOPROSTOL VS. PLACEBO EARLY EMBRYONIC/FETAL DEMISE Blinding was done. Women who failed to pass their uterine contents after 48 hours were offered expectant management, D&C or misoprostol treatment. 71% chose misoprostol treatment. This may have impacted secondary outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
expectant management **Study dates** February 15th 2002 to March 19th 2003 **Source of funding** Riverside Methodist Hospital Medical Research Foundation	Misoprostol: 4 (22.2) Placebo: 3 (18.8) d. Yolk sac/abnormal rise in hCG Misoprostol: 1 (5.6) Placebo: 1 (6.3) **Inclusion criteria** Women presenting with early pregnancy failure, with the diagnosis confirmed by transvaginal ultrasound, using one of the following parameters: - embryonic pole 5-16 mm without cardiac activity - irregular gestational sac with mean sac diameter of 16-50 mm with no embryonic pole - embryo growth of less than 0.6 mm per day over 1 week - yolk sac present with hCG increasing less than 50% over 48 hours Closed cervical os on bimanual examination		Therefore, the main analysis involved 34 patients, of which 16 received placebo and 18 received misoprostol. Treatment protocol Each physician received an opaque randomisation packet containing instruction sheets (physician and patient), data sheets, prescriptions for pain medication, and 2 vials of unmarked hard gelatin capsules containing either placebo, or 800 micrograms of misoprostol. The physician placed the contents of 1 vial into the posterior fornix and secured them with a cotton ball or tampon. Both the physician and the patient were blinded to treatment allocation. Patients then had their blood drawn for progesterone, haemoglobin, hCG, type and screen. Patients received information sheets on misoprostol and the expected side effects. The instruction sheet contained 24 hour contact information. They also received prescriptions for eight 600 mg ibuprofen tablets and 12	products at home 5 days after placebo; 1 patient elected to receive misoprostol after placebo failure and came to the emergency department with heavy bleeding, after which products were removed and she received Methergine) Adverse effects of treatment (number/total (%)) a. Nausea Misoprostol: 4/18 (22.2) Placebo: 3/16 (18.8) b. Vomiting Misoprostol: 1/18 (5.6) Placebo: 3/16 (18.8) c. Diarrhoea Misoprostol: 1/18 (5.6) Placebo: 1/16 (6.3) d. Headache Misoprostol: 3/18 (16.7) Placebo: 2/16 (12.5) e. Dyspepsia Misoprostol: 2/18 (11.1) Placebo: 2/16 (12.5) f. Constipation	of pain and satisfaction. The trial was stopped early because the success rate in the placebo arm was lower than expected. The authors report that the study continued as an open-label registry of patients treated with misoprostol for early pregnancy failure.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Haemoglobin of at least 10 mg/dL **Exclusion criteria** History of inflammatory bowel disease Allergy to misoprostol Vaginal bleeding greater than spotting (defined as requiring less than one sanitary napkin per day) Dilated cervical os Viable first trimester pregnancy or ectopic pregnancy Previous incision on the contractile portion of the uterus (myomectomy or classical caesarean section)		Percocet tablets. A study nurse contacted each patient within the first 24 hours of treatment to check on her progress. Follow-up On day 2, approximately 24 hours after initial administration, patients returned for a repeat ultrasound and recording of side effects within the past 24 hours. If no gestational sac was seen, the patients were instructed to abstain from intercourse and return in 2 weeks. If the ultrasound showed persistence of the gestational sac at 24 hours, the patients received a second blinded dose in the posterior vaginal fornix. These patients returned on day 3, approximately 48 hours after initial treatment. At that time, data was collected on side effects experienced by the patients in the last 24 hours and another ultrasound was performed. If the gestational sac was absent, then the patient was asked to return in 2 weeks. If the gestational sac was still present, the patient was considered a treatment failure. Remaining blinded,	Misoprostol: 1/18 (5.6) Placebo: 1/16 (6.3) Measures of pain a. Incidence of menstrual cramping (number/total (%)) Misoprostol: 11/18 (61.1) Placebo: 5/16 (31.3) b. Incidence of abdominal cramping (number/total (%)) Misoprostol: 3/18 (16.7) Placebo: 1/16 (6.3) c. Highest level of pain during study (mean/10) Misoprostol: 5.6 (n=16) Placebo: 5.2 (n=16) (p=0.806) Satisfaction (number/total (%)) a. Reported satisfaction Misoprostol: 14/15 (93.3) Placebo: 12/15 (80) b. Would choose this method again Misoprostol: 13/16 (81.3) Placebo: 13/16 (81.3) c. Would recommend to others	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			the patients and physicians together chose a course of further treatment: expectant management, D&C or misoprostol. These patients also returned to their physicians for a final study evaluation 2 weeks after uterine evacuation. At the final evaluation, the patient was asked to answer a questionnaire evaluating her satisfaction with the treatment, the likelihood that she would recommend it to others, type of pain medication used and the amount of pain that she experienced. if a woman was bleeding at the 2-week follow-up, a urine pregnancy test was performed. If it was positive, quantitative hCG was drawn and followed to normal. <u>Outcomes reported</u> 1. Successful medical treatment: Complete evacuation of uterine contents within 24 hours of administration of misoprostol or placebo 2. Need for further intervention: Reported as the number of women who required additional	Misoprostol: 16/16 (100) Placebo: 12/16 (75)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			misoprostol or a D&C~~ 3. Unplanned visit to a medical facility 4. Adverse effects: Reported at 24 or 48 hours after treatment 5. Pain: At the final evaluation appointment, patients were asked to view a scale of evenly spaced numbers from 0 to 10, and to circle the number that represented their maximum pain during the study. They also reported incidence of menstrual cramping and abdominal cramping. 6. Satisfaction: Patients were asked at follow-up if they were satisfied with their treatment. <u>Analysis</u> The study design established an accrual goal of 84 women to provide 90% power to detect an expected 35% difference in success rates between study groups, assuming an anticipated success rate of 50% in the placebo group and 85% in the misoprostol group. The chosen alpha error was 0.05. Statistical		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			analysis used Fisher's exact test, Student's t-test, and the Wilcoxon rank sum test as appropriate. All tests were 2 sided and a p-value <0.05 was considered significant.		
Full citation Pang,M.W., Lee,T.S., Chung,T.K.H., Incomplete miscarriage: A randomized controlled trial comparing oral with vaginal misoprostol for medical evacuation, Human Reproduction, 16, 2283-2287, 2001 **Ref Id** 81209 **Country/ies where the study was carried out** Hong Kong **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy, side effects,	**Sample size** N=201 **Characteristics** **Age/years (mean (SD))** Vaginal: 32.4 (6.1) Oral: 32.3 (5.9) (NS) **Gestation/weeks (mean (SD))** Vaginal: 10.60 (2.3) Oral: 10.22 (2.0) (NS) **Admission haemoglobin (mean (SD))** Vaginal: 12.6 (1.1) Oral: 12.4 (1.4) (NS) **Cervical os open**	**Interventions** 800 micrograms vaginal misoprostol, with a repeat dose after 4 hours if needed (n=96) 800 micrograms oral misoprostol, with a repeat dose after 4 hours if needed (n=105)	**Details** All patients admitted to the gynaecology unit with a diagnosis of incomplete miscarriage were invited to participate. Diagnosis was confirmed using transvaginal ultrasound showing evidence of retained products of conception. Patients were suitably randomised using computer generated random numbers in blocks of five, and opaque envelopes. 201 patients were randomised. Two declined treatment following randomisation (one from each arm), and one patient from the oral arm developed a rash after the first misoprostol dose and further medical treatment was abandoned. 198 patients completed the medical treatment regime (95 in the vaginal arm and 103 in the oral arm). 12 were lost to follow up at 2	**Results** **Complete uterine evacuation (number of women/total (%))** Vaginal: 58/96 (60.4) Oral: 67/105 (63.8) (Note: These % were calculated by the technical team in order that the estimate of efficacy is conservative. The authors % differ slightly because they excluded 1 woman from each arm who declined treatment following randomisation, and 1 from the oral arm who developed a rash and therefore treatment was discontinued) **Need for further intervention (number of women/total (%))** Vaginal: 37/95 (38.9) Oral: 36/103 (35.0) (NS) (Note: 1 woman from the oral arm also required a repeat surgery after 2 weeks due to persistent vaginal bleeding and RPOC)	**Limitations** **Lack of blinding** Blinding was not reported. It would have been difficult (but not impossible) to blind participants or those administering treatment; however those assessing outcomes could have been blinded. **Population** Less than 15% of women in each arm had an open cervical os - it is unclear why this should be the case in a population of women with incomplete miscarriage. **Loss to follow-up** 12 patients were lost to follow-up at 2 weeks. 8 could not be contacted, but the other 4 were contacted by phone and reported being asymptomatic after discharge. 3 women were also excluded by the authors - 2 did not receive allocated intervention and 1 developed a rash so treatment was discontinued. For the outcome of treatment success, these women

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and short term complications associated with oral and vaginal administration of misoprostol as the initial management of incomplete miscarriage. **Study dates** September 1998 to March 1999 **Source of funding** Not reported	**(number/total (%))** Vaginal: 12/96 (12.5) Oral: 13/105 (12.4) (NS) **Prior termination of pregnancy (number/total (%))** **- 0** Vaginal: 73/96 (76.0) Oral: 64/105 (61.0) **- 1** Vaginal: 16/96 (16.7) Oral: 30/105 (28.6) **- 2** Vaginal: 3/96 (3.1) Oral: 11/105 (10.5) - **3+** Vaginal: 4/96 (4.2) Oral: 0/105 (0) (the incidence of subjects who had a past termination of pregnancy was higher in the oral arm, p<0.01) There were also no significant differences in parity, gravidity, number of previous miscarriages, or prior		weeks (6 from each arm). **Treatment protocol** Patients were randomised to receive either: - 800 micrograms oral misoprostol - 800µg micrograms misoprostol The dose was repeated after 4 hours if the patient had not passed any products of conception. A repeat transvaginal ultrasound was performed on all subjects the following day. Patients with an intrauterine dimension of <11cm^2 were considered to have an empty uterus and were discharged. The remainder underwent surgical evacuation. **Follow-up** All patients were assessed clinically 2 weeks after discharge to review their symptoms. A urinary pregnancy test was also performed. **Outcomes reported**	**Duration of bleeding/days (median (range))** Vaginal: 8 (0-14) (n=89) Oral: 8 (0-14) (n=97) (NS) **Adverse effects of treatment (number of women/total (%))** **a. Nausea** Vaginal: 7/95 (7.4) Oral: 12/103 (11.7) (NS) **b. Vomiting** Vaginal: 2/95 (2.1) Oral: 6/103 (5.8) (NS) **c. Diarrhoea** Vaginal: 12/95 (12.6) Oral: 62/103 (60.2) (p<0.01) **d. Fever** Vaginal: 11/95 (11.6) Oral: 6/103 (5.8) (NS) (Note: the authors also state that there were no surgical complications such as haemorrhage, uterine	have been included by the technical team in the denominator in order to ensure estimates of efficacy are conservative. **Other information** INCOMPLETE MISCARRIAGES (unclear why so few had open os) ORAL vs. VAGINAL **Interval between first dose and passage of POC/hours (mean (range))** Vaginal: 7.7 (2.5 - 30.8) Oral: 7.7 (2.0 - 35.3) (NS)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	ectopic pregnancy. **Inclusion criteria** Clinical diagnosis of incomplete miscarriage, supported by a urinary pregnancy test and confirmed by ultrasound evidence of RPOC **Exclusion criteria** Intrauterine dimension measuring <11cm^2 (considered to have an empty uterus) Severe blood loss Sepsis Known allergy to prostaglandins or their analogues History of asthma Any reason, in the opinion of the attending physician, that would make the patient unsuitable for misoprostol administration		**1. Complete uterine evacuation:** evaluated on day 1 after treatment **2. Need for further intervention:** The number of women who required a surgical evacuation before discharge. **3. Duration of bleeding:** assessed at 2 week follow-up appointment **4. Adverse effects:** Nausea, vomiting, diarrhoea and fever are reported as immediate side effects. Fever is defined as a temperature of at least 38ºC. **5. Pain:** The number of days of pelvic pain was assessed at the 2 week follow-up appointment **Analysis** Two sample t-tests, chi-squared tests and Mann Whitney tests were used to compare the two arms.	perforation, transfusion or infection in those undergoing surgery) **Measures of pain** **a. Duration of pelvic pain/days (median (range))** Vaginal: 2 (0 - 11) (n=89) Oral: 1 (0 - 14) (n=97) (p=0.02)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Blohm,F., Frid&#x00E9,n BE, Milsom,I., Platz-Christensen,J.J., Nielsen,S., A randomised double blind trial comparing misoprostol or placebo in the management of early miscarriage, BJOG: An International Journal of Obstetrics and Gynaecology, 112, 1090-1095, 2005 **Ref Id** 81264 **Country/ies where the study was carried out** Sweden **Study type** Randomised controlled trial **Aim of the study** To study if misoprostol 400 micrograms, administered vaginally, increased the successful resolution of early miscarriage	**Sample size** N=126 **Characteristics** Age/years (mean (SD)) Misoprostol: 32.1 (4.9) Placebo: 32.1 (6.0) Gestational age/days (mean (SD)) Misoprostol: 72.8 (12.2) Placebo: 77.8 (12.9) Previous miscarriage (%) Misoprostol: 18.8 Placebo: 21.0 Previous legal abortion (%) Misoprostol: 21.9 Placebo: 25.8 Duration of bleeding before recruitment/days (mean (SD)) Misoprostol: 26.6 (9.6) Placebo: 28.8 (10.1)	**Interventions** 400 micrograms of vaginal misoprostol (n=64) Placebo placed vaginally (n=62)	**Details** Women seeking medical attention due to signs of miscarriage in the first trimester, and who fulfilled the inclusion criteria, were invited to participate in the study. 136 women were eligible, of which 126 agreed to participate and were included and randomised. All patients underwent a gynaecological examination, including vaginal ultrasound, which involved measurement of the anterior-posterior diameter of the uterine cavity. Patients were randomised to either misoprostol or placebo by drawing a sealed envelope from a box. Each envelope contained either two placebo tablets or two 200 microgram misoprostol tablets, for self-administration intra-vaginally by the woman at home. 400 micrograms of misoprostol was chosen as this was the standard dose used in medical, legal abortions in their department, following administration of mifepristone. The placebo	**Results** Treatment success (number/total (%)) a. At follow-up (6-7 days) Misoprostol: 52/64 (81.3) Placebo: 32/62 (51.6) b. At completion of study, in the absence of a D&C Misoprostol: 56/64 (87.5) Placebo: 37/62 (59.7) Need for further intervention (number/total (%)) a. In women with an open cervical os Misoprostol: 0/7 (0) Placebo: 2/11 (18.2) b. In women with a closed cervical os Misoprostol: 8/57 (14.0) Placebo: 23/51 (45.1) c. In all women Misoprostol: 8/64 (12.5) Placebo: 25/62 (40.3) (Note: the other 9 women who had incomplete miscarriage at follow-up chose expectant	**Limitations** Maximum score for the visual analogue scale used to judge nausea, vomiting, diarrhoea and pain is not reported Outcomes (with the exception of "need for further intervention") are not reported separately for women with and without an open cervical os on inclusion. **Other information** 400 MICROGRAMS VAGINAL MISOPROSTOL VS. PLACEBO INCLUDES BOTH WOMEN WITH AN OPEN AND WOMEN WITH A CLOSED CERVICAL OS Treatment success, split by anterio-posterior diameter of gestational residue (number/total (%)) a. Misoprostol arm 15-21 mm: 21/26 (80.8) 22-50 mm: 35/38 (92.1) b. Placebo arm 15-21 mm: 11/20 (55) 22-50 mm: 25/42 (59.5) Treatment success was achieved more often in women with a uterine

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
compared with placebo **Study dates** **Source of funding** University of Goteborg Hjalmar Svensson Research Foundation	Open cervical os on inclusion (number/total (%)) Misoprostol: 7/64 (10.9) Placebo: 11/62 (17.7) **Inclusion criteria** Circulatory stable (stable blood pressure and haemoglobin > 90 g/L) Gestational residue 15 - 50 mm Non-viability of the conceptus confirmed and accepted by both the physician and patient Above the age of 18 years old **Exclusion criteria** Signs of genital infection (3 or more of the following criteria: purulent vaginal discharge, elevated body temperature > 38º C, pain on palpation of the uterus and/or		tablets were identical in appearance to the active misoprostol tablets, and were delivered to the independent hospital pharmacy where they were inserted into numbered envelopes in blocks of 10, according to a random table system. The randomisation list was retained by the pharmacy and was not broken until after completion of the study when statistical analyses were performed. Patients were enrolled by clinicians who were unaware of the randomisation sequence. Compliance of taking misoprostol or placebo tablets was checked at the return visit, and all patients reported that they had taken the medication as instructed. During the initial consultation, the patients underwent a vaginal ultrasound examination, physical examination and laboratory tests. The women were informed about expected pain and bleeding associated with miscarriage. Patients were provided with paracetamol alone or in combination with codeine for pain. Anti-D	management) Adverse effects a. Nausea: VAS/mm (mean (SD)) Misoprostol: 17.4 (24.7) Placebo: 14.9 (23.8) (p=0.57) b. Vomiting: VAS/mm (mean (SD)) Misoprostol: 8.1 (20.2) Placebo: 7.3 (21.7) (p=0.85) c. Diarrhoea: VAS/mm (mean (SD)) Misoprostol: 7.5 (15.0) Placebo: 8.9 (20.4) (p=0.69) d. Infection: incidence (number/total (%)) Misoprostol: 3/64 (4.7) Placebo: 0/62 (0) (Note: the patients were treated with antibiotics, and no further intervention was needed) Pain: severity using VAS (mean (SD)) Misoprostol: 60.4 (31.0) Placebo: 43.8 (37.1)	size of 22-50 mm, but this difference was not significant.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	adnexa, serum C-reactive protein > 10 mg/L) Not able to understand the information regarding the study Possible allergy or medical contraindications for analgesics or misoprostol		immunoglobulin was administered to all Rh-negative women. If the women had unacceptable pain or bleeding, they were instructed to return to the ward and a D&C was done. <u>Follow-up</u> All women were scheduled for a follow-up examination within one week (6-7 days) after the primary visit. The women were then divided into two groups: "successful" and "failed" treatment. If the anterior-posterior diameter for the gestational residue was < 15 mm, the patient was considered to have had successful treatment, provided a urine pregnancy test performed 4 weeks after the primary visit was negative. Women who had a gestational residue > 15 mm were considered to be treatment failures, and were given the option of further expectancy or a D&C. They were then followed until the pregnancy test was negative. All patients were asked to complete an anonymous, self-administered questionnaire, which	(p<0.007)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			included forced-choice questions relating to past obstetric history, general health, need for pain treatment, sick leave and duration of vaginal bleeding. Outcomes reported 1. Success treatment: success at 6-7 day follow-up, and success rate on completion of the study without a D&C are reported 2. Need for further intervention: the number of women requiring a D&C 3. Adverse effects: assessed using the questionnaire, collected at the last follow-up visit. Nausea, vomiting and diarrhoea were assessed using a visual analogue scale (maximum score not reported, likely to be 100). Incidence of infection is also reported. Women were judged to have an infection if three or more of the following criteria were observed within one month of the initial consultation: purulent vaginal discharge, elevated body temperature (> 38º C) for 24 hours, pain on palpation of uterus and/or adnexa, and C-		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			reactive protein > 10 mg/dL. 4. Pain: severity of pain was assessed using a visual analogue scale (maximum score not reported, likely to be 100) on the questionnaire, collected at the last follow-up visit <u>Analysis</u> A power calculation calculated that 60 women would be needed in each arm to achieve 80% power using an alpha value of 0.05. The results of the two groups were compared using students t test and Fishers exact test.		
Full citation Kovavisarach,E., Sathapanachai,U., Intravaginal 400 microg misoprostol for pregnancy termination in cases of blighted ovum: a randomised controlled trial, Australian and New Zealand Journal of Obstetrics and Gynaecology, 42, 161-163, 2002	**Sample size** N=54 **Characteristics** <u>Age/years (mean (SD))</u> Misoprostol: 26.2 (5.3) Placebo: 26.9 (5.1) (p=0.602) <u>Gestational age/weeks (mean (SD))</u>	**Interventions** 400 micrograms of vaginal misoprostol (n=27) Placebo (n=27)	**Details** After obtaining written informed consent, eligible women were randomly allocated to receive either two 200 microgram tablets of misoprostol or two tablets of a placebo. The administration time was recorded, and women were given a prescription for 20 tablets of acetaminophen. After treatment, women rested for 30 minutes and were then discharged from	**Results** <u>Outcome of medical treatment (number/total (%))</u> <u>a. Complete miscarriage</u> Misoprostol: 17/27 (63.0) Placebo: 5/27 (18.5) (P<0.001) <u>b. Incomplete miscarriage</u> Misoprostol: 8/27 (29.6) Placebo: 3/27 (11.1) (P<0.001)	**Limitations** <u>Randomisation</u> Method of randomisation not stated <u>Blinding</u> Blinding not reported <u>Method of administration</u> The method of drug administration (i.e. physician or self administered) is not reported. It is also not stated whether the placebo was

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 81292 **Country/ies where the study was carried out** Thailand **Study type** Randomised controlled trial **Aim of the study** To investigate the effectiveness and side effects of intravaginal misoprostol 400 micrograms compared with a placebo for facilitating complete miscarriage in cases of blighted ovum **Study dates** July 1st 1998 to January 31st 1999 **Source of funding** Not reported	Misoprostol: 10.6 (1.4) Placebo: 10.9 (1.2) (p=0.293) Previous miscarriage (n (%)) Misoprostol: 5 (18.5) Placebo: 2 (7.4) Previous elective abortion (n (%)) Misoprostol: 3 (11.1) Placebo: 7 (25.9) **Inclusion criteria** Maximum gestational age of 12 weeks Blighted ovum Closed cervix **Exclusion criteria** Medical or obstetric complication Pelvic infection Allergy to misoprostol		the hospital. The patients were then reassessed about 24 hours later and a history of events following drug administration was obtained. Physical and vaginal examinations were performed. The patients were asked to return to the hospital before the appointment if they experienced: - severe pain that did not improve after taking acetaminophen - a moderate amount of bleeding - passage of products of conception through the introitus Follow-up Any patients who had retained products of conception per os, or exhibited heavy vaginal bleeding was sent for immediate curettage. All other patients were examined by vaginal ultrasound. If the gestational sac was absent, the patient was scheduled to return in one week for a follow-up evaluation. If the gestational sac or products of conception were	c. No miscarriage Misoprostol: 2/27 (7.4) Placebo: 19/27 (70.4) (p<0.001) Adverse effects (number/total 9%)) a. Nausea and/or vomiting Misoprostol: 2/27 (7.4) Placebo: 1/27 (3.7) (p=0.552) b. Diarrhoea Misoprostol: 2/27 (7.4) Placebo: 0/27 (0) (p=0.150) c. Fever Misoprostol: 4/27 (14.8) Placebo: 0/27 (0) (p<0.05) Pain: incidence of lower abdominal pain (number/total (%)) Misoprostol: 20/27 (74.1) Placebo: 6/27 (22.2) (p<0.001)	administered vaginally or orally. **Other information** 400 MICROGRAMS VAGINAL MISOPROSTOL VS. PLACEBO BLIGHTED OVUM ONLY Time interval from insertion to complete miscarriage/hours (mean (SD)) Misoprostol: 14.9 (6.9) Placebo: 21.8 (4.9) (p<0.001)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			still present, the patient was offered a uterine curettage and scheduled to return in one week for a follow-up evaluation. <u>Outcomes reported</u> 1. Complete miscarriage: uterine contents completely expelled within 24 hours of initial drug administration without uterine curettage 2. Adverse effects: nausea and/or vomiting, diarrhoea and fever are reported within 24 hours after drug administration 3. Pain: incidence of lower abdominal pain within 24 hours of drug administration <u>Analysis</u> Chi-squared test, Fisher's exact test and student's t-test were used to analyse data where appropriate. $p<0.05$ was considered statistically significant.		
Full citation Paritakul,P., Phupong,V., Comparative study between oral and sublingual 600 microg	**Sample size** N = 64 **Characteristics**	**Interventions** 600 micrograms of oral misoprostol (n = 32) 600 micrograms of	**Details** Following informed consent procedures, any eligible women were hospitalised and randomised into one of two treatment arms.	**Results** **<u>Treatment success (n/total (%))</u>** Oral: 28/32 (87.5) Sublingual: 27/32 (84.4)	**Limitations** **<u>Blinding</u>** There is no reported blinding. It would have been difficult to blind the participants, however the physicians

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
misoprostol for the treatment of incomplete abortion, Journal of Obstetrics and Gynaecology Research, 36, 978-983, 2010 **Ref Id** 154648 **Country/ies where the study was carried out** Thailand **Study type** Randomised controlled trial **Aim of the study** To evaluate and compare the effectiveness, side effects and patient acceptability of oral and sublingual misoprostol for the treatment of incomplete miscarriage **Study dates** July 2007 to August	**Age/years (mean±SD)** Oral: 32.2±7.4 Sublingual: 29.0±6.7 (p = 0.071) **Gestational age/weeks (mean±SD)** Oral: 10.4±1/8 Sublingual: 10.5±2.7 (p = 0.956) **Inclusion criteria** Less than 14 weeks gestation Incomplete miscarriage, diagnosed clinically: - history of vaginal bleeding in the current pregnnacy - pregnancy retained in the uterus - open cervical os with or without products present in the cervical canal Positive pregnancy test Evidence of retained products by transvaginal	sublingual misoprostol (n = 32)	Randomisation was performed using a random number table. The co-investigator generated the allocation sequence. When a woman met the study inclusion criteria study staff selected a sequentially number opaque envelope which then assigned women to the allocated treatment. **Treatment protocol** Women in both groups received a 600 microgram dose of misoprostol, in three tables of 200 each. Drug administration was done by a nurse. Women in the sublingual arm were instructed to keep the drug under their tongue for 15 - 20 minutes. In the oral group, they were swallowed whole with 50 ml of water. **Follow-up** Women were admitted to the hospital for 48 hours to monitor side effects and complications. They were counselled to report any passing of tissue and to complete a diary of side effects. At 48 hours after administration of misoprostol, a physical	**Need for unplanned intervention (n/total (%))** Oral: 2/32 (6.3) Sublingual: 5/32 (15.6) (Note: these were all from the treatment failures and were women who chose to have a curettage at 48 hours) **Adverse effects (n/total (%))** **a. Nausea** Oral: 7/32 (21.9) Sublingual: 8/32 (25.0) **b. Vomiting** Oral: 0/32 (0) Sublingual: 0/32 (0) **c. Diarrhoea** Oral: 5/32 (15.6) Sublingual: 9/32 (28.1) **d. Fever/chills** Oral: 9/32 (28.1) Sublingual: 14/32 (43.8) **Measures of pain** **a. Incidence of pain/cramps (n/total (%))**	assessing the treatment success and need for further intervention could have been blinded to treatment allocation. **Other information** ORAL vs. SUBLINGUAL INCOMPLETE MISCARRIAGE **Duration of miscarriage/hours (mean±SD)** Oral: 18.6±16.1 Sublingual: 21.1±17.1

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
2008 **Source of funding** None reported	ultrasound Good health **Exclusion criteria** Intrauterine diameter < 11 cm^2 in sagittal plus transverse plane Haemodynamically unstable Suspected septic abortion History of allergt to misoprostol Suspected ectopic pregnacny		exam and transvaginal ultrasound were done to evaluation if the miscarriage had completed. Complete miscarriage was confirmed by a history of passing tissue vaginally, combiend with the finding of an empty uterus. If the woman had a complete miscarriage, she was discharged and followed up at one week. If she still had an incomplete miscarriage at 48 hours, she could choose wheher to have an immediate surgical evacuation or to go home and wait 5 days. If a woman still did not have complete miscarriage on day 7, a surgical evacuation was indicated. **Analysis** A sample size calculation calculated that 32 women were needed in each arm. Analysis was done uising chi-square, Fisher-exact test and the independent t-test as appropriate. p<0.05 was considered significant. **Outcomes reported** 1. Success of medical treatment: complete	Oral: 8/32 (25.0) Sublingual: 10/32 (31.3) **b. Pain level/100 (mean±SD)** Oral: 22.2±15.0 Sublingual: 29.1±21.2 (p = 0.139) **Incidence of heavy bleeding (n/total (%))** Oral: 0 (0) Sublingual: 0 (0) **Measures of satisfaction (n/total (%))** **a. Reported being satisfied or very satisfied** Oral: 28/32 (87.5) Sublingual: 27/32 (84.4) **b. Would choose this method again** Oral: 30/32 (93.8) Sublingual: 29/32 (90.6) **c. Would recommend to a friend** Oral: 30/32 (93.8) Sublingual: 29/32 (90.6)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			miscarriage at 48 hours after misoprostol 2. Need for unplanned intervention: curettage required 3. Adverse effects: incidence of fever/chills, diarrhoea, nausea and vomiting are reported 4. Bleeding: heavy bleeding was defined as use of more than 2 sanitary pads per hour for two consecutive hours 5. Pain: incidence of pain/cramps is reported; severity is measured using a 100 mm visual analogue scale 6. Satisfcation: assessed using questionnaire		

What is the effectiveness of surgical management of miscarriage in an outpatient (office) setting compared with any other setting for improving women's clinical and psychological outcomes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Edwards,S., Tureck,R., Fredrick,M., Huang,X., Zhang,J., Barnhart,K., Patient acceptability of manual versus electric vacuum aspiration for early pregnancy loss, Journal of Women's Health, 16, 1429-1436, 2007 **Ref Id** 65225 **Country/ies where the study was carried out** USA **Study type** Observational comparative study (secondary analysis of data collected during a randomised multi centre trial) **Aim of the study** To compare the safety, efficacy, post procedure quality of life, and acceptability of manual vacuum aspiration (MVA) performed as an outpatient with electric	**Sample size** Total n = 157 EVA n = 68 MVA n = 89 **Characteristics** No significant differences were observed between the two groups in maternal age, marital status, education and weight. Women in EVA group were less likely to be non Hispanic white and more likely to be Hispanic and non Hispanic black, Asian or others (p<0.01). Women in EVA group (all except one) were treated in University of Miami and University of Pennsylvania clinical centres. Women in MVA group had their treatment in clinical centres of Columbia University and University of Pittsburgh (the differences between two centres not reported) Women in office setting group had lower mean uterine size (wk) compared with women in operating room group (7.3 weeks [SD 1.0] vs. 8.1 weeks	**Interventions** Electric vacuum aspiration Manual vacuum aspiration	**Details** This study is a subgroup analysis of a large RCT comparing vaginal misoprostol with vacuum aspiration. Out of 652 women with first trimester pregnancy failure, n= 157 women underwent either an EVA (n = 68) or MVA (n = 89) Data were extracted comparing the safety, efficacy, and acceptability of MVA in an office setting with local anaesthesia with EVA in an operating room environment with spinal or general anaesthesia or monitored anaesthesia care (MAC). **Analgesia:** EVA : Performed under either general anaesthesia, MAC, or spinal anaesthesia MVA : analgesia was provided with a paracervical block using 10 -20 ml of lidocaine. **Post procedure** Post procedure symptoms were	**Results** **Safety and side effects of surgical treatment of early pregnancy failure** Haemorrhage requiring hospitalisation with or without blood transfusion EVA n = 1/88 (1.1%) MVA n = 0/67 (0.0%) *p = 0.38 Hospitalisation for endometritis EVA n = 0 MVA n = 0 *p = NA Fever (temperature ≥ 8.0°C) EVA n = 4/83 (4.8%) MVA n = 1/63 (1.6%) *p = 0.29 Emergency hospital visit on the same day of treatment EVA n = 4/88 (4.6%) MVA n = 3/67 (4.5%) *p = 0.98 Change in haemoglobin between day 1 and day 15, g/dL, mean ± SD EVA: -0.18 ± 0.96 (n = 74)	**Limitations** Women in office setting group had lower mean uterine size (wk) compared with women in operating room group Allocation to MVA or EVA group was based on clinic attended thus associated aspects of procedure will have altered systematically depending on local protocols **Other information** Fetal demise was defined as lack of cardiac activity at a crown-rump length (CRL) between 5 and 40 mm. Criteria for non viable pregnancy included a gestational sac with a mean diameter between 16 and 45 mm without an embryo or an abnormal rise in hCG level of ≤ 15 mm over 2 days with the yolk sac present. Success on day 30: on day 30 women's symptoms and determining final outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
vacuum aspiration (EVA) performed in an in-patient hospital setting in women experiencing a first-trimester miscarriage **Study dates** March 2002 to March 2004 at four university medical centres **Source of funding** Funded with federal funds from the National Institute of Child Health and Human Development, National Institute of Health, Bethesda, Maryland	[SD 1.5] p < 0.01) **Inclusion criteria** Women with first trimester pregnancy failure (non viable pregnancy, incomplete and inevitable spontaneous miscarriage) who were willing to comply with study protocol and follow up scheduled visit and who had access to telephone. **Exclusion criteria** Known or suspected ectopic pregnancy, hemoglobin < 9.5 mg/dL, known bleeding disorders or use of anticoagulants, thermodynamic instability, or known or suspected intravenous malformation		assessed by a telephone interview on day 8. The severity of symptoms were determined using a numerical questionnaire that addressed the presence or absence of fever or chills, passage of tissue, abdominal or pelvic pain, vaginal bleeding, medication, emergency hospital visits and tiredness. **Pain** The intensity of pain was determined using a 10 cm visual analogue scale (VAS) was completed within 48 hours after the procedure. **Quality of life** For the assessment of quality of life the SF-36R Health survey was used. The tool measured eight parameters: Physical functioning, bodily pain, role limitation due to physical health problems, general health perception, social functioning, vitality, mental health, and role limitation due to emotional problems. **Depression** Depression was assessed using Depression Happiness Scale (a self report questionnaire containing 25 items measuring aspect of happiness and	MVA: -0.14 ± 0.77 (n = 57) *p = 0.80 Decrease in haemoglobin ≥ 2 g/Dal EVA n = 4/74 (5.4%) MVA n = 1/57 (1.8%) *p = 0.28 **Women's symptoms Bleeding: EVA n = 72/80 (90%) MVA n = 100/100 (100%) *p = 0.01 Chills: EVA n = 30/79 (38.0%) MVA n = 28/62 (45.2%) *p = 0.36 Headache: EVA n = 30/80 (37.5%) MVA n = 28/62 (45.2%) *p = 0.58 Light headed: EVA n = 28/80 (35%) MVA n = 19/62 (30.7%) *p = 0.58 Fainted: EVA n = 2/79 (2.5%) MVA n = 0/62 (0%) *p =0.21 Tired: EVA n = 61/80 (76.3%) MVA n = 52/62 (83.9%)	were assessed via telephone call. Successful management was defined as no need for a second surgical procedure to complete the miscarriage within 30 days of first procedure.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			unhappiness). **Stress** Stress was assessed with stress sub scale of the Depression Anxiety Stress Scales (DASS). **Treatment acceptability** Treatment acceptability was assessed by questioning women as to whether or not they would choose same treatment if they had an early pregnancy loss in the future.	*p = 0.26 Nausea: EVA n = 24/80 (30%) MVA n = 19/62 (30.7%) *p = 0.93 Vomiting: EVA n = 6/80 (7.5%) MVA n = 4/62 (6.5%) *p = 0.81 Tissue passed: EVA n = 14/79 (17.7%) MVA n = 16/59 (27.1%) *p = 0.19 Diarrhoea: EVA n = 9/80 (11.3%) MVA n = 5/62 (8.1%) *p = 0.53 Abdominal pain: EVA n = 73/79 (92.4%) MVA n = 61/62 (98.4%) *p = 0.10 Pain severity score, mean ± SD EVA: 2.8 ± 2.4 (n = 79) MVA: 3.7 ± 2.3 (n = 62) *p = 0.03 *Chi square test (or Fisher exact test) and Student's t-test were used for categorical and continuous	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				variables, respectively. **Symptoms reported in participant's diary within 48 hours after treatment **<u>Efficacy of the treatment according to various scenarios</u>** <u>Success by day 30:</u> EVA n = 81/83 (97.6%) MVA n = 59/62 (95.2%) *p = 0.43 Assuming that loss to follow-up was a success: EVA n = 86/88 (97.7%) MVA n = 64/67 (95.5%) *p = 0.44 Assuming that loss to follow up was a failure: EVA n = 81/88 (92.1%) MVA n = 59/67 (88.1%) *p = 0.41 <u>Success in embryonic/fetal demise (unknown was treated as missing)</u> EVA n = 54/55 (98.2%) MVA n = 31/32 (96.9%) *p = 0.70 <u>Success in an anembryonic gestation (unknown was treated as missing)</u> EVA n = 24/25 (96.0%) MVA n = 24/25 (96.0%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				*p = 1.0 <u>Success in incomplete or inevitable miscarriage</u> EVA n = 3/3 (100.0%) MVA n = 4/5 (80.0%) *p = 0.63 *Chi square test (or Fisher exact test) and Student's t-test were used for categorical and continuous variables, respectively. **Quality of life*** <u>Cut down on work or other activities (EVA vs. MVA)**</u> OR: 2.8 (95% CI 1.4 to 5.8) p <0.01 <u>Accomplished less than you would like OR (EVA vs. MVA)**</u> OR: 2.6 (95% CI 1.2 to 5.3) p = 0.01 <u>Missed school or work (yes) OR (EVA vs. MVA)</u> OR: 3.2 (95% CI 1.5 to 6.5) p < 0.01 <u>Need help from friend and family (yes) (EVA vs. MVA)</u> OR: 3.9 (95% CI 1.9 to 8.1) p < 0.01	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				*Adjusted for race, vaginal bleeding, uterine size, presence of fetal pole, CRL, and gestational sac size **Ordinal response variable was used in logistic regression model. The original data was ordered from all time to none of the time **Acceptability** Recommend this procedure again: probably or absolutely EVA n = 73/84 (86.9%) MVA n = 49/63 (77.8%) *p = 0.08 Use this treatment again: probably or absolutely EVA n = 65/84 (77.4%) MVA n = 44/63 (69.8%) *p = 0.56 *Chi square test (or Fisher exact test) and Student's t-test were used for categorical and continuous variables, respectively.	
Full citation Dalton,V.K., Harris,L., Weisman,C.S., Guire,K., Castleman,L., Lebovic,D., Patient preferences, satisfaction, and resource use in office evacuation of early	**Sample size** The sample size was calculated to detect a 15% difference in overall satisfaction with a power of 90% with P = 0.05; this required enrolment of 54	**Interventions** MVA without sharp curettage in an office setting Electric suction with or without	**Details** Diagnosis of early pregnancy failure was confirmed by either a combination of ultrasound diagnosis and abnormally progressing β-hCG levels or by serial ultrasound examinations	**Results** **Women's satisfaction by treatment type** Total satisfaction score (median) Office: 19/20	**Limitations** Operating room group had larger mean uterine size (p = 0.03) Uneven sample size in two arms (50 vs. 115)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pregnancy failure, Obstetrics and Gynecology, 108, 103-110, 2006 **Ref Id** 69336 **Country/ies where the study was carried out** 2004 **Study type** Prospective observational study **Aim of the study** To examine women's treatment preferences and satisfaction with an office-based procedure for early pregnancy failure and to compare resource use and cost between office and operating room management of early pregnancy failure **Study dates** From July 2002 until July 2004 **Source of funding** Two study investigators received funding	women into each group. Total n = 165 women n = 115 women in the office group n = 50 women in the operating room group **Characteristics** No difference was observed between the groups regarding the type of provider, although women with obstetrician-gynaecologists appeared to be more likely to have their procedure in the operating room than those with other provider types, and this difference was statistically significance (P = .05) No difference was observed between the groups regarding race, education, mean age, parity, previous pregnancy failures, previous D&Cs, preoperative hematocrit. Women in office setting group had lower mean uterine size (wk) compared with women in operating room group (8.18 weeks vs. 8.86 weeks p =	sharp curettage in an operating room	alone. Gestational age was estimated by using fetal pole and mean gestational sac diameter. These measurements were documented within 72 hours of the procedure Each study participant chose between an office or an operating room uterine evacuation after being counselled by her primary physician or midwife about both surgical options. Counselling was not formally standardised across physician or midwives, but hands-on training sessions were conducted, and each department was given written descriptions and preoperative checklists to aid in presenting the options to women. Women opting to have their uterine evacuations performed in the office were referred by their primary physicians or midwives to the obstetrics and gynaecology clinic, where one of two physicians either performed the procedure themselves or supervised house officers. Uterine evacuations were completed using MVA without sharp curettage. Methylergonovine or oxytocin was administered for uterine atony as indicated. Uterine contents were examined for	Operating room: 20/20 p = 0.32 <u>Highly satisfied on total satisfaction (defined as a score of 18, 19 or 20)</u> Office n = 81/110 (73%) Operating room n= 36/46 (78%) p = 0.55 <u>Maximum total satisfaction (maximum score given on both items)</u> Office n = 51/110 (46%) Operating room n = 26/46 (56%) p = 0.15 <u>Would choose the same procedure again</u> Office n = 93/110 (89%) Operating room n= 45/46 (98%) p = 0.11 <u>Would recommend same procedure to a friend</u> Office n= 94/110 (90%) Operating room n = 43/43* (100%) p = 0.02 * Only 43 were available for this question **Complication by treatment type**	**Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
from Ipas, a manufacturer of a manual vacuum aspirator. They have both received honoraria from Ipas for unrelated work in the past 3 years (2003 to 2006)	0.03). **Inclusion criteria** Women 18 years of age and older presenting to the University of Michigan Department of Obstetrics and Gynaecology for surgical management of a first-trimester early pregnancy failure **Exclusion criteria** Exclusion criteria were bleeding disorders, haemoglobin less than 8.0, severe cardiopulmonary disease, uncontrolled seizures, severe anxiety or inability to tolerate pelvic exams, molar pregnancies greater than 10 weeks, uncontrolled type 1 diabetes, and untreated mucopurulent cervicitis. Women with more than 12 weeks 6 days of gestation by ultrasound examination were not considered for enrolment. Women were also excluded if they were not offered both the office and operating room-based surgical options by their primary physicians or midwives.		completeness after the procedure and sent to pathology for confirmation. For women opting for the operating room, procedures were typically performed by the woman's primary gynaecologist. Uterine evacuations were completed by using electric suction with or without sharp curettage. Postoperatively, the uterine contents were grossly examined for products of conception and sent to pathology for microscopic confirmation. **Data Collection** Data were collected using a combination of self-administered questionnaires, observation, and chart review. Questionnaire items were developed using expert opinion, consensus, and adaptation of previously published questions. Pretesting was done in 3 office and 2 operating room patients, and subsequent changes were made to improve clarity. Participants completed a procedure self-administered questionnaire at the time of enrolment.	Any complication (post procedure infection, need for re-evacuation, blood loss, unplanned hospital admissions, emergency room visits within 2 weeks) Office n = 9 /115 (8%) Operating room n = 20/50 (40%) p < 0.01 Molar pregnancy confirmed by histology Office n = 14/115 (12%) Operating room n = 9/50 (18%) p = 0.22 Post procedure infection Office n = 2/115 (2%) Operating room n = 1/50 (2%) p = 0.99 Need for re-evacuation Office n = 4/115 (3%) Operating room n = 1/50 (2%) p = 0.68 Blood loss (mean ml ± SD) Office 70 ± 106 Operating room 311 ± 344 p < 0.001 Median blood loss (ml) Office n = 50 ml	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Treatment priorities Women's treatment priorities were measured using patient-reported level of importance (not important to extremely important) of a series of items, such as privacy and "I wanted to be asleep". Each woman was asked to rate her level of preference and expectations about pain during the procedure using a 10-point scale. Strong preference was defined as a score of 7 or higher. **Pain** Immediately before discharge, participants completed a second questionnaire addressing pain, bleeding, and satisfaction with care. Using a 10-point scale, each participant recorded the pain level she experienced during and after the procedure. **Satisfaction** Satisfaction was measured using two items: "How satisfied are you with the communication that occurred between you and your care providers during this experience?" and "Overall, how satisfied were you with your experience?" Responses were measured using a 10-point	Operating room 200 ml Received uterotonic agent Office n = 10/115 (9%) Operating room n = 11/50 (22%) p = 0.02 Unplanned hospital admissions Office n = 1/115 (<1%) Operating room n = 2/50 (4%) p = 0.22 Emergency room visits within 2 weeks Office n = 3/115 (3%) Operating room n = 3/50 (6%) p = 0.37	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			scale. A total satisfaction score was obtained by summing these two scores. Other items addressed the likelihood of selecting the same procedure again and recommending the procedure to a friend faced with a pregnancy loss. **Resource use** Resource use was estimated from patient time at the health care facility and procedure length expressed in minutes. **Analgesia:** MVA: Anaesthesia consisted of oral lorazepam (1 mg), ibuprofen (800 mg), and/or propoxyphene napsylate (100 mg/acetaminophen 650 mg), with paracervical block (10 mL of 1% lidocaine). EVA: Anaesthesia options included intravenous sedation, regional anaesthesia, or general anaesthesia according to the patient's request and/or the anaesthesiologist's recommendation. **Analysis** The mean cost and time spent between the two groups were compared by using unpaired *t* tests. Analysis of women's treatment preferences was done		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			by creating dichotomous variables from the scale and comparing the two groups with either Pearson χ^2 or Fisher exact test. Satisfaction was compared with Mann-Whitney *U* and Pearson χ^2 after creating a dichotomous variable. Differences between expected and experienced level of pain were compared by using Mann-Whitney *U*, and logistic regression was used to examine the relationship between satisfaction and the difference between the expected level of pain and the experienced level of pain. Statistical analysis was performed with SPSS 12.0.1 software.		
Full citation De Jonge,E.T., Pattinson,R.C., Makin,J.D., Venter,C.P., Is ward evacuation for uncomplicated incomplete abortion under systemic analgesia safe and effective? A randomised clinical trial, South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 84, 481-483, 1994 **Ref Id** 78046 **Country/ies where the study**	**Sample size** Total n = 142 n= 73 randomised to the ward group n = 68 randomised to the theatre group **Characteristics** **<u>Mean age</u>** Ward: 24 yr Theatre: 25 yr p = ns **<u>Hb (g/dl) (mean ± SD) on admission</u>** Ward: 10.8 ± 2.45	**Interventions** Evacuation under systemic analgesia in the office setting (ward) Evacuation under general anaesthesia in the theatre	**Details** Eligible women were randomised into two groups, those for evacuation under systemic analgesia and those for evacuation under general anaesthesia. Randomisation was done using numbered sealed opaque envelopes drawn by the clinician on the consecutive basis. Both groups were evaluated for delay between admission and evacuation; complication (anaesthetic and procedure related); acceptability, measured retrospectively by the level of fear and/or pain experienced by	**Results** <u>Blood transfusion (no. of women)</u> Ward: n = 13 Theatre: n = 24 p < 0.03 <u>Blood transfusion (no. of units)</u> Ward: n = 37 Theatre: n = 65 p < 0.03 <u>Time delay from admission to evacuation: median (range)</u> Ward: 7 h 15 min (15 min - 63 h)	**Limitations** Not clear if the assessors were blinded to the group allocation. Unclear allocation concealment Study was underpowered based on the power calculation. The power calculation estimated that a sample size of 91 women was needed to establish a difference of 50% in two groups in terms of blood transfusion. The study reported that the sample size of 182 could

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
was carried out South Africa **Study type** Prospective randomised clinical trial **Aim of the study** To compare evacuation under systemic analgesia (fentanyl and midazolam) in a treatment room (ward group) with evacuation under general anaesthesia in theatre (theatre group). **Study dates** From February to May 1992 **Source of funding** Supported by a grant from the H. E. Griffin Trust	Theatre: 10.4 ± 1.34 p = ns **Inclusion criteria** History of amenorrhoea followed by abdominal cramping and vaginal bleeding; uterine size ≤14 weeks of gestation, evaluated clinically before randomisation; dilated cervical os and palpable products of conception; no foul smelling products; temperature <37.5°C; no excessive vaginal bleeding requiring immediate surgical evacuation; haemoglobin concentration >90 g/l after resuscitation; and no contraindication to prostaglandin treatment. **Exclusion criteria** Not reported		the women (grading: 1- none; 2 - mild; 3 -moderate; 4 - severe; 5 - very severe) **<u>Ward evacuation analgesia</u>** Analgesia technique was: pre-oxygenation for at least 3 minutes with 6 - 7 litres oxygen delivered through a close - fitted mask; fentanyl 1.5 µg/kg given slowly intravenously up to a maximum of 100 µg, followed by midazolam administrated slowly intravenously and titrated against the consciousness level of the woman to a maximum of 15 mg. **<u>Analgesia in theatre</u>** The analgesia used for evacuation in theatre was: pre-oxygenation; thiopentone 3,0 - 5,0 mg/kg intravenously, succinyldicholine1,0 mg/kg intravenously; routine intubation because none of the women were starved; inhalation of oxygen and nitrous oxide (50/50) 70 ml/kg and halothane 0.5 - 1.0% with spontaneous respiration. **<u>Equipment</u>** All evacuations, both in the ward and in the theatre, were performed with a sharp curette by a trained house officer or	Theatre: 12 h 38 min (1h 5 min - 70 h 15 min) p < 0.0003 <u>Hb (g/dl) (mean ± SD) after evacuation</u> Ward: 10.8 ± 2.86 Theatre: 10.7 ± 1.34 p = ns <u>Acceptability (fear) n = 73</u> Level 1 (no fear): Ward n= 36 Theatre: n =36 Level 2 (mild fear): Ward n= 18 Theatre: n =11 Level 3 (moderate fear): Ward n= 14 Theatre: n = 12 Level 4 (severe fear): Ward n= 2 Theatre: n = 6 Level 5 (very severe fear): Ward n= 3 Theatre: n =3 <u>Theatre acceptability n = 73</u> Level 1 (no fear): Ward n= 54 Theatre: n = 65 Level 2 (mild fear): Ward n= 12 Theatre: n = 3 Level 3 (moderate fear): Ward n= 5 Theatre: n = 0 Level 4 (severe fear):	not be achieved because of hospital strikes and unrest. However, despite this a statistically significant difference was demonstrated. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			registrar **Analysis** Categorical data were compared using the Chi-squared test. Where data were not normally distributed, the Mann-Whitney U test was used. **Acceptability** Acceptability was evaluated by an observer not directly involved in the surgical procedure	Ward n= 1 Theatre: n = 0 Level 5 (very severe fear): Ward n= 1 Theatre: n = 0	
Full citation Blumenthal,P.D., Remsburg,R.E., A time and cost analysis of the management of incomplete abortion with manual vacuum aspiration, International Journal of Gynecology and Obstetrics, 45, 261-267, 1994 **Ref Id** 81146 **Country/ies where the study was carried out** USA **Study type** Quasi experimental before and after study	**Sample size** MVAC n = 17 SC n = 18 **Characteristics** No statistical significant differences were observed between the two groups in maternal age and parity. Women in MVAC group had lower gestational age compared with women in SC group (8 weeks [SD 2.2] vs. 10 weeks [SD 2.8] p < 0.01) **Inclusion criteria** Women in their first trimester of pregnancy with incomplete abortion	**Interventions** Manual vacuum aspiration curettage (MVAC) either in emergency room or in a labour room Traditional suction curettage (SC) in the operating room	**Details** Women were considered to have an incomplete abortion if they had a positive pregnancy test, abdominal cramping and /or bleeding and the evidence of an open cervical os, tissue in the cervical os or other clinical sign of inevitable abortion or abortion in progress. **SC procedure** Between January 1990 and July 1991, all cases were managed traditionally: The Emergency Room (ER) staff followed the usual routine in triaging and assessing women with suspected incomplete miscarriage. Once the women were triaged by ER staff, the gynaecologist saw the women, if the uterus were less than 12	**Results** Time comparison of manual vacuum aspiration (MVAC n = 17) and electric suction curettage (SC n = 18) Waiting time [time from emergency room admission to operation] (SD) MVAC: 3.45 h (2.0) SC: 7.18 h (4.9) p < 0.01 Procedure time [time required for the procedure] (SD) MVAC: 19 min (9.0) SC: 33 min (8.0) p < 0.01 Total hospital time [time from emergency room admission to discharge	**Limitations** Small sample size Statistically significant difference in gestational age between the two groups **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study *To examine the cost effectiveness of performing manual vacuum aspiration curettage (MVAC) either in emergency room or in a labour room on the labour corridor as an alternative to the traditional suction curettage (SC) in the operating room.* **Study dates** January 1990 to July 1992 **Source of funding** Funded by a grant from The Leonard Laufe Fund, 303E. Main St. P.O.Box 100, Carrboro, North Carolina 27510, USA.	**Exclusion criteria** Not reported		weeks size, women were prepared for SC. The SC was performed in the operating room as soon as the room was available Analgesia was administered by an anaesthetist in the operating room. Sedation was achieved with a combination of short acting benzodiazepines and narcotics. Dosage was dependant on the clinical judgement of the anaesthetist. Dosage given in operating room were generally higher than dosage given in ambulatory setting. There were no women for whom general anaesthesia was used. After the procedure, women were observed briefly in the recovery room then either discharged from the ambulatory surgical unit, or gynaecology floor. **MVAC** After July 1991, all cases were managed using MVAC in either the emergency room or the labour ward: Once the diagnosis was established, an MVAC procedure was performed in the gynaecology examination room of emergency department. If the MVAC could not be accomplished in emergency department, the women were	home] (SD) MVAC: 5.66 h (2.3) SC: 19.26 h (11.1) $p < 0.01$	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			taken to the labour ward corridor where the MVAC procedure was performed. All procedures were performed by resident house staff under supervision of attending physician who were familiar and practised in the use of MVAC equipment. Procedure was based on the standard outpatient protocol for anaesthesia in the emergency room (50 -150 µg fentanyl, 1-3 mg medazolam). After the completion of the procedure women were observed as an outpatient in a labour room or in the emergency room to ensure stable vital signs. Women were discharged home with a follow up appointment to the gynaecology clinic within 1 week. **Data collection** Data on hospital charges and times (e.g. waiting time, procedure time) were obtained for all cases of incomplete abortion presenting to hospital between January 1990 and July 1992. Between January 1990 and July 1991, all cases were managed traditionally. After July 1991, all cases were managed using MVAC in either the emergency room or the labour ward		

How effective is surgical management of tubal ectopic pregnancy compared with medical management for improving women's clinical and psychological outcomes?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Fernandez,H., Pauthier,S., Doumerc,S., Lelaidier,C., Olivennes,F., Ville,Y., Frydman,R., Ultrasound-guided injection of methotrexate versus laparoscopic salpingotomy in ectopic pregnancy, Fertility and Sterility, 63, 25-29, 1995 **Ref Id** 75248 **Country/ies where the study was carried out** France **Study type** Prospective randomised study **Aim of the study** To compare local injection of	**Sample size** n = 20 treated by laparoscopic linear salpingotomy n = 20 treated with MTX injection **Characteristics** No statistically significant differences were observed between the two groups in gestational age, parity, gravidity and age. Women in the two groups were similar in terms of smoking, infertility, appendectomy, past history of EP and /or tubal pregnancy, pelvic inflammatory disease, induction of ovulation and contraception failure **Inclusion criteria** All women with EP were evaluated according to a pre-treatment score (the score was based on six criteria graded from 1 to 3: gestational age, hCG level, progesterone level,	**Interventions** Group 1: treated with a single dose of MTX (local injection of 1 mg/kg into EP under vaginal sonographic control) Group 2: women were treated by laparoscopic salpingotomy	**Details** **Randomisation:** Included women were divided into two groups, using a random number table. **Methotrexate group** Group 1: treated with single dose of MTX. The procedure was performed without anaesthesia, under vaginal sonographic control. An 18 gauge needle was inserted into a needle introducer. Penetration and aspiration of the ectopic sac was followed by an injection of 1 mg/kg MTX into the sac. Women were treated on an outpatient basis unless they lived very far from hospital or when the procedure was performed after 4 p.m. (n = 10) **Laparoscopy:** Group 2: women were treated by laparoscopy using a triple-puncture technique with three 5 mm trocars and a 10 mm non operative laparoscope	**Results** **Success rate (return to hCG <10 mIU/mL)** Group 1 (methotrexate) (n = 20) n = 19/20 Group 2 (surgery) (n = 20) n = 19/20 **hCG levels preoperative (mIU/mL) mean ± SD** Group 1 (methotrexate) (n = 20) 4,948 ± 7682 (range 320 to 26,600) Group 2 (n = 20) 2,160 ± 1,756 (range 119 to 4,600) p < 0.05 **Resolution time (d) mean ± SD** Group 1(methotrexate) (n = 20) 28.8 ± 10.0 (range 13 to 47) Group 2 (n = 20) 13.6 ± 3.7 (range 8 to 18) p < 0.01 **Postoperative hospital stay (h) mean ± SD** Group 1 (methotrexate) (n = 20) 24 ± 6.2 Group 2 (n = 20) 46 ± 8.4 p < 0.05 **Tubal patency (HSG)** Group 1 (methotrexate)(n = 17)	**Limitations** No power calculation Unclear allocation concealment Initial hCG was higher in group 1 (p < 0.05) Follow up for fertility was too short **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
methotrexate (MTX) under sonographic control to laparoscopic salpingotomy for conservative management of ectopic pregnancy (EP) **Study dates** Between September 1992 and October 1993 **Source of funding** Not reported	abdominal pain, volume of the hemotosalpinx as assessed by ultrasound) Women with a score ≤ 13 were included in the trial. **Exclusion criteria** 30 women were excluded for the various reasons, e.g., no visualisation of EP, score > 13, suspicion of ruptured tubal pregnancies, liver or kidney disease and /or abnormal laboratory results with elevated liver enzymes or neutropenia that contraindicated MTX treatment.		connected to a video camera. A linear salpingotomy was performed on the surface of the antimesosalpinx proximal portion of the EP, and an aquapurator was used to flush the tube once the ectopic sac was removed. Women were hospitalised for 2 days as is usual in France, according to the French Health Service. **Follow up:** All women were followed up by telephone after each hCG control. All women were aware of the possibility of treatment failure (defined by the resistance of a high hCG levels and/or the onset of the abdominal pain) In cases of failure women were managed by laparoscopy or by additional injection of intramuscular MTX in group 2. **Treatment success:** Treatment success was defined as completed elimination of tubal pregnancy (serum hCG < 10 mIU/ml) **hCG level:** Human chorionic gonadotrophin levels were collected on days 2, 5 and 10 after the procedure and weekly until normalisation (10	n = 15/17 Group 2 (n = 18) n = 16/18 **Recurrent EP** Group 1 (methotrexate)(n = 20) n = 0/20 Group 2 (n = 20) n = 1/20 **Women desiring pregnancy with a follow up > 6 months** Group 1 (methotrexate)(n = 20) n = 10/20 Group 2 (n = 20) n = 10/20 **Hematosalpinx (mm) mean ± SD** Group 1 (methotrexate)(n = 20) 19.8 ± 9.9 (range 6 to 40) Group 2 (n = 20) 16 ± 7.2 (range 5 to 31) p = ns **Ongoing or a term pregnancy (follow up)** Group 1(methotrexate) (n = 10) n = 6/10 Group 2 (n = 10) n = 2/10	

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<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>mIU/mL). A liver function test was performed and red and white cell counts were obtained on day 10.

Hysterosalpingography (HSG) was performed in women 2 months after the return of the first menstrual period

<u>Analysis</u>
Parameters in the two groups were compared by Student's t-test and by the X^2 test.</td><td>Successful treatment rate
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>19</td><td>20</td></tr><tr><td>Methotrexate</td><td>19</td><td>20</td></tr></table>
Pregnancy rate
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>2</td><td>10</td></tr><tr><td>Methotrexate</td><td>6</td><td>10</td></tr></table>
Recurrent EP
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>1</td><td>20</td></tr><tr><td>Methotrexate</td><td>0</td><td>20</td></tr></table></td><td></td></tr>
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<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Resolution time
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Surgery</td><td>13.60</td><td>3.70</td><td>20</td></tr>
<tr><td>Methotrexate</td><td>28.80</td><td>10.00</td><td>20</td></tr>
</table>
Hospital stay
<table>
<tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr>
<tr><td>Surgery</td><td>46.00</td><td>8.40</td><td>20</td></tr>
<tr><td>Methotrexate</td><td>24.00</td><td>6.20</td><td>20</td></tr>
</table></td><td></td></tr>
<tr><td>Full citation

Fernandez,H., Yves Vincent,S.C., Pauthier,S., Audibert,F., Frydman,R., Randomized trial of conservative laparoscopic treatment and methotrexate administration in ectopic pregnancy and subsequent fertility, Human Reproduction, 13, 3239-3243, 1998</td><td>Sample size

Methotrexate n = 51 (local injection n = 29, Intramuscular (IM) injection n = 22)

Salpingotomy n = 49

Characteristics

No statistically significant differences were observed between the two groups in age, parity, gravidity, smoking, appendectomy, history of tubal surgery, history of PID, CT</td><td>Interventions

Group 1: treated with a single dose of MTX either 1 mg/kg injected transvaginally into the ectopic pregnancy without analgesia and under transvaginal sonographic control or IM injection for those whose sac could not be easily or safely punctured.

Group 2: women were</td><td>Details

<u>Randomisation:</u>

Included women were divided into two groups, using a random number table. For each next allocation of the treatment, the clinicians were blinded until women were recruited to the trial.

<u>Methotrexate group</u>

Group 1: treated with a single dose of MTX. The treatment</td><td>Results

Result have been reported earlier for 40 women (20 treated by local MTX under sonographic guidance and 20 by laparaoscopic salpingostomy) in the study of Fernandez 1995

<u>Success rate (return to hCG < 10 mIU/mL)</u>
Methotrexate n total = 51
Local Injection n = 27/29 (93.1%)
IM injection n = 18/22 (81.8%)
Salpingotomy n = 47/49 (95.9%)

<u>Postoperative stay (h)</u>
Methotrexate n = 51</td><td>Limitations

Under-powered study (needed n = 260 in each arm to determine a significant difference in success rate)
Not clear if the outcome assessors were blinded
More women in MTX group had a previous ectopic pregnancy (p <</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 75250 **Country/ies where the study was carried out** France **Study type** Prospective randomised study **Aim of the study** To compare local injection of methotrexate (MTX) to salpingotomy, with treatment success and fertility as the main outcome measure **Study dates** Between 1st September 1992 and 30th October 1995 **Source of funding** Not reported	serology > 1/64, induction of ovulation and contraception failure. Women in MTX group had higher history of ectopic pregnancy compared with women in surgery group ($p < 0.05$) Mean gestational age in MTX local (days): 47.9 ± 9.4, in MTX IM (days): 48 ± 11.1, Surgical (days): 48.06 ± 11.8 Pretreatment hCG in MTX local (IU/L): 3805 ± 5710, MTX IM (IU/L): 3120 ± 5280, surgical (IU/L): 2591 ± 3.269 **Inclusion criteria** All women with EP (visualised by transabdominal or transvaginal ultrasound) were evaluated according to pre-treatment score (the score was based on six criteria graded from 1 to 3; gestational age, hCG level, Progesterone level, abdominal pain, volume of the hemotosalpinx as assessed by ultrasound) Women with a score < 13 were included in the trial. No eligible woman chose not to participate. **Exclusion criteria** 132 women were excluded for	treated by laparoscopic salpingotomy.	started immediately after the diagnosis. The procedure was performed without anaesthesia, under vaginal sonographic control. An 18 gauge needle was inserted into a needle introducer. Penetration and aspiration of the ectopic sac was followed by an direct injection of 1 mg/kg MTX into the sac for 29 women and IM for the 22 women whose sac could not be safely or easily punctured. Women were treated on an outpatient basis unless they lived very far from hospital or when the procedure was performed after 4 p.m. (n = 21) **Laparoscopy** Group 2: women were treated by laparoscopy using a triple-puncture technique with three 5 mm trocars and a 10 mm non operative laparoscope that was introduced through the umbilicus and connected to a video camera. A linear salpingotomy was performed on the surface of the antimesosalpinx proximal portion of the EP, and a grasping forceps was used to flush the tube once the ectopic sac was removed. Women were hospitalised for	Local Injection 24 ± 8.7 IM injection 24 ± 1.2 Salpingotomy 46 ± 8.4 **Resolution time (day)** Methotrexate n = 51 Local Injection 28.6 ± 18.6 IM injection 29.9 ± 18.9 Salpingotomy 13.6 ± 6.1 (7-31) **Second injection of methotreaxte** Methotrexate total n = 51 Local Injection n = 4/29 IM injection n = 3/22 Salpingotomy n = 2/49 **First reproductive performance after EP (follow - up > 1 year n = 100)** Pregnancy not desired Methotrexate n = 51 n = 14 (27.4%) Salpingotomy n = 49 n = 12 (24.5%) Lost to follow up Methotrexate n = 51 n = 10 (7.4%) Salpingotomy n = 49 n = 12 (24.5%) Spontaneous ongoing or term pregnancy (excludes those who who did not desire a pregnancy) Methotrexate n = 51 n = 21 (56.7%) Salpingotomy n = 49 n = 15 (40.5%)	0.05) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	various reasons that included no visualisation of EP (n = 20), score ≥ 13, suspicion of ruptured tubal pregnancies (n = 58), liver or kidney disease and/or abnormal laboratory results with the elevated liver enzymes or neutropenia that contraindicated MTX treatment (n = 2).		2 days as is usual in France, according to the French Health Service. **Follow up:** All women were followed up by telephone after each hCG control. all women were aware of possibility of treatment failure (defined by the resistance of a high hCG levels and/or the onset of the abdominal pain) In the cases of the failure women in group 1 managed by laparoscopy or by additional injection of MTX women women were asymptomatic, and in group 2 by i.m. injection of MTX. **Treatment success:** Treatment success was defined as completed elimination of tubal pregnancy (serum hCG < 10 mIU/ml) Human chorionic gonadotrophin levels were collected on days 2, 5 and 10 after the procedure and weekly until normalisation (10 mIU/mL). A liver function test was performed and red and white cell counts were obtained on day 10. Hysterosalpingography (HSG) was performed in women 2 months after the return of the	Miscarriage (excludes those who who did not desire a pregnancy) Methotrexate n = 51 n = 1 (2.7%) Salpingotomy n = 49 n = 1 (2.7%) Recurrent EP (excludes those who who did not desire a pregnancy) Methotrexate n = 51 n = 1 (2.7%) Salpingotomy n = 49 n = 5 (13.5%) Ongoing or term pregnancy after IVF (excludes those who who did not desire a pregnancy) Methotrexate n = 51 n = 4 (10.8%) Salpingotomy n = 49 n = 2 (2.5%) Mean time to pregnancy (months) Methotrexate n = 51 n = 6.22 ± 3.34 Salpingotomy n = 49 n = 7.25 ± 6.34	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			first menstrual period **Analysis** Parameters in the two groups were compared by Student's t-test and by the X^2 test.		
Full citation Hajenius,P.J., Engelsbel,S., Mol,B.W., van,der,V, Ankum,W.M., Bossuyt,P.M., Hemrika,D.J., Lammes,F.B., Randomised trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy, Lancet, 350, 774-779, 1997 **Ref Id** 75306 **Country/ies where the study was carried out** Netherlands **Study type** Randomised trial **Aim of the study** To compare systemic	**Sample size** Total: n = 100 women Systemic methotrexate n = 51 Laparoscopic salpingostomy n = 49 **Characteristics** Mean (SD) age in years Methotrexate: 31.3 (5.9) Salpingostomy; 31.8 (4.4) Median (range) parity Methotrexate: 0 (0 - 5) Salpingostomy; 31.8 (4.4) Mean (SD) duration of gestation in days Methotrexate: 46.6 (18.5) Salpingostomy; 46.7 (10.7) Clinical symptoms: None Methotrexate: n = 5/51 Salpingostomy: n = 6/49 Abdominal pain only Methotrexate: n = 7/51	**Interventions** Systemic methotrexate (1mg/kg im MTX on days 0, 2, 4, 6 alternated folinic acid 0.1 mg/kg oral on days 1, 3, 5, 7) Laparoscopic salpingostomy	**Details** Study conducted in six Dutch hospitals: the Academic Medical Centre, the Onze Lieve Vrouwe Gasthuis, the University Hospital Free University in Amsterdam, and the University Hospitals of Groningen, Nijmegen, and Utrecht. Ectopic pregnancy was diagnosed on the basis of a non-invasive strategy combining transvaginal sonography and measurement of serum human chorionic gonadotropin (HCG). **Systemic methotrexate** In women allocated to systemic methotrexate, treatment was started immediately after laparoscopy and completed on an outpatient basis. One full therapeutic course consisted of four doses of methotrexate given intramuscularly (1.0 mg/kg, on days 0, 2, 4, 6;	**Results** **Primary treatment success** Methotrexate 42/51 (82%) Salpingostomy 35/49 (72%) Rate ratio (95% CI) 1.2 (0.93–1.4) **Tubal preservation** Methotrexate 46/51 (90%) Salpingostomy 45/49 (92%) Rate Ratio (95% CI) 0.98 (0.87–1.1) **Homolateral tubal patency on** Methotrexate 23/37 (62%) Salpingostomy 23/35 (66%) Rate ratio (95% CI) 0.95 (0.67–1.3) **Hysterosalpingogram** **Overall homolateral tubal patency** Methotrexate 23/42 (55%) Salpingostomy 23/39 (59%)	**Limitations** **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>methotrexate and laparoscopic salpingostomy in the treatment of tubal pregnancy and to examine treatment success, tubal preservation, and homolateral tubal patency.

Study dates

between Jan 1, 1994 and Sept 1, 1996

Source of funding

Funded by grant OG 93/007 from the Health Insurance Funds Council, Amstelveen, the Netherlands.</td>
<td>Salpingostomy: n = 12/49

<u>Vaginal bleeding only</u>
Methotrexate: n = 15/51
Salpingostomy: n = 10/49

<u>Abdominal pain and vaginal bleeding only</u>
Methotrexate: n = 24/51
Salpingostomy: n = 21/49

<u>pre-existing tubal pathology</u>
Methotrexate: n = 21/51
Salpingostomy: n = 16/49

<u>Spontaneous pregnancy</u>
Methotrexate: n = 45/51
Salpingostomy: n = 38/49

<u>Insemination</u>
Methotrexate: n = 4/51
Salpingostomy: n = 2/49

<u>IVF - ET</u>
Methotrexate: n = 2/51
Salpingostomy: n = 9/49

<u>Median (range) preoperative serum HCG (IU/L)</u>
Methotrexate: 1950 (110 - 19500)
Salpingostomy; 2100 (228-18400)

<u>Localisation of tubal pregnancy:</u>
<u>Isthmic</u></td>
<td></td>
<td>Ledertrexate, Lederle Pharmaceutical Division, Cyanamid, Etten-Leur, Netherlands), and four doses of folinic acid administered orally (0.1 mg/kg, days 1, 3, 5, and 7, hospital preparation; calcium folinate 5H Uitgeest, Netherlands), followed by 7 days without medication.and grasping forceps. After haemostasis had been achieved the tubal incision was left open to allow secondary healing.

During the methotrexate course patients were instructed not to use alcohol or aspirin, to refrain from sexual intercourse, to avoid exposure to sunlight, to drink at least 1.5 L fluid daily, and to use 0.9% saline mouthwashes or, in case of stomatitis, chlorhexidine 0.12% mouthwashes.

Since folinic acid might negatively influence the effect of systemic methotrexate, all women were instructed to discontinue any prenatal vitamins.

<u>Laparoscopic salpingostomy</u>
In patients allocated to laparoscopic salpingostomy,</td>
<td><u>Rate ratio (95% CI)</u>
0.93 (0.64–1.4)

Successful treatment rate
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>35</td><td>49</td></tr><tr><td>Methotrexate</td><td>42</td><td>51</td></tr></table></td>
<td></td>
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</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Methotrexate: n = 6/51 Salpingostomy: n = 5/49 <u>Ampullary</u> Methotrexate: n = 37/51 Salpingostomy: n = 43/49 <u>Fimbrial</u> Methotrexate: n = 8/51 Salpingostomy: n = 1/49 <u>Mean (SD) diameter of tubal pregnancy (mm)</u> Methotrexate: 23 (9.6) Salpingostomy; 20 (7.9) <u>Median (range) haemoperitoneum (mL)</u> Methotrexate: 50 (0 - 800) Salpingostomy; 30 (0 - 200) **Inclusion criteria** Women with laparoscopically confirmed unruptured tubal pregnancy and no active bleeding. **Exclusion criteria** Exclusion criteria were unstable vital signs, fetal cardiac activity, sonographically detected interstitial, cervical, ovarian, or heterotopic pregnancy,		the intervention immediately followed laparoscopy. The 5 mm suprapubic trocar was replaced with a 10 mm disposable trocar, and one or two additional 5 mm ports were inserted in the right and left hypochondrium for introduction of grasping forceps, a microdiathermy needle, and a suction/irrigation unit. A monopolar linear incision was made over the bulging antimesenteric portion of the tube. The ectopic mass was removed by use of an irrigation probe for hydrodissection Surgery was done by trained laparoscopic surgeons or by other consultants and senior registrars under supervision of the experienced surgeons. All women were discharged, if possible, on the following day. Serial serum HCG measurements were made to assess treatment response. In patients treated with systemic methotrexate, persistent trophoblast was defined as a serum HCG concentration above 40% of		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	contraindications to systemic methotrexate (leucopenia, thrombocytopenia, or high concentrations of liver enzymes or serum creatinine), and contraindications to laparoscopic surgery (documented extensive pelvic adhesions, large fibroid uterus, or severe ovarian hyperstimulation syndrome).		the initial value on day 14 and was treated with a second course of methotrexate. In patients treated by salpingostomy, persistent trophoblast was defined as rising or stable HCG concentrations postoperatively and was treated with a course of systemic methotrexate. Transvaginal sonography was done in both treatment groups routinely within 1 week after the start of treatment or whenever complications were suspected. Women who received systemic methotrexate were followed up until resolution of the ectopic mass was completed. **Randomisation** Randomisation was done by means of a computer program. Pre-existing tubal pathology was defined as previous ectopic pregnancy, previous tubal surgery, previous pelvic inflammatory disease, or proven tubal pathology by hysterosalpingography or		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			laparoscopy. **Laparoscopy** Laparoscopy was done under general anaesthesia with a 10 mm laparoscope introduced through the umbilicus and a 5 mm suprapubic trocar. Reasons for exclusion at this stage were: tubal rupture, active bleeding, non-tubal pregnancy, and impossibility of laparoscopic salpingostomy.The secondary exclusion criteria were assessed by a surgeon unaware of the randomisation outcome so that there was adequate concealment of the treatment allocation. **Analysis** Analysis was by intention to treat; all randomised women were taken into account, except for those secondarily excluded. A sample size of 100 women were chosen to detect a difference in tubal patency rate, in favour of systemic methotrexate, of 18%, with a two-sided 2 test at p = 0.05 and with a power of 80%. Treatment success was defined as complete elimination of the tubal pregnancy (serum HCG < 2		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			IU/L). The success rate was calculated after primary treatment (i.e. one systemic methotrexate course or salpingostomy alone). Tubal preservation rates was calculated after primary treatment plus any additional therapeutic intervention. Homolateral tubal patency rates were calculated by including those women who underwent salpingectomy in the denominator. Overall tubal patency rates were also compared with adjustment for pre-existing tubal pathology and initial serum HCG concentration by logistic regression analysis. All comparisons were made by calculation of rate ratios and the corresponding 95% CI. The median number of days for undetectable serum HCG concentrations was calculated in each treatment group and compared by Wilcoxon statistics. Serum HCG clearance curves were constructed for both primary treatments. An 80% tubal patency rate		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			was expected after laparoscopic salpingostomy. **Hysterosalpingography** Hysterosalpingography was done 3 months after completion of treatment to assess tubal patency. The hysterosalpingograms were assessed by four observers who were unaware of the site of the tubal pregnancy and of the treatment allocation. Women who gave written informed consent were randomly assigned one of the two treatment modalities before a confirmatory laparoscopy.		
Full citation Krag Moeller,L.B., Moeller,C., Thomsen,S.G., Andersen,L.F., Lundvall,L., Lidegaard,O., Kjer,J.J., Ingemanssen,J.L., Zobbe,V., Floridon,C., Petersen,J., Ottesen,B., Success and spontaneous pregnancy rates following systemic methotrexate versus laparoscopic surgery for tubal pregnancies: a randomized trial, Acta	**Sample size** Total: 1265 women were diagnosed with a tubal pregnancy n = 395 (31.2%) were eligible for randomisation n = 106 (8.4%) gave written informed consent and were randomised, 53 in each study group **Characteristics** There were no significant differences between the two study groups in the baseline characteristics (age, parity,	**Interventions** Single dose of systemic Methotrexate (MTX , 1 mg/kg) Salpingotomy (surgical procedure)	**Details** **Randomisation:** Women were recruited to a prospective, computer-randomised multicenter study at seven departments of gynaecology and obstetrics in Denmark from March 1997 to September 2000. Individual randomisation in blocks of 6–8 attached to each centre was executed by phoning a computer program where a voice mail immediately communicated the treatment. The women were randomised to receive	**Results** Total number in methotrexate group n = 53 Total number in surgery group n = 53 Loss of follow up n = 2 (1 in each arm) **The grand total number of pregnancies in the randomised groups** **Number of spontaneous pregnant women (excluded IVF)** Methotrexate n = 38/52 (73%) Surgery n = 32/52 (62%) **Number of spontaneous pregnant women (included IVF)** Methotrexate n = 44/52 (85%)	**Limitations** Study was underpowered based on power calculation.The power calculation estimated that a sample size of 422 patients was needed to establish a difference in spontaneous pregnancy rates of 10% between the two treatments. The inclusion was stopped after three

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Obstetricia et Gynecologica Scandinavica, 88, 1331-1337, 2009 **Ref Id** 75390 **Country/ies where the study was carried out** Denmark **Study type** A randomised trial **Aim of the study** To evaluate success rates and subsequent fertility following either treatment with a single dose of MTX or laparoscopic surgery in women with unruptured tubal pregnancies **Study dates** March 1997 to September 2000 **Source of funding** Not reported	weight, fertility surgery, pelvic inflammatory disease, number of women with two tubes at randomisation, number of women with at least one tube after end of treatment, previous spontaneous abortion, former induced abortion and former ectopic pregnancies) There were no significant differences between the two study groups in the clinical symptoms (pain, β - hCG before treatment in IU/L [hCG in MTX median (IU/L): 2259 (176 - 41000), surgical (IU/L): 3200 (72 - 42859)], Hemoperitoneum at surgery) There were no significant differences between the two study groups in the ultrasound findings (Gestational sac diameter [gestational sac in MTX: median 12 mm (5-25), Surgical: 14 mm (7-29) Pretreatment], adnexal diameter, pseudogestational sac) **Inclusion criteria** Women were included if they were hemodynamic stable, spoke Danish, and had a wish for future fertility. The diagnosis of an unruptured		either a single dose of systemic MTX (Methotrexate, 1 mg/kg, Wyeth Lederle, Copenhagen, Denmark) (n =53) or salpingotomy (n =53). **Surgical procedure:** The surgical procedure was performed laparoscopically. A linear incision was made medial to the swollen part of the tube with a monopolar microdiathermy needle. The product of conception was removed by manipulation, hydrodissection, and suction. Once hemostasis was obtained, the tubal incision was left open for spontaneous healing. **Methotrexate:** Women received a single dose of systemic MTX (Methotrexate, 1 mg/kg, Wyeth Lederle, Copenhagen, Denmark) **Follow up:** Both study groups were monitored by using serial plasma-hCG measurements on Days 4 and 7 following treatment and weekly thereafter until the plasma hCG concentration was below 5 IU/L. If a rise in plasma-hCG or a steady state was observed seven days after the	Surgery n = 41/52 (79%) **Total spontaneous pregnancies including live births, spontaneous abortion and ectopic pregnancy:** Methotrexate: 79 Surgery: 76 **Live births** Methotrexate: 49/79 (62%) Surgery: 38/76 (50%) **Spontaneous abortions** Methotrexate: 14/79 (18%) Surgery: 19/79 (25%) **Ectopic pregnancies** Methotrexate: 4/79 (5%) Surgery: 8/76 (11%) **Total number of IVF pregnancies including live births, spontaneous abortion and ectopic pregnancy:** Methatrexate: 12/79 (15%) Surgery: 11/76 (15%) **Number of Live births** Methotrexate: 9/79 (11%) Surgery: 8/76 (11%) **Spontaneous abortions** Methatrexate: 3/79 (4%) Surgery: 1/76 (1%) **Ectopic pregnancies** Methatrexate: 0/76 (0%) Surgery: 2/76 (3%)	years and six months due to recruitment problems. **Other information** The ultrasonography was performed by a specialist in gynaecology or by the department of ultrasonography at the specific hospital. Plasma-hCG measurements were analysed using a monoclonal-based assay at the hospital.

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<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
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<td>tubal pregnancy was based on medical history, physical examination, including transvaginal ultrasonography, and rising plasma-hCG concentrations. Only women with a rise in plasma-hCG levels by three consecutive measurements or with an extrauterine location of a live conception with a gestational sac diameter of less than 3.6 cm were eligible. Women with plasma-hCG below 2000 IU/L were eligible for randomisation only if the rate of increase was below 20%/24 hours and with no ultrasonographic sign of intrauterine pregnancy. There were no inclusion restrictions regarding upper plasma-hCG concentrations.

Exclusion criteria

Women were excluded if they did not fulfil the inclusion criteria or had a heterotopic pregnancy, hepatic, renal or cardiac disease, anaemia, leukocytopenia, thrombocytopenia, or abuse of alcohol.</td>
<td></td>
<td>MTX treatment, the women were advised to have a second dose of MTX.

Women undergoing surgery were discharged according to the procedure of the individual hospital. If the woman showed signs of intra abdominal bleeding during the time of follow-up, laparoscopy or laparotomy was performed.

The median follow up period was 8.6 years (range 6.9 - 10.3) years.

<u>Analysis</u>
Analysis of the outcomes was made on an intention-to-treat basis. A c^2- test was used for nominal unpaired data, while a Mann–Whitney U-test was used for comparison of ordinal unpaired variables and T-test for unpaired parametric data.

<u>Successful treatment:</u>
A successful treatment was defined as an uneventful decline in plasma-hCG to less than 5 IU/L. Persistent trophoblast was defined as rising plasma-hCG later than on Day 4.

<u>Data Collection:</u>
A posted questionnaire was</td>
<td><u>Further intervention needed</u>
Methotrexate n = 14/53 (n=1 second dose MTX and n = 13 surgical treatment of which 11 salpingectomy) (26%)

<u>Total IVF-pregnancies including live births, spontaneous abortion and ectopic pregnancy</u>
Surgery n = 7/53 (13%)(n = 5 MTX treated and n = 2 salpingectomy)
Surgery n = 39/53 (74%)

<u>Further intervention needed</u>
Methotrexate n = 14/53 (n = 1 second MTX, n =13 surgical treatment of which 11 salpingectomy)
Surgery n = 7/53 (n = 5 mTX treated, n = 2 salpingectomy)

Successful treatment rate
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Surgery</td><td>46</td><td>53</td></tr>
<tr><td>Methotrexate</td><td>39</td><td>53</td></tr>
</table>
Pregnancy rate
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Surgery</td><td>32</td><td>52</td></tr>
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<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
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<td>used to collect information regarding subsequent fertility. Non-responders were contacted by telephone. The Danish Birth Registry and the Danish Registry of in vitro fertilisation (IVF)-pregnancies were scrutinised to obtain further information in relation to pregnancies, abortion, EP, and/or any assisted reproduction procedures.

<u>spontaneous intrauterine pregnancy</u>
Cumulative probability of spontaneous intrauterine pregnancy over time was calculated for each group by use of Proportional Regression Model (Cox Regression Models and Life-Tables) and analysed following the intention-to-treat principle. The starting point for the calculation was the date of treatment.
The end point was the primary outcome measure, i.e. the date of accomplished spontaneous intrauterine pregnancy, where after the women were censored. The endpoint for the women who did not conceive, was the date of the enquiry to the Danish Birth Registry.
The spontaneous intrauterine pregnancy rate included IUI, but not IVF or ICSI-treated</td>
<td>
<table>
<tr><td>Methotrexate</td><td>38</td><td>52</td></tr>
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Recurrent EP
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Surgery</td><td>2</td><td>52</td></tr>
<tr><td>Methotrexate</td><td>0</td><td>52</td></tr>
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Need for further interventions
<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Surgery</td><td>4</td><td>53</td></tr>
<tr><td>Methotrexate</td><td>14</td><td>53</td></tr>
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<td></td>
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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			women.		
Full citation Saraj,A.J., Wilcox,J.G., Najmabadi,S., Stein,S.M., Johnson,M.B., Paulson,R.J., Resolution of hormonal markers of ectopic gestation: a randomized trial comparing single-dose intramuscular methotrexate with salpingostomy, Obstetrics and Gynecology, 92, 989-994, 1998 **Ref Id** 75570 **Country/ies where the study was carried out** USA **Study type** Prospective randomised clinical trial **Aim of the study**	**Sample size** Total n = 75 hemodynamically stable women with a diagnosis of ectopic pregnancy n = 37 treatment with methotrexate n = 37 laparoscopic salpingostomy **Characteristics** Women in both groups were similar in regards to age, gravidity, weight, ectopic pregnancy size, initial serum hCG, initial serum progesterone, prior ectopic pregnancy, history of salpingitis and history of infertility. Ectopic pregnancy size in MTX (cm): mean 2.7± 1, Surgical (cm): 2.7 ± 0.3 Pretreatment hCG in MTX mean (IU/L): 3162 ± 772, surgical (IU/L): 3357 ± 766 **Inclusion criteria** Hemodynamically stable women with a diagnosis of ectopic pregnancy	**Interventions** Single dose methotrexate (1mg/kg IM) treatment Laparoscopic salpingostomy	**Details** Women were randomised to treatment with single-dose IM methotrexate (1 mg/kg) or laparoscopic salpingostomy. All women had initial, day 4, and weekly serum hCG and progesterone measurements taken until hCG levels were less than 15 mIU/mL. Methotrexate therapy was repeated if post treatment day 7 hCG levels did not decrease by 15%, as compared with day 4 levels. Success rate was defined as ectopic resolution without the need for the alternative mode of therapy.	**Results** The mean (/-standard deviation) time required for serum progesterone concentrations to decrease to less than 1.5 ng/ml Laparoscopic salpingostomy: 7.8 /-1.7 days Methotrexate: 17.6 /-2.2 days P < 0.01 Success rates Laparoscopic salpingostomy: 91.4% (33 of 36) Methotrexate: 94.7% (36 of 38) Mean time required for hCG concentrations to decrease to less than 15 mIU/ml Laparoscopic salpingostomy: 20.2 /-2.7 days Methotrexate therapy: 27.2 /-2.3 days (P < 0.05) Additional methotrexate injections Laparoscopic salpingostomy: Methotrexate therapy: n = 6/38 (15.8%) Initial serum hCG levels for women receiving additional methotrexate doses 4830 /-1588 mIU/ml Initial serum hCG levels for women receiving one dose	**Limitations** Randomisation not reported. Allocation not clear. No power calculation **Other information**

<table>
<tr>
<th>Study details</th>
<th>Participants</th>
<th>Interventions</th>
<th>Methods</th>
<th>Outcomes and Results</th>
<th>Comments</th>
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<tr>
<td>To evaluate resolution of serum hCG and progesterone in patients with ectopic pregnancy receiving single-dose intramuscular (IM) methotrexate as compared with those undergoing laparoscopic salpingostomy

Study dates

Between June 1995 and April 1997

Source of funding

Not reported</td>
<td>Exclusion criteria

Lack of of desire for future fertility, cardiac motion documented on transvaginal ultrasound, hematocrit less than 30%, white blood cell count less than 2000/mm^3 platelet count less than 100,000/mm^3 elevated liver enzymes, medical disease (including hepatic, renal,or cardiac disease), and alcohol abuse.</td>
<td></td>
<td></td>
<td>2133 /-393 mIU/ml
P = 0.07

Successful treatment rate

<table>
<tr><th></th><th>Events</th><th>Total</th></tr>
<tr><td>Surgery</td><td>33</td><td>36</td></tr>
<tr><td>Methotrexate</td><td>36</td><td>38</td></tr>
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<tr>
<td>Full citation

Zilber,U., Pansky,M., Bukovsky,I., Golan,A., Laparoscopic salpingostomy versus laparoscopic local methotrexate injection in the management of unruptured ectopic gestation, American Journal of Obstetrics and Gynecology, 175, 600-602, 1996

Ref Id</td>
<td>Sample size

Total = 48
Laparoscopic linear salpingostomy n = 24
Laparoscopic local methotrexate n = 24

Characteristics

Inclusion criteria

Women with desired future fertility
The largest diameter of the tubal pregnancy did not</td>
<td>Interventions

Local methotrexate injection (25 mg was injected into the pregnancy site)
Linear salpingostomy</td>
<td>Details

Women were randomised for either linear salpingostomy or local methotrexate injection.
<u>Linear salpingostomy:</u>
Linear salpingostomy was performed by sharply opening the tube on the antimesosalpingeal border over ectopic gestation with a fine needle electrode. Fine forceps suction were used to remove the product of the conception. The tubal incision was left open and allowed to</td>
<td>Results

<u>Operative time (min)</u>
Salpingostomy
85.6 ± 6.0
Methotrexate
52.9 ± 3.0
p < 0.0001

<u>Hospital stay (days)</u>
Salpingostomy
1.7 ± 0.2
Methotrexate
3.0 ± 0.4
p < 0.01</td>
<td>Limitations

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
75702 **Country/ies where the study was carried out** Israel **Study type** Prospective randomised trial **Aim of the study** To determine whether laparoscopic salpingostomy is preferable to laparoscopic methotrexate injection in the management of unruptured tubal gestation. **Study dates** Between January 1991 to December 1992 **Source of funding** Not reported	exceed 3 cm The tubal serosa was intact and no active bleeding could be observed The pelvis could be fully visualised **Exclusion criteria**		heal by secondary intention. **Local methotrexate injection:** Tube was grasped by an atraumatic forceps through a second puncture. Methotrexate (25 mg, diluted in 3 ml of physiologic solution) was injected into the pregnancy site through the tubal wall by means of an 18-gauge spinal needle 15 cm long, introduced under laparoscopic guidance. Each woman's vital sign were observed for the first 24 hours. **Post follow up:** Included daily serial measurements of serum β hCG titer. Women were kept in hospital until hCG level fell on two consecutive days or reached a level of 10 mIU/ml. Subsequently, each women was seen every 48 hours on an ambulatory basis and clinically examined, serum β hCG levels were monitored until dropping below 10 mIU/ml. **Statistical analysis:** Parity was compared using Mann-Whitney test as the data were not distributed normally. The intrauterine	**Incidence of persistent trophoblastic activity** Salpingostomy 5% Methotrexate 14% p = ns **Time interval until beta-human chorionic gonadotropin disappearance (<10 mIU/ ml)** Salpingostomy 13.9 days Methotrexate 13.7 days p = ns **Subsequent intrauterine pregnancy** Salpingostomy 83.5% Methotrexate 81% **Reproductive outcomes in women attempting to conceive after treatment** **Women with miscarriage** Salpingostomy n = 1/18 (5.5%) Methotrexate n = 0/16 (0%) **Repeat tubal pregnancy** Salpingostomy n = 1/18 (5.5%) Methotrexate n = 0/16 (0%) **Women with intrauterine pregnancy** Salpingostomy n = 14/18 (78%)	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>pregnancy rate was compared with X^2 test and the other parameters were compared with t test.</td><td>Methotrexate n = 13/16 (81%)

Pregnancy rate
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>14</td><td>18</td></tr><tr><td>Methotrexate</td><td>13</td><td>16</td></tr></table>
Recurrent EP
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>1</td><td>18</td></tr><tr><td>Methotrexate</td><td>0</td><td>16</td></tr></table>
Resolution time
<table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Surgery</td><td>13.90</td><td></td><td>24</td></tr><tr><td>Methotrexate</td><td>13.70</td><td></td><td>24</td></tr></table></td><td></td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Hospital stay
<table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Surgery</td><td>1.70</td><td>0.20</td><td>24</td></tr><tr><td>Methotrexate</td><td>2.00</td><td>0.40</td><td>24</td></tr></table>Need for further interventions
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>1</td><td>24</td></tr><tr><td>Methotrexate</td><td>4</td><td>24</td></tr></table></td><td></td></tr>
<tr><td>Full citation

Colacurci,N., De,Franciscis P., Zarcone,R., Fortunato,N., Passaro,M., Mollo,A., Russo,G., Time length of negativization of hCG serum values after either surgical or medical treatment of ectopic pregnancy, Panminerva Medica,</td><td>Sample size

Total n = 33
Group 1: 15
Group 2: 15
n = 3 excluded

Characteristics

The two groups were similar in age, parity, gestational age,</td><td>Interventions

Single dose methotrexate (MTX) or linear salpingotomy</td><td>Details

Based on the hospital number, women were randomly allocated to either linear salpingotomy treatment group (group 1; n = 16) or single dose MTX group (group 2: n = 17). One woman in group 1 and 2 women in group 2 with a rising value of hCG were treated with an additional MTX and therefore</td><td>Results

<u>Resolution time (mean ± SD)</u>
Group 1 (Surgery): 33.6 ± 6.6
Group 2 (MTX): 31.5 ± 7.8
p = 0.42

The course of hCG mean value declined more rapidly in group 1 than group 2 but the analysis of the data with one way ANOVA test did not show statistically significant differences between the two</td><td>Limitations

Randomisation based on the hospital number
Unclear allocation concealment
Unclear if the outcome assessors were blinded to the study group allocation</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>40, 223-225, 1998

Ref Id

91108

Country/ies where the study was carried out

Italy

Study type

Randomised trial

Aim of the study

The aim of this study was to compare the time length until the human chorionic gonadotrophin titer became negative after medical or surgical treatment of ectopic pregnancy

Study dates

January 1994 to March 1995

Source of funding

Not reported</td>
<td>and pre-treatment hCG values

Inclusion criteria

Women were included if they were hemodynamically stable, USG-TV demonstrated an unruptured ectopic pregnancy <4 cm in greatest dimension

Exclusion criteria

hCG serum value > 10.000 mul/ml, hepatic or renal dysfunction, abnormal blood cell count</td>
<td></td>
<td>excluded from the study</td>
<td>groups (p = 0.80)

Resolution time
<table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Surgery</td><td>33.60</td><td>6.60</td><td>15</td></tr><tr><td>Methotrexate</td><td>31.50</td><td>7.80</td><td>15</td></tr></table></td>
<td>Small sample size

Other information</td>
</tr>
<tr><th>Full citation</th><th>Sample size</th><th>Interventions</th><th>Details</th><th>Results</th><th>Limitations</th></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Dias,Pereira G., Hajenius,P.J., Mol,B.W., Ankum,W.M., van,der,V, Fertility outcome after systemic methotrexate and laparoscopic salpingostomy for tubal pregnancy, Fertility and Sterility, 70, S411, 1998-, 1998

Ref Id

118748

Country/ies where the study was carried out

Netherland

Study type

Follow up of a randomised clinical trial (Hajenius et al., 1997)

Aim of the study

To assess fertility outcome in women who had either methotrexate therapy or laparoscopic salpingostomy for tubal pregnancy</td>
<td>Total n = 90

Characteristics

Inclusion criteria

Women with laparoscopically confirmed unruptured tubal pregnancy and no active bleeding, participated in the original clinical trial (Hajenius et al., 1997) who desired pregnancy

Exclusion criteria

Exclusion criteria were unstable vital signs, fetal cardiac activity, sonographically detected interstitial, cervical, ovarian, or heterotopic pregnancy, contraindications to systemic methotrexate (leucopenia, thrombocytopenia, or high concentrations of liver enzymes or serum creatinine), and contraindications to laparoscopic surgery (documented extensive pelvic adhesions, large fibroid uterus, or severe ovarian hyperstimulation syndrome).</td>
<td>Systemic MTX 1.0 IM on days 0, 2, 4, 6 alternated folinic acid 0.1 mg/kg oral on days 1, 3, 5, 7
Laparoscopic salpingostomy</td>
<td>This study is a follow up a randomised clinical trial conducted in six Dutch hospitals between January 1994 and September 1996. Eighteen months after the completion of the trial, fertility outcomes in participants who desired pregnancy were assessed. All women were contacted by telephone and were interviewed about whether they had tried to conceive and the occurrence of spontaneous pregnancies.

140 women were originally randomised, n = 40 were excluded on the basis of no tubal pregnancy, tubal rupture, and/or active bleeding. n= 16 were lost to follow up and n = 16 had no desire for future pregnancy. n= 74 women tried to conceive; 34 after methotrexate and 40 after laparscopic salpingostomy.

<u>Randomisation:</u>
By a computer program with block randomisation. Randomisation was done before confirmation laparoscopy

<u>Power calculation</u>
Tubal pregnancy rate after</td>
<td><u>Cox's proportional hazards estimates of the relative risks for:</u>
Spontaneous intrauterine pregnancy
RR 0.89 (0.42 to 1.9)
Spontaneous repeat ectopic pregnancy
RR 0.77 (0.17 to 3.4)

<u>Kalplan Meier curves for the cumulative intrauterine rate at 18 months:</u>
Methotrexate: 36%
Salpingostomy: 43%

Pregnancy rate

<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>16</td><td>40</td></tr><tr><td>Methotrexate</td><td>12</td><td>34</td></tr></table>
Recurrent EP

<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>4</td><td>40</td></tr><tr><td>Methotrexate</td><td>3</td><td>34</td></tr></table></td>
<td>Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Initial trial date: January 1994 to September 1996 Follow up for assessing fertility outcome conducted 18 months after the trial ended **Source of funding** Not reported (initial study were funded by the Health insurance Funds Council, Amstelveen, The Netherlands)			laparoscopic salpingostomy was assumed to be 80%. A sample size of 100 women would allow to detect a difference in tubal pregnancy rate of 18%. <u>Analysis:</u> Kaplan-Meier curves were used for showing the cumulative intrauterine pregnancy rate.		
Full citation Sowter,M.C., Farquhar,C.M., Petrie,K.J., Gudex,G., A randomised trial comparing single dose systemic methotrexate with laparoscopy for the treatment of unruptured tubal pregnancy, BJOG: An International Journal of Obstetrics and Gynaecology, 108, 192-203, 2001 **Ref Id**	**Sample size** Total: n = 62 women Laparoscopic surgery n = 26 Methotrexate n = 22 **Characteristics** **<u>Age (years):</u>** Methotrexate: 29.7 (5.4) Laparoscopy: 30.4 (4.6) **<u>Parity:</u>** Methotrexate: 0 (0 - 5) Laparoscopy: 0 (0 - 6) **<u>Gestation (days):</u>** Methotrexate: 43.4 (14.3)	**Interventions** Single dose systemic methotrexate (50 mg/m^2) Laparoscopic surgery for treatment (salpingotomy was preferred over salpingectomy)	**Details** Women who gave written informed consent were randomised to either single dose intramuscular methotrexate or laparoscopic surgery. **<u>Randomisation</u>** Unblocked randomisation generated by a computer programme was used and allocation details were contained in sequentially numbered opaque envelopes sealed by a third party. Envelopes were opened in the presence of the women entering the trial after written	**Results** **Laparoscopic surgery** All 28 women randomised to laparoscopic surgery were treated laparoscopically. Of the 25 women in the surgery group who had an ectopic pregnancy confirmed, n = 16 underwent salpingotomy and n = 2 women had aspiration of fimbrial tubal abortion performed. In n = 7 women salpingectomy was performed because of tubal rupture (n = 2), post salpingotomy bleeding (n = 3), women request and (n = 1) dense peritubal adhesions (n = 1). In the MTX group n = 4 women underwent salpingectomy and n = 1 underwent salpingotomy during follow up.	**Limitations** No study design limitations **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
118808 **Country/ies where the study was carried out** New Zealand **Study type** Randomised trial **Aim of the study** To compare single dose systemic methotrexate (50 mg/m^2) with laparoscopic surgery for the treatment of unruptured tubal pregnancy. **Study dates** From 28 July 1997 to 27 September 1998 **Source of funding** Not reported	Laparoscopy: 43.5 (15.8) **Clinical symptoms:** **None:** Methotrexate: n = 1/34 Laparoscopy: n = 1/28 **vaginal bleeding only:** Methotrexate: n = 2/34 Laparoscopy: n = 2/28 **Abdominal pain only:** Methotrexate: n = 3/34 Laparoscopy: n = 1/28 **Abdominal pain and vaginal bleeding:** Methotrexate: n = 28/34 Laparoscopy: n = 24/28 **Duration of vaginal bleeding (days):** Methotrexate: 7 (1 - 21) Laparoscopy: 6 (1 - 14) **Duration of pain (days):** Methotrexate: 3 (1 - 20) Laparoscopy: 3 (1 - 8) **Pretreatment hCG (IU/l):** Methotrexate: 927 (137 - 4866) Laparoscopy: 775 (89 - 4800) **Pretreatment haemoglobin (g/dl):** Methotrexate: 12.4 (11.1 -		informed consent had been given. Women not eligible for trial entry or declining randomisation were offered surgical management. **Surgery** Persistent trophoblast was diagnosed and methotrexate (50 mg/m^2 IM) administered if there was 50% fall in b-hCG level by day seven following surgery or levels began to plateau or rise thereafter. Women allocated to laparoscopy underwent surgery as soon as they had been adequately prepared and theatre space was available. If possible, salpingotomy was always performed in preference to salpingectomy. Prior to performing the salpingotomy the mesosalpinx was injected. The salpingotomy was performed using a monopolar microdiathermy needle and the salpingotomy incision left open to permit secondary healing. Women were reviewed as outpatients between post-operative day five and seven. **Methotrexate** Women allocated to methotrexate received a	**Successful treatment:** n = 26/28 (93%) **Persistent trophoblast** n = 2/28 (7%) (both treated with MTX; 1 successful response and 1 required second laparoscopy) **Methotrexate group n = 34:** **Successful treatment:** n = 22/34 (65%) (with a single dose of methotrexate). n = 9/34 (26%) needed second dose of methotrexate (n = 5 no further treatment needed, n = 2 had third dose MTX [1 no further treatment and 1 fourth dose MTX] and n = 2 operated on). n = 3/34 (9%) operated on. **Complications:Haematological abnormalities**: **Median time for b-hCG levels to fall to less than 5 IU/L:** Laparoscopic surgery: 15 days (range 5 - 49) Methotrexate: 28 days (range 14 - 71) 95% CI of difference in median duration of follow up 2 - 14 days P = 0.01 Initial serum b-hCG concentrations were significantly lower in women who required only a single dose of methotrexate (median b-hCG 495 IU/l) when compared with women requiring	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	14.7) Laparoscopy: 13.0 (10.5 - 14.4) **Ectopic pregnancy visible on TVS:** Methotrexate: n = 28/34 (82%) Laparoscopy: n = 22/28 (79%) **Inclusion criteria** Women were eligible for entry into the trial if they had serum b-hCG concentration below 5000 IU/L and adnexal mass less than 3.5 cm in diameter, minimal haemoperitoneum on transvaginal ultrasound (estimated to be < 300 ml), and no adnexal fetal heart. Both women with and without any desire for future fertility were eligible for entry into the study. **Exclusion criteria** Exclusion criteria were: unstable vital signs, generalised peritonism on abdominal palpation, a falling serum b-hCG concentration, diagnostic uncertainty requiring laparoscopy, an ultrasonically		single intra muscular dose of 50 mg per m^2 of body surface area. Women were treated on an outpatient basis and were reviewed clinically on day 4 when a serum bhCG was measured. **Follow up:** Women were reviewed clinically on day 7 and a serum b-hCG, serum aspartate transaminase, and full blood count were measured. Thereafter, women were seen weekly for a clinical review and measurement of serum b-hCG. Women were advised to avoid alcohol and drink at least 1.5 l of fluid daily during the initial stages of follow up, and refrain from sexual intercourse until follow up was complete. A second dose of methotrexate was given if the serum b-hCG concentration had failed to fall by more than 15% between day 4 and 7 or was plateauing or rising after day 7. Further doses of methotrexate were given if the serum b -hCG concentration still failed to fall and no contraindication to methotrexate had developed. Laparoscopy or laparotomy was performed if the patient showed signs clinically or on ultrasound scanning of tubal	either more than one dose of methotrexate or surgery (median b-hCG 1805 IU/l) (P < 0.0.01). At an initial b-hCG of under 1000IU/L women had a 12% chance of requiring further doses of methotrexate (2 of 17 women), but at an hCG concentration over 1500 IU/l women had a 70% (7 of 10 women) chance of requiring either further methotrexate or surgical intervention. Initial serum b-hCG concentration in the methotrexate group was also strongly correlated with the duration of follow up (r . 0.443; P < 0.0.001). **Psychological outcomes and side effects** **SF-36 physical functioning scores, state anxiety scale and CES - depression scale on day 0 of follow up:** No significant differences were observed between the laparoscopy and methotrexate group in general health, physical functioning, physical role, bodily pain, vitality, social functioning, role - emotional, mental health and CES depression. Significant differences observed between the two groups in state of anxiety (median score Laproscopy: 51 [44 to 60], methotrexate: 48 [34 to 53] p = 0.05) **Fallopian tube conserved:** Laparoscopic surgery: n = 18 (64%) 27	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	diagnosed interstitial, cervical, ovarian or heterotopic pregnancy, contraindications to methotrexate (i.e. leukopaenia, thrombocytopaenia, or elevated serum liver enzymes or creatinine); and contraindications to laparoscopy (i.e. documented severe pelvic adhesions, large fibroid uterus, or ovarian hyperstimulation syndrome).		rupture during follow up, or if she required further medical therapy but had developed a contraindication to further methotrexate.	(44%) women (9 in the laparoscopic surgery group; 18 women in the methotrexate group) declined this investigation: 13 had no plans for further pregnancies; 4 preferred to continue to try to conceive without hysterosalpingography; 2 conceived before hysterosalpingography could be arranged; 1 requested referral for assisted reproduction clinic without further investigation; 7 did not reply to the invitation). Methotrexate: n = 31 (91%) **Pain on day 4 follow up** Women undergoing laparoscopy reported more severe shoulder tip pain compared with laparoscopy group (p = 0.001) **Side effects** In the laparoscopic surgery group one woman developed a port-site haematoma and two women were prescribed oral antibiotics post-operatively for umbilical port-site infections. In the methotrexate group, two women had an elevated aspartate transaminase level and one woman had mild neutropaenia following a second dose of methotrexate. These haematological abnormalities returned to normal within one week. **Vaginal bleeding on day 10 follow up** Women who had received MTX reported more severe and greater duration of bleeding when compared with	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				laparoscopy group (p < 0.001) **Hysterosalpingography 3 month follow up:** Laparoscopic surgery: n = 5/9 (55%) had patent Fallopian tube Methotrexate: n = 8/13 (91%) had patent Fallopian tube **SF-36 physical functioning scores, state anxiety scale and CES - depression scale on day 4 of follow up:** No significant differences were observed between the laparoscopy and methotrexate group in physical role, bodily pain, vitality, social functioning, emotional role, mental health and CES depression and state of anxiety. Statistically significant differences observed between the two groups in physical functioning (median score Laproscopy: 43 [25 to 60], methotrexate: 73 [45 to 87] p = 0.001) **SF-36 physical functioning scores, state anxiety scale and CES - depression scale on day 10 of follow up:** No significant differences were observed between the laparoscopy and methotrexate group in physical role, bodily pain, vitality, social functioning, emotional role, mental health and CES depression and state of anxiety. Statistically significant differences observed between the two groups in physical functioning (median score Laproscopy: 70 [53 to 95],	

<table>
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<tr><td></td><td></td><td></td><td></td><td>methotrexate: 93 [85 to 89] p = 0.006)

<u>SF-36 physical functioning scores, state anxiety scale and CES - depression scale on day 28 of follow up:</u>
No significant differences were observed between the laparoscopy and methotrexate group in general health, physical role, physical functioning, bodily pain, vitality, social functioning, emotional role, mental health and CES depression and state of anxiety.

Successful treatment rate
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>26</td><td>28</td></tr><tr><td>Methotrexate</td><td>22</td><td>34</td></tr></table>
Resolution time
<table><tr><th></th><th>Mean</th><th>SD</th><th>Total</th></tr><tr><td>Surgery</td><td>15.00</td><td></td><td>28</td></tr><tr><td>Methotrexate</td><td>28.00</td><td></td><td>34</td></tr></table></td><td></td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Need for further interventions
<table><tr><th></th><th>Events</th><th>Total</th></tr><tr><td>Surgery</td><td>2</td><td>28</td></tr><tr><td>Methotrexate</td><td>12</td><td>34</td></tr></table></td><td></td></tr>
<tr><td>Full citation

Nieuwkerk,Pythia T., Hajenius,Petra J., Ankum,Willem M., Van der Veen,Fulco, Wijker,Wouter, Bossuyt,Patrick M.M., Systemic methotrexate therapy versus laparoscopic salpingostomy in patients with tubal pregnancy. Part I. Impact on patients' health-related quality of life, Fertility and Sterility, 70, 511-517, 1998

Ref Id

124725

Country/ies where the study was carried out

Netherland</td><td>Sample size

Systemic MTX n = 42
Laparoscopic salpingostomy n = 37

Characteristics

<u>Age (y)</u>
MTX: 31.1 ± 6.3
Salpigostomy: 32.1 ± 4.2

<u>Gestational age</u>
MTX: 45.6 ± 17.0
Salpigostomy: 47.5 ± 10.6

Clinical symptoms:
<u>None</u>
MTX: n = 3/42
Salpigostomy: n= 4/37

<u>Vaginal bleeding</u>
MTX: 20/42
Salpigostomy: 14/37

<u>Initial serum HCG level (mIU/mL)</u></td><td>Interventions

Standard health related quality of life questionnaires administered 2 days, 2 weeks, 4 weeks, and 16 weeks after confirmative laparoscopy</td><td>Details

Women were allocated to systemic methotrexate therapy or laparoscpic salpingostomy. in women allocated to systemic methotrexate, laparoscopy was completed with no intervention.

<u>Medical treatment:</u>
Consisted of four doses of methotrexate IM (1.0 mg/kg, days 0, 2, 4, and 6) alternated with four doses of folic acid administered orally (0.1 mg/kg, days 1, 3, 5 and 7) followed by 7 days without medication, was started immediately after laparoscopy and completed on an outpatient basis. Persistent trophoblast was treated with second course of methotrexate.

<u>Laparoscopic salpingostomy:</u></td><td>Results

Health related quality of life (mean ± SD)

<u>Pain* 2 days after confirmative laproscopy:</u>
Medical: 79 ± 21
Surgical: 68 ± 23
P = ns

<u>Pain* 2 weeks after confirmative laproscopy:</u>
Medical: 51 ± 33
Surgical: 38 ± 26
P = ns

<u>Pain* 4 weeks after confirmative laproscopy:</u>
Medical: 34 ± 33
Surgical: 25 ± 28
P = ns

<u>Pain* 16 weeks after confirmative laproscopy:</u>
Medical: 19 ± 27
Surgical: 15 ± 21</td><td>Limitations

Randomisation and allocation concealment not reported
Not clear if the assessors were blinded to group allocations

Other information</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Multicenter randomised clinical trial **Aim of the study** To compare health-related quality of life of women after systemic methotrexate therapy versus laparoscopic salpingostomy for tubal pregnancy. **Study dates** January 1994 to September 1996 **Source of funding** Supported by grant OG 93/007 from the Health Insurance Funds Council, Amstelveen, the Netherlands.	MTX: 1,700 (110 - 17,500) Salpigostomy: 2,450 (228 - 18,400) **Inclusion criteria** Sufficient Dutch or English skills to complete questionnaires Hemodynamically stable women with laparoscopy confirmed unruptured tubal pregnancy without signs of active bleeding **Exclusion criteria** Not reported		Salpingostomy were followed by laproscopy. Persistent trophoblast was treated with additional systemic methotrexate. In both treatment homolateral tubal patency was assessed by hysterosalpingography 3 months after the completion of treatment. Measurement of health related quality of life: It was assessed with use of several standard self administered psychometric measures with established reliability and validity: The medical outcomes study short form 20: A generic instrument, comprising six sub-scales; physical functioning, role functioning, social functioning, mental health, health perceptions, and pain. The Rotterdam Symptoms Checklist: Comprising four sub-scales; physical symptoms, psychological distress, activity level, and a single item measuring overall quality of life. The State - trait Anxiety	P = ns Depression** 2 days after confirmative laproscopy: Medical: 52 ± 10 Surgical: 46 ± 11 P < 0.05 Depression** 2 weeks after confirmative laproscopy: Medical: 49 ± 12 Surgical: 44 ± 11 P = ns Depression** 4 weeks after confirmative laproscopy: Not reported Depression** 16 weeks after confirmative laproscopy: Medical: 38 ± 11 Surgical: 33 ± 12 P = ns **Scores range from 20 - 80, with the higher score indicating more depression Over all quality of life* 2 days after confirmative laproscopy: Medical: 67 ± 20 Surgical: 52 ± 28 P < 0.05 Over all quality of life* 2 weeks after confirmative laproscopy: Medical: 50 ± 22 Surgical: 38 ± 24	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Inventory: Measures state and trait anxiety. State anxiety refers to momentarily experienced anxiety and trait anxiety refers to the general tendency of an individual to be anxious and it is considered a personality trait. Self rating Depression Scale: Measures the subjective experience of depression as characterised by affective, cognitive, behavioural and psychological symptoms. Women were asked by their physicians to fill out the questionnaires. The first set of questionnaires was completed after randomisation but before confirmative laparoscopy. Women received three sets of questionnaires when they were discharged from the hospital, these were completed at home, 2 days 2 weeks and 4 weeks after confirmative laproscopy and returned in sealed envelopes. Women received the fifth set of questionnaires 16 weeks after confirmative laproscopy. Analysis Health related quality of life was studied on an intention to treat analysis	P < 0.05 Over all quality of life* 4 weeks after confirmative laproscopy: Not reported Over all quality of life* 16 weeks after confirmative laproscopy: Medical: 27 ± 20 Surgical: 23 ± 20 P = ns Social functioning* 2 days after confirmative laproscopy: Medical: 30 ± 29 Surgical: 48 ± 39 P < 0.05 Social functioning* 2 weeks after confirmative laproscopy: Medical: 45 ± 29 Surgical: 68 ± 32 P < 0.05 Social functioning* 4 weeks after confirmative laproscopy: Medical: 69 ± 28 Surgical: 78 ± 30 P = ns Social functioning* 16 weeks after confirmative laproscopy: Medical: 91 ± 18 Surgical: 89 ± 19 P = ns *Scores range from 0 - 100, with the higher score indicating better functioning **Scores range from 20 - 80, with the	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				higher score indicating more depression	

What is the effectiveness of laparotomy compared with laparoscopic techniques for managing tubal ectopic pregnancy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Baumann,R., Magos,A.L., Turnbull,A., Prospective comparison of videopelviscopy with laparotomy for ectopic pregnancy, British Journal of Obstetrics and Gynaecology, 98, 765-771, 1991 **Ref Id** 77172 **Country/ies where the study was carried out** UK **Study type** Prospective comparative observational study **Aim of the study** To compare operative laparoscopy with laparotomy for the management of ectopic pregnancy (EP) in haemodynamically	**Sample size** N=92 (nb: this is number of surgeries, not number of women. 5 women had laparoscopies on two separate occasions) **Characteristics** The two groups were similar in age, history of laparotomy, gestation, size, site and state of EP, and volume of haemoperitoneum at time of surgery. **Age/years (mean (SD))** Laparotomy: 28.9 (5.7) Laparoscopy: 28.2 (5.1) **Gestation/weeks (mean (SD))** Laparotomy: 6.6 (1.2) Laparoscopy: 7.0 (1.90 **Size of EP/cm (mean (SD))** Laparotomy: 4.2 (2.1) Laparoscopy: 3.6 (1.4) **Non-tubal EP (number/total)**	**Interventions** Laparotomy n=27 **Comparator** Laparoscopy n=65 (note: this is 60 women, because five women had laparoscopies on two separate occasions)	**Details** 87 women were treated on 92 occasions at the Churchill Hospital, Oxford during the study period. Most presented with acute lower abdominal pain or pelvic tenderness, and were found to have a positive urinary pregnancy test with no evidence of an IUP in ultrasound. (14 further women were excluded because they were clinically shocked on admission and required immediate laparotomy) The mode of management was decided before the diagnostic laparoscopy, according to the surgical preference of the on-call team. The lower number of laparotomies reflects the interest in less invasive surgery in Oxford. **Laparotomy** Patients were operated on by registrars and senior registrars on call according to standard surgical techniques. Following laparoscopic confirmation of the diagnosis, a Pfannenstiel incision was made to remove the pregnancy. Drains were	**Results** **Conversion to laparotomy (number of events/total)** Laparoscopy: 2/65 2 women required immediate laparotomy, but both had non-tubal EP. One was in a woman with an ovarian EP, a result of 60ml organised haemoperitoneum which could not be aspirated successfully. The other was in a woman with a leaking right cornual pregnancy, and due to arterial bleeding from the tube. **Intraoperative blood loss/ml (mean (SD))** Laparotomy: 269.0 (258.9) Laparoscopy: 206.1 (235.9) Not significant (no p-value given) **Length of hospital stay / days (mean (SD))** Laparotomy: 5.2 (1.4) Laparoscopy: 1.7 (1.2)	**Limitations** **Non-tubal ectopic pregnancies** This study includes some non-tubal ectopic pregnancies: Laparotomy: 2/27 (both in cornua) Laparoscopy: 5/65 (2 in cornua, 3 in ovary) **Other information** **Type of surgery** **Laparotomy:** Salpingotomy: 2/27 (7%) Salpingectomy: 20/27 (74%) Extraction/expression: 3/27 (11%) Salpingo-oophorectomy: 2/27 (7%) Excision of ovarian pregnancy: 0/27 (0%) **Laparoscopy:** Salpingotomy: 29/65 (45%) Salpingectomy: 28/65 (43%) Extraction/expression: 4/65 (6%) Salpingo-oophorectomy: 1/65 (2%) Excision of ovarian pregnancy: 1/65 (2%) Conversion: 2/65 (3%) Note: less invasive surgery was encouraged at the study site

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stable women. **Study dates** March 1st 1988 to August 31st 1989 **Source of funding** Grants towards the cost of equipment: - Mason Medical Research Foundation - Trust Deed of the Oxford and District Hospitals Improvement Fund - Oxford Hospital Services Development Loan of instruments: - Karl Storz GmbH of Tuttlingen, West Germany - Rimmer Brothers, UK	Laparotomy: 2/27 Laparoscopy: 5/65 **Tubal rupture (number/total)** Laparotomy: 5/27 Laparoscopy: 12/65 **Inclusion criteria** Extrauterine pregnancy **Exclusion criteria** Clinically shocked		not routinely used. **Laparoscopy** 65 emergency videopelviscopies were performed by two of the authors, on 60 women. All women were counselled before surgery and consented to possible laparotomy. Both groups continued to be managed by their surgeons while in hospital. Early mobilisation was encouraged, with discharge as soon as medically safe. Venous blood for hCG assay was taken within 12 hours of surgery, after 1 week and after 6 weeks. Results were compared using two-tailed Student's t-test	p<0.001 (no test statistic given) **Need for further surgery (number of events/total)** Laparotomy: 0/27 Laparoscopy: 2/65 (laparoscopic salpingectomies due to retained trophoblast)	**Skill of surgeon** Laparotomy: 9 done by senior registrar, 18 by registrar, 0 by SHO Laparoscopy: 56 done by senior registrar, 0 by registrar, 19 by SHO
Full citation Chatwani,A., Yazigi,R., min-Hanjani,S., Operative laparoscopy in the management of tubal ectopic pregnancy, Journal of Laparoendoscopic Surgery, 2, 319-324, 1992	**Sample size** N=117 **Characteristics** Mean age, gravidity, parity, estimated gestational age, initial hCG levels and racial backgrounds of the two groups were similar. There was no significant difference	**Interventions** Laparotomy n=61 **Comparator** Laparoscopy n=56	**Details** Diagnosis was based on clinical symptomatology and positive urine or blood tests, and confirmed by a lack of intrauterine pregnancy on vaginal or abdominal ultrasonography **Laparotomy** Laparotomy was done through	**Results** **Conversion to laparotomy (number of events/total)** Laparoscopy: 1/56 1 patient required an immediate laparotomy, following an initial laparoscopic salpingectomy, when haemostasis could not be assured at the end of the	**Limitations** **Follow-up (only relevant for fertility outcomes)** The authors state that mean follow-up was 13.1 months but give no further details on how follow-up was done. Loss to follow-up is not reported. The denominator for the fertility outcomes is not stated - unable to

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Ref Id 77216 **Country/ies where the study was carried out** USA **Study type** Prospective comparative observational study **Aim of the study** To demonstrate advantages of laparoscopy over laparotomy, such as decreased length of hospital stay and reduction in overall cost. A secondary objective was to introduce wider use of operative laparoscopy into the residency training program at Temple. **Study dates** October 1989 to March 1992	in the number of patients with history of PID, ectopic pregnancy, endometriosis, or pelvic surgery. Mean age: 24.2 years **Tubal rupture (%)** Laparotomy: 79% Laparoscopy: 21% **Inclusion criteria** Diagnosis of ectopic pregnancy **Exclusion criteria** Not stated		a low midline or Pfannenstiel's incision in the standard manner (not described). Haemostasis was acheived with the use of bipolar electrocoagulation or surgical clips. **Laparoscopy** Laparoscopic salpingectomy was carried out using the endoloop. Salpingostomy was done after vasopressin (20U in 50ml saline) was injected into the tube overlying the implantation site. An incision was made over the antimesenteric portion of the fallopian tube until products of conception were exposed. Electrocautery or a carbon dioxide laser was used. The tissue was removed either by gentle application of forceps or extruded using suction-irrigation. When required, haemostasis was achieved using the carbon dioxide laser (defocused beam) or electrocautery. When haemostasis was assured, the tube was left open. Salpingostomy was always done where clinically feasible, otherwise a partial or total salpingectomy was performed.	procedure. **Need for further surgery (number of events/total)** Laparotomy: does not directly state how many Laparoscopy: 1/56 (required laparotomy for persistent trophoblastic tissue) **Readmission to hospital (number of events/total)** Laparotomy: 1/61 Laparoscopy: 1/56 Both were readmitted due to persistent trophoblastic tissue. No statistical test reported **Length of hospital stay/days (mean)** Laparotomy: 4.70 Laparoscopy: 1.27 $p < 0.05$ (no test statistic given) **Subsequent IUP (number of events/total)** Laparotomy: 12/35 Laparoscopy: 9/33	determine whether this refers to those available for follow-up, or those desiring pregnancy? **Other information** Women with tubal rupture were more likely to undergo laparotomy, reflecting the comfort level of most surgeons when the patient is more critical. **Type of Surgery** **Laparotomy:** Salpingostomy: 10/61 (16%) Salpingectomy: 51/61 (84%) **Laparoscopy:** Salpingostomy: 24/56 (43%) Salpingectomy: 32/56 (57%) **Subsequent IUP by surgery type** **Salpingostomy:** 4/22 (18.2%) - Laparotomy: 0/3 (0%) - Laparoscopy: 4/19 (21.1%) **Salpingectomy:** 17/46 (37.0%) - Laparotomy: 12/32 (37.5%) - Laparoscopy: 5/14 (35.7%)

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Source of funding Not stated.			Early ambulation was encouraged post-operatively, and patients were discharged when clinically indicated. Follow-up included weekly hCG assays until non-pregnant levels. Method of long-term follow up is not described, neither is loss to follow-up. Statistical analysis was performed using the SPSS statistical package.		
Full citation Federici,D., Conti,E., Muggiasca,M.L., Ferrari,S., Arcaini,L., Brambilla,T., Meroni,M., Agarossi,A., Laparoscopic conservative surgery in tubal pregnancy, Minimally Invasive Therapy, 3, -201, 1994 **Ref Id** 77283 **Country/ies where the study was carried out** Italy **Study type**	**Sample size** N=30 **Characteristics** Mean age: 33.1 years Eleven women were nulliparous, while the other nineteen had an average parity of 1.4. 13/30 patients reported with triad of symptoms: amennorhea, pelvic pain and vaginal bleeding. In 17 cases the only symptom was menstrual delay, and these cases had a positive urinary pregnancy test without evidence of an IUP on ultrasound.	**Interventions** Laparotomy n=7 **Comparator** Laparoscopy n=23	**Details** During the study period, 30 women underwent conservative surgical treatment for tubal pregnancy at the Department of Gynaecology and Obstetrics at the University of Milan. (n.b. 4 further women were exluded because they presented with shock and required an immediate laparotomy) Serum hCG levels combined with a vaginal ultrasound were used to make a diagnosisof ectopic pregnancy in 18 cases. All patients underwent a diagnostic laparoscopy for confirmation of the diagnosis. Patients were treated with either a laparotomy or a	**Results** **Conversion to laparotomy (number of events/total)** Laparoscopy: 0/23 **Length of hospital stay/days (mean (SD))** Laparotomy: 7.3 (0.9) Laparoscopy: 2.8 (0.7) p<0.001 (no test statistic given) **Need for further surgery (number of events/total)** Laparotomy: 0/7 Laparoscopy: 0/23 (n.b. one patient from the laparoscopy group had	**Limitations** **Sample size** Small sample size, particularly in laparotomy group. **Other information**

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Prospective comparative observational study **Aim of the study** To compare operative laparoscopy with laparotomy for the conservative management of tubal pregnancy. **Study dates** May 1992 to April 1993 **Source of funding** Not stated	**Gestation/weeks (mean)** Laparotomy: 7 Laparoscopy: 6 **Size of EP/cm (mean)** Laparotomy: 3.6 Laparoscopy: 3.1 **Pre-operative hCG/UI per litre (mean)** Laparotomy: 2173 Laparoscopy: 1322 **Tubal rupture (number/total)** Laparotomy: 0/7 Laparoscopy: 0/23 **Haemoperitoneum present (number/total)** Laparotomy: 3/7 Laparoscopy: 10/23 **Inclusion criteria** Undergoing conservative surgical treatment for a tubal pregnancy **Exclusion criteria**		laparoscopy. The type of surgery was decided by the on-call surgical team before the diagnostic laparoscopy, depending on their preference and experience. Linear salpingostomy was performed in both groups. **Laparotomy** Following the diagnostic laparoscopy, a Pfannenstiel incision was made and the tubal wall was incised using a fine-needle electrode along the antimesenteric border of the ectopic pregnancy at the point of maximum bulge. A vasopressin solution (0.5 IU/ml) was injected in to the distended tubal wall. The products of conception were removed using forceps. After irrigation, haemostasis was achieved with bipolar electrocoagulation, and the salpingostomy was allowed to heal by secondary intention. **Laparoscopy** A 10mm Panoview operating laparoscope was inserted through an infraumbilical incision, after achieving pneumoperitoneum with carbon dioxide. Two auxiliary 5mm trocars were inserted	persistent trophoblastic activity, but it was successfully managed expectantly)	

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	Shock		suprapubically at the lateral aspects of an imaginary Pfannenstiel incision. Vasopressin was injected into the distended tubal wall using a 22-gauge spinal needle passed directly in to the abdominal wall. Linear salpingostomy was performed uing a unipolar needle electrode introduced through the contralateral auxiliary trocar. The incision was made on the antimesenteric border of the tube, and the products of conception were removed using forceps with blunt jaws, passed through the operating channel of the laparoscope and extracted together with the laparoscope through the 10mm trocar sleeve. Ringers solution was used to irrigate, and haemostasis was then achieved with bipolar coagulating forceps. The salpingostomy was allowed to heal by secondard intention. Weekly post-operative surveillance of serum hCG levels was done until normalisation ANOVA was used to compare the operating groups.		

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Full citation Lo,L., Pun,T.C., Chan,S., Tubal ectopic pregnancy: an evaluation of laparoscopic surgery versus laparotomy in 614 patients, Australian and New Zealand Journal of Obstetrics and Gynaecology, 39, 185-187, 1999 **Ref Id** 77410 **Country/ies where the study was carried out** Hong Kong (Chinese) **Study type** Prospective comparative observational study **Aim of the study** To identify factors which might lead to a delay in diagnosis, and to compare operative laparoscopy with laparotomy in the immediate treatment of tubal ectopic	**Sample size** N=535 **Characteristics** The data below shows the distribution of women with shock and tubal rupture between the two groups, out of the total cases initially deemed suitable. Women in shock were excluded from analysis, therefore are not included in the study population. Those with tubal rupture are included. **Shock** Laparotomy: 68/ 232 Laparotomy: 11/382 Total: 79/614 **Tubal rupture** Laparotomy: 126/232 Laparotomy: 114/382 Total: 240/614 **Inclusion criteria**	**Interventions** Laparotomy n=164 **Comparator** Laparoscopy n=371	**Details** This study was a prospective audit conducted in 9 obstetrics and gynaecology training units in Hong Kong. A standard data sheet with 4 sections (history and clinical findings on admission, progress in hospital, operative information and immediate outcome) was pre-tested in three hospitals for one month before adoption for use. One co-ordinator was appointed by each hospital to recruit cases and collect data. 630 data forms were returned, of which 16 forms were initially excluded from the study as per the exclusion criteria, and 79 later excluded from analysis due to being in shock, resulting in a study population of 535. 93 of the laparotomies were preceded by a diagnostic laparoscopy Methods of assessing intraoperative blood loss are not described.	**Results** **Conversion to laparotomy (number of events/total)** Laparoscopy: 6/371 (Reasons not reported) **Intraoperative blood loss/ml (mean)** Laparotomy: 110.4 Laparoscopy: 129.2 (NOTE: this has been reported in the paper as 12.9.2 - the technical team have provisionally assumed the value should be 129.2, due to the reported non-significant result of the statistical test) Not significant (no p-value or test statistic reported) **Length of hospital stay/days (mean)** Laparotomy: 5.3 Laparoscopy: 2.65 p=0.0001 (no test statistic reported) **Need for further surgery (% (number of events/total))** Laparotomy: 0.6% (0.984/164)	**Limitations** Methods of assessing intraoperative blood loss are not described. Standard deviations are not reported. **Other information** **Type of surgery (includes women with shock)** **Laparotomy:** Salpingectomy: 199/232 (85.8%) Salpingotomy: 9/232 (3.88%) Salpingo-oophorectomy:1/232 (0.43%) Cornual resection: 17/232 (7.33%) Other: 6/232 (2.59%) **Laparoscopy:** Salpingectomy: 268/382 (70.16%) Salpingotomy: 92/382 (24.08%) Salpingo-oophorectomy: 1/382 (0.26%) Cornual resection: 1/382 (0.26%) Other: 20/382 (5.24%) **Skill of surgeon** Most specialists and post-MRCOG trainees would perform laparoscopic surgeries, whereas pre-MRCOG trainees mostly performed laparotomy.

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pregnancy. **Study dates** July 1st 1996 to June 30th 1997 **Source of funding** Not stated	Operative diagnosis of tubal ectopic pregnancy **Exclusion criteria** Duplication of cases Incomplete data entry of vital information Non-tubal ectopic pregnancy Shock (defined as a fall in systolic pressure of 30 mmHg and diastolic of 20 mmHg, or signs of peripheral circulatory failure)			Laparoscopy: 0.8 (2.968/371) (reported as a % in the study, which has also been converted to a raw number by the technical team) **Readmission to hospital (% (number of events/total))** Laparotomy: 1.2% (1.968/164) Laparoscopy: 2.2% (8.162/371) (reported as a % in the study, which has been converted to a raw number by the technical team)	There was variation between operating time, and proportion of women treated with laparoscopy, between the facilities. 11.2% of laparoscopies took over 2 hours, illustrating the learning process.
Full citation Lundorff,P., Thorburn,J., Hahlin,M., Kallfelt,B., Lindblom,B., Laparoscopic surgery in ectopic pregnancy. A randomized trial versus laparotomy, Acta Obstetricia et Gynecologica Scandinavica, 70, 343-348, 1991	**Sample size** N=105 **Characteristics** Age, gestational age, size and location of EP, blood loss at diagnostic laparoscopy, and hCG level were not significantly different between the two groups. Women were also classified	**Interventions** Laparotomy n=57 **Comparator** Laparoscopy n=48	**Details** 109 women fulfilled the entry criteria (of which 4 were later excluded, as described in the limitations). They were stratified into 6 sub-groups on the basis of age and risk determinants for which they were scored: previous EP, IUCD in situ, history of infertility, previous abdominal operations (see table in characteristics)	**Results** **Length of hospital stay/days (mean (SEM))** Laparotomy: 5.4 (0.2) Laparoscopy: 2.2 (0.1) $p < 0.001$ (no test statistic reported) **Need for further surgery (number of events/total)**	**Limitations** **Absence of an intention-to-treat analysis** 4 women, randomised to receive a laparoscopy, were excluded: 2 had tubal abortions and were managed by laparoscopic procedures without salpingostomy, in 1 case it was not possible to achieve significant pneumoperitoneum therefore a laparotomy was done, and in 1 case, manipulation of the affected tube caused major

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 77418 **Country/ies where the study was carried out** Sweden **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy of laparoscopic treament with conventional conservative surgery (laparotomy) for tubal pregnancy. **Study dates** May 1, 1987 to June 30, 1989 **Source of funding** The Swedish Medical Research Council The Goteborg Medical Society	into risk groups, based on risk scores and age. Risk scores were calculated using:previous EP, IUCD in situ, history of infertility, previous abdominal operations. There was no significant difference between the risk scores of the groups. **Inclusion criteria** Diameter of tubal gestation < 4cm Ampullary gestation accessible for laparoscopic approach Trained laparoscopist on duty Haemodynamic stability **Exclusion criteria** Pre-operative hCG titre above 10,000 IU/l (if levels were known)		Women were randomised to laparoscopy or laparotomy by sealed envelopes from six different boxes based on the age/risk score sub-groups. All surgeries were performed by the authors. The affected tube was left open for secondary healing. **<u>Laparotomy</u>** Vasopressin injection and a salpingotomy with a diathermy knife was performed, and the pregnancy products were squeezed through the opening. 4 patients in the laparotomy required a salpingectomy, and 4 cases required resection of the tube. **<u>Laparoscopy</u>** An 8-10 mm laparoscope was introduced throught the umbilicus. Two 5 mm trocars were inserted suprapubic in the right and left side of the lower pelvis for introduction of grasping forceps, diathermy knife, and suction-irrigation unit. Vasopressin was injected via a 0.8mm syringe. The tube was opened with a fine diathermy knife over the implantation site, with a longitudinal incision (10-15mm). Pregnancy products	Laparotomy: 2/57 Laparoscopy: 6/48 No significant difference (p-value not reported) Further surgery was a result of persistent trophoblastic activity and/or bleeding. (Note: in addition to those requiring surgery, 2 patients required methotrexate due to persistent trophoblast and 4 patients were managed expectantly due to abdominal pain. This paper does not report which group they belonged to, therefore these outcomes are reported in Lundorff 1997, elsewhere in the evidence table)	bleeding from the mesosalpinx and a laparotomy was necessary. **Other information** Authors reported standard error of means only - this was used by the techical team to calculate standard deviations. No test statistics are reported, simply p-values in the case of significant results. **<u>Type of Surgery:</u>** **Laparotomy:** Salpingotomy: 49/57 (85.96%) Salpingectomy: 4/57 (7.02%) Tube resection: 4/57 (7.02%) **Laparoscopy:** Salpingotomy: 48/48 (100%)

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			were removed with the suction-irrigation unit or forceps. After surgery, patients were followed by serial hCG determinations on day 2, 7, then weekly until non-pregnant levels. Serum hCG was done using a time-resolved fluoro-assay. Length of hospital stay and need for further surgery were reported for each patient. Statistical comparisons of the two groups were performed using Fishers permutation test (two-tailed)		
Full citation Lundorff,P., Thorburn,J., Lindblom,B., Fertility outcome after conservative surgical treatment of ectopic pregnancy evaluated in a randomized trial, Fertility and Sterility, 57, 998-1002, 1992 **Ref Id** 77421 **Country/ies where the study was carried out**	**Sample size** N=87 **Characteristics** Characteristics of original trial participants are described in Lundorff et al 1991 The characteristics of the specific women desiring pregnancy that form this study population are not described **Inclusion criteria** Participation in original trial (for inclusion criteria, see	**Interventions** Laparotomy n=45 **Comparator** Laparoscopy n=42	**Details** In the initial study, 105 patients were randomised to receive either a laparotomy (n=57) or a laparoscopy (n=48) A second-look laparoscopy was done in 64 patients who desired pregnancy 12 weeks after primary surgery, consisting of 35 patients from the laparotomy group and 29 patients from the laparoscopy group. Adhesiolysis by electrocautery was performed in 33 of the 45 cases in which adhesions were found. 23/35 from the laparotomy group and	**Results** **<u>Subsequent IUP (number of events/total)</u>** Defined as women who had an intrauterine conception within the study period (from the time of their surgery until August 1990), which includes full-term deliveries, on-going intrauterine pregancies, induced abortions and miscarriages. Laparotomy: 20/45 Laparoscopy: 22/42 Not significant (no test	**Limitations** **<u>Variable follow-up period</u>** Women were all followed until August 1990, not for a set period after their surgery, therefore they did not all have the same period at-risk of pregnancy. 1 patient was lost to follow-up, and therefore her desire for pregnancy and fertility outcomes were not assessed. **Other information** This is follow-up data from Lundorff et al 1991, it is the same trial.

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Sweden **Study type** Randomised controlled trial **Aim of the study** To evaluate the fertility outcomes following laparoscopy versus laparotomy for treatment of ectopic pregnancy. **Study dates** Initial trial date was May 1987 to June 1989. Follow-up was to August 1990. **Source of funding** Swedish Medical Research Council Goteborg Medical Society	above Lundorff et al 1991) Desiring pregnancy **Exclusion criteria** See original trial exclusion criteria (Lundorff et al 1991)		10/29 from laparoscopy group received adhesiolysis (not significant). Questionnaires regarding wish for pregnancy and outcomesuse of contraceptives, and time at risk for pregnancy were sent to all 105 patients one year after the surgery, and at the end of the study period in August 1990. 85 patients immediately answered the final questionnaire, and in 20 cases a repeat letter was sent. They reported number of deliveries, on-going IUP, induced abortions, miscarriages and ectopic pregnancies. Statistical analysis was done using Fischer's exact test.	statistic or p-value reported) **Subsequent viable IUP (number of events/total)** Defined as women who have a term delivery, a late on-going intrauterine pregnancy, or an induced abortion within the study period (from the time of their surgery until August 1990). Laparotomy: 16/45 Laparoscopy: 14/42 Statistical test not reported **Future EP (number of events/total)** Defined as the women who had at least one further ectopic pregnancy during the study period (from the time of their surgery until August 1990). Laparotomy: 5/45 Laparoscopy: 4/42 Statistical test not reported for this comparison, only for difference between first subsequent EP (not significant)	

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Full citation Lundorff,P., Laparoscopic surgery in ectopic pregnancy, Acta Obstetricia et Gynecologica Scandinavica - Supplement, 164, 81-84, 1997 **Ref Id** 77424 **Country/ies where the study was carried out** Sweden **Study type** Randomised controlled trial **Aim of the study** To compare the efficacy of laparoscopic treatment versus conventional conservative abdominal surgery for tubal pregnancy. **Study dates** May 1st 1987 to June	**Sample size** N=105 **Characteristics** Age, gestational age, size and location of EP, blood loss at diagnostic laparoscopy, and hCG level were not significantly different between the two groups. Women were also classified into risk groups, based on risk scores and age. Risk scores were calculated using:previous EP, IUCD in situ, history of infertility, previous abdominal operations. There was no significant difference between the risk scores of the groups. **Inclusion criteria** Diameter of tubal gestation < 4cm Ampullary gestation accessible for laparoscopic approach Trained laparoscopist on duty Haemodynamic stability	**Interventions** Laparotomy n=57 **Comparator** Laparoscopy n=48	**Details** 109 women fulfilled the entry criteria (of which 4 were later excluded, as described in the limitations). They were stratified into 6 sub-groups on the basis of age and risk determinants for which they were scored: previous EP, IUCD in situ, history of infertility, previous abdominal operations. Women were randomised to laparoscopy or laparotomy by sealed envelopes from six different boxes based on the age/risk score sub-groups. All surgeries were performed by the authors. The affected tube was left open for secondary healing. **Laparotomy** Vasopressin injection and a salpingotomy with a diathermy knife was performed, and the pregnancy products were squeezed through the opening **Laparoscopy** An 8-10 mm laparoscope was introduced throught the umbilicus. Two 5 mm trocars were inserted suprapubic in the right and left side of the lower pelvis for introduction of	**Results** **Abdominal pain (number of events/total)** Laparotomy: 3/57 Laparotomy: 1/48 All were managed by expectant observation. **Need for methotrexate (number of events/total)** Laparotomy: 0/57 Laparoscopy: 2/48 (due to persistent trophoblast)	**Limitations** **Absence of an intention-to-treat analysis** 4 patients initially randomised to receive laparoscopy were excluded. Of these exclusions, two were surgeries that converted to laparotomy (due to inability to achieve sufficient pneumoperitoneum in one case, and major bleeding from the mesosalpinx in the other). **Other information** This paper reports the same trial as Lundorff et al 1991. Only outcomes not reported in the original trial paper are reported here, to avoid duplication.

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30th 1989 **Source of funding** The Swedish Medical Research Council The Goteborg Medical Society	**Exclusion criteria** Pre-operative hCG titre above 10,000 IU/l (if levels were known)		grasping forceps, diathermy knife, and suction-irrigation unit. Vasopressin was injected via a 0.8mm syringe. The tube was opened with a fine diathermy knife over the implantation site, with a longitudinal incision (10-15mm). Pregnancy products were removed with the suction-irrigation unit or forceps. After surgery, patients were followed by serial hCG determinations on day 2, 7, then weekly until non-pregnant levels. Serum hCG was done using a time-resolved fluoro-assay. Statistical comparisons of the two groups were performed using Fisher's permutation test (two-tailed)		
Full citation Mehra,S., Gujral,A., Mehra,G., Endoscopic vs. conventional surgery for tubal gestation, International Journal of Gynecology and Obstetrics, 61, 297-298, 1998 **Ref Id** 77445	**Sample size** N=111 **Characteristics** **Mean gestational age/weeks (mean (SD))** Laparotomy: 6.40 (1.0) Laparoscopy: 6.41 (1.4) **Size of**	**Interventions** Laparotomy n=25 **Comparator** Laparoscopy n=86	**Details** Women with tubal pregnancy in the ampullary, isthmoampullary, or infundibular part of the tube, and where tubal damage was minimal, were given linear salpingostomy. Where tubal damage was extensive and future fertility was not required, salpingectomy was done. Fimbrial expression and segmental resection were	**Results** **Blood loss/ml (mean (SD))** Laparotomy: 150 (44.9) Laparoscopy: 140 (51.9) No significant difference **Length of hospital stay/hours (mean (SD))** Laparotomy: 84.5 (12.2)	**Limitations** **Reporting of methods** Very few details are given about methods, analysis and outcomes. Statistics are particularly poorly reported, and the table with means and standard deviations are not labelled as such - it had to be assumed by the technical team. No details of surgical complications or conversions to laparotomy are reported. Method of assessing

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out India **Study type** Prospective comparative observational study **Aim of the study** To evaluate laparotomy and laparoscopy for management of tubal gestation **Study dates** January 1991 to December 1995 **Source of funding** Not stated	**pregnancy/centimetres (mean (SD))** Laparotomy: 3.26 (0.7) Laparoscopy: 2.88 (1.1) **Inclusion criteria** Women undergoing laparotomy or laparoscopy for ectopic pregnancy **Exclusion criteria** None stated		done on pregnancies in the terminal ampulla and isthmus respectively. All women were followed up for 18 months after surgery.	Laparoscopy: 35.6 (14.1) p<0.05 **Subsequent intrauterine pregnancy (% (number of events/total))** Laparotomy: 42% (10.5/25) Laparoscopy: 54% (46.44/86) The data was reported as a percentage, which has also been converted here to a raw number by the technical team. They report p<0.05, however, statistical analysis of risk ratios performed in GRADE does not support this result. **Future ectopic pregnancy (% (number of events/total))** Laparotomy: 5% (1.25/25) Laparoscopy: 4.54% (3.904/85) This is reported as "recurrence rate" in the paper. The data was reported as a percentage, which has also been converted here to a raw number by the technical team.	blood loss is not stated. **Fertility outcomes** The outcome of the IUP is not reported, and the denominator is not defined for the outcome of intrauterine pregnancy or recurrence rate. Therefore, their population could have included women with no desire to become pregnant. **Other information** Length of hospital stay was reported in hours, but was converted to days by the technical team. **Type of surgery (%)** **Laparotomy:** Salpingectomy: 48 Linear salpingostomy: 32 Segmental resection: 8 Fimbrial expression: 8 **Laparoscopy:** Salpingectomy: 53.5 Linear salpingostomy: 33.7 Segmental resection: 5.8 Fimbrial expression: 5.3

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mol,B.W., Hajenius,P.J., Engelsbel,S., Ankum,W.M., van,der,V, Hemrika,D.J., Bossuyt,P.M., An economic evaluation of laparoscopy and open surgery in the treatment of tubal pregnancy, Acta Obstetricia et Gynecologica Scandinavica, 76, 596-600, 1997 **Ref Id** 77462 **Country/ies where the study was carried out** The Netherlands **Study type** Cost-effectiveness analysis **Aim of the study** To economically evaluate laparoscopy and open surgery for the treatment of tubal	**Sample size** N=255 **Characteristics** Characteristics and p-values are reported for 4 separate groups: radical open, radical laparoscopy, conservative open and conservative laparoscopy. However, they have been combined by the technical team: **Tubal rupture (number/total)** Laparotomy: 42/140 Laparoscopy: 8/115 **Gestational age/days (mean)** Laparotomy: 51.2 Laparoscopy: 49.5 **Inclusion criteria** Women undergoing primary surgical treatment for a tubal pregnancy in the Academic Medical Centre or the Onze Lieve Vrouwe Gasthuis during the study period. **Exclusion criteria**	**Interventions** Laparotomy n = 140 **Comparator** Laparoscopy n = 115	**Details** Data was collected retrospectively for patients operated on before September 1993. After September 1993, data was collected prospectively. 287 patients were initially included in the study, but 32 were excluded, as per the exclusion criteria. Tubal pregnancy was diagnosed using transvaginal sonography and serum hCG monitoring. It was then confirmed either laparoscopically or by open surgery. The choice of treatment depended on the clinical situation and the skills of the operating gynaecologist. Data on clinical symptoms, hCG levels on day of operation, gestational age (calculated from the start of the last menstrual period), presence of peri-tubal adhesions and tubal rupture were recorded. Economic resources were recorded, including conversions to laparotomy, hospital stay (in days),	**Results** **Conversion to laparotomy (number of events/total)** Laparoscopy: 1/115 **Need for blood transfusion (number of events/total)** Laparotomy: 10/140 Laparoscopy: 1/115 **Thromboembolic disease (number of events/total)** Laparotomy: 1/140 Laparoscopy: 0/115 **Respiratory morbidity (number of events/total)** Laparotomy: 2/140 Laparoscopy: 0/115 (Note: Both suffered pneumonia) **Length of hospital stay/days (mean (SD))** Laparotomy: 8.89 (2.33) Laparoscopy: 2.93 (1.08) (nb: these are pooled means and SD calculated by NCC	**Limitations** Data from January 1992 to September 1993 was collected retrospectively **Other information** **Type of surgery** In the paper, radical and conservative surgery were split. However, for the purposes of our analysis of laparotomy versus laparoscopy, the technical team pooled the data, and calculated pooled means and standard deviation. **Laparotomy:** Conservative: 22/140 (15.7%) Radical: 118/140 (84.3%) **Laparoscopy:** Conservative: 76/115 (66.1%) Radical: 39/115 (33.9%)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pregnancy. **Study dates** Academic Medical Centre: January 1992 to December 1995 Onze Lieve Vrouwe Gasthuis: September 1993 to December 1995 **Source of funding** Partially supported by the Dutch Health Insurance Council, Amstelveen.	Being in shock at the time of the operation Heterotopic pregnancies Insufficient data		complications, and reinterventions, as well as other costs not related to this review topic.	technical team) **Need for any reintervention (number of events/total)** This includes methotrexate, further surgery and expectant management Laparotomy: 1/140 (after conservative surgery) Laparoscopy: 18/115 (17 after conservative surgery, 1 after radical surgery) Re-intervention was needed in 19 patients with persistent trophoblast: 16 patients were managed with methotrexate, 1 patient was given methotrexate but later required a radical laparotomy, 1 patient was given a salpingectomy, and 1 was managed expectantly. The study does not report which secondary interventions were given to which patients.	
Full citation Murphy,A.A., Nager,C.W., Wujek,J.J., Kettel,L.M., Torp,V.A., Chin,H.G., Operative laparoscopy versus laparotomy for the	**Sample size** N=63 **Characteristics** **Ethnic Origin**	**Interventions** Laparotomy n=37 (Note: for background	**Details** Patients were allocated to either laparotomy or laparoscopy on alternative months. Once enrolled, the specific operating procedure was determined by the	**Results** **Intraoperative blood loss/cc (mean (SD))** Laparotomy: 115 (115) [n=36] Laparoscopy: 62 (61)	**Limitations** **Loss to follow-up (only affects fertility outcomes)** In the comparisons of long-term fertility, 77% of the laparoscopy group were available for follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
management of ectopic pregnancy: a prospective trial, Fertility and Sterility, 57, 1180-1185, 1992 **Ref Id** 77468 **Country/ies where the study was carried out** USA **Study type** Non-randomised trial **Aim of the study** To compare prospectively operative laparoscopy to laparotomy in the management of haemodynamically stable patients with ectopic pregnancy. **Study dates** April 1988 to December 1989 **Source of funding** Not stated	50% Hispanic, 35% White, 15% Black/Asian. **Age/years (mean (SD))** Laparotomy: 27.4 (6.0) Laparoscopy: 28.2 (6.1) **Unruptured tube (%)** Laparotomy: 57 Laparoscopy: 73 **Haemoperitoneum present (%)** Laparotomy: 62 Laparoscopy: 54 There were no significant differences in gravidity, parity, history of infertility, previous EP, previous PID, prior abdomino-pelvic surgery or desire for future fertility. **Inclusion criteria** Suspected ectopic pregnancy **Exclusion criteria** Unstable vital signs	characteristics, intraoperative blood loss and type of procedure performed, n is reported as 36. This is not explained by the authors, but could be a result of missing data) **Comparator** Laparoscopy n=26	operating team, accounting for operative findings and desire for future fertility. Linear salpingostomy was procedure of choice for those desiring future fertility, but if tubal damage prevented this, a segmental resection was performed where appropriate. All patients underwent a diagnostic laparoscopy, for confirmation of the EP. **Laparotomy** Surgery was performed through a Pfannenstiel incision (<7cm). A linear salpingostomy was done, using fine-tip needle electrocautery with expression of the trophoblastic tissue. Tubes were allowed to heal by secondary intention. If conservative surgery was desired but a linear salpingostomy could not be performed, a partial salpingectomy was done. Salpingectomy was performed in the standard fashion. Lysis of adhesions was also done if required. Patients were encouraged to leave the hospital whenever they felt comfortable to do so. If a conservative procedure	p < 0.001 (no test statistic reported) **Need for a blood transfusion (number of events/total)** Laparotomy: 2/37 Laparoscopy: 1/26 No statistical test reported **Respiratory morbidity (number of events/total)** Laparotomy: 1/37 (pneumonia) Laparoscopy: 0/26 No statistical test reported **Length of hospital stay/hours (mean (SD))** Laparotomy: 634 (17) Laparoscopy: 26 (19) p < 0.005 (no test statistic reported) **Need for further surgery (number of events/total)** Laparotomy: 0/37 Laparoscopy: 2/26	(20 people), whereas only 57% of the laparotomy group were available for follow-up (21 people). The authors state that many participants had risk factors for infertility and therefore pregnancy rates should be interpreted with caution. **Exclusions** 36 patients were initially allocated to the laparoscopy group, but 10 were excluded due to: - unavailability of equipment (3) - attending physician not trained in laparoscopy (3) - pregnancy location was interstitial (1) - dense adhesions (1) - uncontrollable bleeding from the mesosalpinx (1) - excessive size of gestation, 8cm in width. (1) nb. this was at the beginning of the study, and since then ectopic gestations of this size have been managed with laparoscopy. There is also some unexplained missing data for one patient from the laparotomy group. **Other information** Unlike the other included studies, length of hospital stay is reported in hours. The technical team

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			was performed, serial hCG levels were done post-operatively. **<u>Laparoscopy</u>** Laparoscopy was performed through a sub-umbilical incision using a 10mm straight laparoscope or an 11mm operating laparoscope. Up to three 5-mm suprapubic ancillary puncture sites were used, and occasionally a puncture site was enlarged to accomodate a 10-mm trocar through which a morcellator was placed. Where possible, a video camera equipped with a beam splitter was used. Salpingostomy incisions were made using a fine-tip needle cautery or knife electrode. The ectopic bed was irrigated. When necessary, haemostasis was obtained using microtip cautery or Kleppinger bipolar forceps. In some cases, dilute vasopressin (0.2 IU/mL) was injected into the mesosalpinx. Tubes were left to heal by secondary intention. Salpingectomy was done by coagulating with bipolar forceps and cutting along the mesosalpinx and across the proximal fallopian tube using scissors. Surgical specimens	(Early in their experience, two patients in the laparoscopy group had to undergo a second laparoscopic procedure (salpingectomy)). **<u>Need for methotrexate (number of events/total)</u>** Laparotomy: 0/37 Laparoscopy: 1/26 **<u>Subsequent IUP (number of events/total)</u>** Laparotomy: 5/10 Laparoscopy: 7/8 No significant difference (test statistic and p-value are not reported) **<u>Future EP (number of events/total)</u>** Laparotomy: 2/10 Laparoscopy: 0/8 No significant difference (test statistic and p-value are not reported)	converted this to days for later inclusion in the evidence profile: **Length of stay/days (mean(SD))** Laparotomy: 26.417 (0.708) Laparoscopy: 1.083 (0.792) **<u>Type of Surgery</u>** **Laparotomy:** Salpingectomy: 19/36 (52.8%) Linear salpingostomy: 10/36 (27.8%) Segmental resection: 7/36 (19.4%) Fimbrial expression: 0/36 (0%) **Laparoscopy:** Salpingectomy: 9/26 (34.6%) Linear salpingostomy: 11/26 (42.3%) Segmental resection: 3/26 (11.5%) Fimbrial expression: 3/26 (11.5%) **<u>Skill of surgeon</u>** Laparotomies were performed by junior residents, assisted by a senior resident and attending physician Laparoscopies were performed by a senior resident (16) or an attending physician being trianed in laparoscopy (10). A surgeon trained in operative laparoscopy was present in all cases. The skills of the surgeons increased as the study progressed,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			were withdrawn through the 10mm subumbilicar trocal sleeve. The pelvis was irrigated at the end of each procedure. Postoperative hCG levels were followed in patients undergoing a conservative procedure Blood loss was estimated by the anaesthesiologist and staff gynaecologist at the end of the case. Available patients were contacted by telephone for follow-up and asked when they resumed normal activity. Follow up data from 6 and 24 months was obtained where possible. They were asked if they were attempting pregnancy, and pregnancy outcome was ascertained. Subsequent IUP and EP are reported as the number of people with a pregnancy during the follow-up people, out of the women who were contacted that were attempting pregnancy. Rates of follow-up varied between groups (see limitations). Data was analysed using a group t-test, ANOVA or chi-squared.		and they attempted more difficult cases

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Rizzuto,M.I., Oliver,R., Odejinmi,F., Laparoscopic management of ectopic pregnancy in the presence of a significant haemoperitoneum, Archives of Gynecology and Obstetrics, 277, 433-436, 2008 **Ref Id** 77544 **Country/ies where the study was carried out** UK **Study type** Prospective comparative observational study **Aim of the study** To assess the trend in the use of operative laparoscopy in the management of patients with ruptured ectopic pregnancy and significant	**Sample size** N = 37 (nb. these patients were a subset (selected according to the inclusion criteria) of a total of 313 women who had surgical management of an ectopic pregnancy during the study period) **Characteristics** Blood loss ranged from 800ml to 3500ml (determined at surgery) The number of surgeries done using each technique varied through the study period: **2003:** 2 laparotomy, 3 laparoscopy **2004:** 1 laparotomy, 5 laparoscopy **2005:** 2 laparotomy, 12 laparoscopy **2006:** 0 laparotomy, 12 laparoscopy **Total:** 5 laparotomy, 32 laparoscopy **Inclusion criteria**	**Interventions** Laparotomy n=5 **Comparator** Laparoscopy n=32	**Details** Patients with signs of hypovolemic shock were initiallty resuscitaed with IV fluids and/or whole blood. 54% of the patients were stabilised before surgery (using IV fluids or transfusion). **Laparotomy** Patients who underwent a direct laparotomy were those considered to be persistently unstable, despite resuscitation with crystalloids, colloids and blood transfusion (reported in results). No further specific details are given. **Laparoscopy** When women were transferred to theatre, they went directly to the operating room and any further resuscitation (as required by the senior anaesthetist) took place. In the lithotomy position, the direct entry technique was used as long as the patient did not have a midline scar from a previous surgery (none did). 3 ancillary ports were inserted under direct vision: 10mm supra-pubic port, and a lateral 5mm port in each iliac fossa. The 10mm port allowed use of	**Results** **Conversion to laparotomy** **By year (number/total laparoscopies (%)):** 2003: 1/3 (33.3%) 2004: 0/5 (0%) 2005: 2/12 (16.7%) 2006: 0/12 (0%) **By amount of haemoperitoneum (number/total laparoscopies (%))** 800-1500ml: 0/12 (0%) 1600-2500ml: 1/12 (8.3%) 2600-3500ml: 2/8 (25%) The reasons for conversion were poor vision and difficulty in achieving quick haemostasis, as judged by the operating surgeon. (note: 54% patients had to be stabilised before surgery using IV or transfusion, and out of these patients. This included the 3 patients that required a conversion to laparotomy, but haemodynamic instability was not the reason for the conversion in any of the three)	**Limitations** **Small sample size** Few (5) laparotomies were conducted, which is likely to be a result of the fact that in 2003, it became departmental policy that patients with EP requiring surgery should be managed with operative laparoscopy where feasible. Patients who underwent a direct laparotomy were those considered to be persistently unstable, despite resuscitation with crystalloids, colloids and blood transfusion (reported in results). **Study population** This is a slightly different study population than many of the other studies, in that it only includes women with a ruptured EP and significant haemoperitoneum. **Other information** **Skill of surgeon:** The operation surgeon was not the minimal access lead during year 1 of the study. In the early years, the women were operated on out-of-hours and the minimal access lead was not informed. However, later, a surgeon was made available on call for the patients. During the course of the study, more

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
haemoperitoneum. **Study dates** January 2003 to December 2006 **Source of funding** Not stated	Patients with a clinical or laparoscopic assessment of significant haemoperitoneum **Exclusion criteria** None stated		a large suction bore cannula to allow aspiration of the pneumoperitoneum and blood clot. Following aspiration, a pre-formed endoscopic loop was applied around the tube to secure haemostasis. Once haemostasis was achiece, the procedure was completed as a routine operative laparoscopy for EP (no further details given)	**Need for a blood transfusion** 14 patients required intra-operative or post-operative transfusions, however, the study does not report which group they belonged to. **Length of hospital stay** Laparotomy: all discharged on day 3-4 after surgery Laparoscopy: all discharged on day 1-2 after surgery (no means given) **Need for further surgery** Not directly reported, but they state that there were no postoperative complications and that all patients were discharged.	equipment for advanced laparoscopy was acquired, as well as dedicated expertise for laparoscopic management. All laparoscopies were conducted by the senior most surgeon on the team. From 2004, these were experienced laparoscopic surgeons who either operated directly on the patients or supervised senior trainees.
Full citation Vermesh,M., Silva,P.D., Rosen,G.F., Stein,A.L., Fossum,G.T., Sauer,M.V., Management of unruptured ectopic gestation by linear salpingostomy: a prospective,	**Sample size** N=60 **Characteristics** 80% Mexican-American, 10% White, 5% Asian, 5% Black	**Interventions** Laparotomy n=30 **Comparator** Laparoscopy	**Details** At time of admission, patients with interviewed about their plans for future child-bearing. All participants were given a diagnostic laparoscopy, and excluded if the EP fulfilled the exclusion criteria.	**Results** **Conversion to laparotomy (number of events/total)** Laparoscopy: 2/30 Two patients required an immediate laparotomy (one received a salpingectomy, and one received ligation of	**Limitations** **Other information** This trial also reports some limited short-term fertility outcomes. However, these are reported in a later follow-up study (Vermesh & Presser 1992), and therefore are not described here.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomized clinical trial of laparoscopy versus laparotomy, Obstetrics and Gynecology, 73, 400-404, 1989 **Ref Id** 77660 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To compare the morbidity, costs, length of hospital stay and fertility outcomes after a linear salpingostomy by laparoscopy versus laparotomy. **Study dates** October 1986 to February 1988. **Source of funding** Supported in part by a	No significant differences between the groups in: age, height, weight, gravidity, gestational age, haematocrit, ectopic size, pre-operative hCG levels. There was also no significant difference in the number of patients with histories of pelvic inflammatory disease, endometriosis, previous EP and use of an IUD between the two groups. **Inclusion criteria** Stable vital signs Suspected diagnosis of ectopic gestation, for which an operative investigation was planned Aged over 18 years old Haematocrit > 30% **Exclusion criteria** Tube containing gestation was ruptured Largest diameter of haematosalpinx > 5cm Location of EP in sites other	n=30	Randomisation was done at the time of the laparoscopy, by drawing in sequence and unmarked, opaque envelope containing a coded card. Surgery was performed by the authors, by opening the tube using a fine-needle electrode and removing the products of conception with fine forceps. The site was irrigated with Ringer's lactate and hemostasis was accomplished via coagulation by electrocautery. Vasopressin (5 IU in 20mL of saline) was given in some cases. Other fertility factors were assessed during the surgery, but lysis of adhesions was the maximum amount of surgery directed to the contralateral tube. **Laparoscopy** 10mm Semm spoon forceps were used to remove trophoblastic tissue, and the incision was left open to heal. Post-operative follow up included hCG measurements at 3 day intervals until disappearance, and a hysterosalpingography at 12 weeks. Methods of assessing intra-operative blood loss are	the meso-salpingeal vessels). Both had a haematosalpinx of 5 cm. **Intraoperative blood loss/ml (mean (SEM))** Laparotomy: 195 (24) Laparoscopy: 79 (18) p < 0.001 (no test statistic given) **Need for further surgery (number of events/total)** Laparotomy: 1/30 (patient received a laparoscopic salpingectomy, due to rising hCG titres) Laparoscopy: 2/30 (1 received a laparoscopic salpingectomy due to rising hCG titres, and 1 recieved a salpino-oophorectomy due to torsion of the contralateral adnexum) **Length of hospital stay/days (mean (SEM))** Laparotomy: 3.3 (0.2) Laparoscopy: 1.4 (0.1) p <0.001 (no test statistic given)	Standard errors were reported for the outcomes, which were converted to standard deviations by the technical team.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
grant from the National Institutes of Health (USA)	than the isthmus or ampulla Pelvic adhesions precluding complete visualisation of EP		not stated. Need for further surgery was reported as the number of patients requiring a second surgery as a result of short-term complications. Comparisons of clinical data and hospital stay were carried out by student t-test or Wilcoxon rank sum test. Histories and fertility outcomes were compared using Fishers Exact Test. Correlations were determined by linear regression analysis.		
Full citation Vermesh,M., Presser,S.C., Reproductive outcome after linear salpingostomy for ectopic gestation: a prospective 3-year follow-up, Fertility and Sterility, 57, 682-684, 1992 **Ref Id** 77663 **Country/ies where the study was carried out** USA **Study type**	**Sample size** N=40 (60 patients participated in the original: 30 assigned to laparotomy, and 30 assigned to laparoscopy. This study considers fertiliy outcomes among those who had attempted to conceive, after 3 years of follow-up.) **Characteristics** Characteristics of all trial participants are recorded in Vermesh et al 1989. This study does not report the specific characteristics of the women who were attempting	**Interventions** Laparotomy n=21 **Comparator** Laparoscopy n=19	**Details** Patients with a diagnosis of ectopic gestation were initially randomised to receive either a linear salpingostomy by laparotomy or laparoscopy. Patients were followed up for 3 years after their surgery, using periodic office visits, telephone calls and letters. Patients were asked about changes in lifestyle, contraception, and encouraged to notify the clinic of any pregnancy or operation. The paper reports number of viable IUP, spontaneous abortions and EP. If contact with a patient was interrupted, data was obtained from hospital records and/or records from the Public Health	**Results** **<u>Subsequent IUP (number of events / total)</u>** Defined as the number of women with IUP conceptions within the study period (includes viable IUP and spontaneous abortions) Laparotomy: 15/21 Laparoscopy: 13/19 Statistical test not reported for this difference, only for the total conceptions (including EP) **<u>Subsequent viable IUP (number of events/total)</u>** Defined as the number of	**Limitations** **<u>Loss to follow-up</u>** Laparotomy: 7/30 (23.3%) Laparoscopy: 8/30 (26.7%) **Other information** This is follow-up data from Vermesh et al 1989, it is the same trial.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial **Aim of the study** To compare the reproductive outcome of women randomised to receive treatment of EP by either laparoscopy or laparotomy, 3 years after the surgery. **Study dates** The initial trial was conducted between October 1986 and February 1988. Patients were followed up for 3 years after their surgery. **Source of funding** No funding source stated for this paper, but the initial trial was part funded by a grant from the National Institutes of Health.	to conceive. **Inclusion criteria** Participation in the original trial (see Vermesh et al 1989 for inclusion criteria) Having attempted to conceive since the surgery **Exclusion criteria** See Vermesh et al 1989 for exclusion criteria for original trial		Department. Statistical comparisons of the reproductive data between women in the two groups were performed using Fisher's exact test.	women with viable IUP conceptions within the study period. Laparotomy: 11/21 Laparoscopy: 12/19 Statistical test not reported **Future EP (number of events/total)** Defined as the number of women having at least one further ectopic pregnancy within the study period. Laparotomy: 4/21 Laparoscopy: 1/19 Not significant (test statistic and p-value not reported)	
Full citation El Tabbakh,M.N., El Sayes,M.S.., Tubal Ectopic Pregnancy: Laparoscopy vs.	**Sample size** N = 207	**Interventions** Laparotomy	**Details** This prospective study was conducted in the Department of Obstetrics and Gynaecology of two private hospitals in	**Results** **Conversion to laparotomy (number of events/total (%))**	**Limitations** **Differential follow-up** The two groups had different follow-up protocols, with the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Laparotomy, Kasr El Aini Medical Journal, 8, 367-382, 2002 **Ref Id** 96249 **Country/ies where the study was carried out** Kuwait **Study type** Prospective comparative observational study **Aim of the study** To compare the efficiency of laparoscopic treatment versus conventional abdominal surgery for tubal ectopic pregnancy and to review the clinical presentation, evaluate methods of diagnosis and identifying risk factors **Study dates** March 1999 to October 2001	**Characteristics** **Presenting symptoms (%)** Abdominal pain: 96 Short period of amenorrhea: 89 Vaginal bleeding: 79 **Age/years (mean SD))** Laparotomy: 28.5 (4.6) Laparoscopy: 27.6 (5.7) **Parity (mean (range))** Laparotomy: 2.02 (0-6) Laparoscopy: 2.04 (0-7) **Gestation at diagnosis/weeks (mean (SEM))** Laparotomy: 8.5 (1.8) Laparoscopy: 8 (1.7) **Presence of haemoperitoneum** Laparotomy: 13/23 (56.5) Laparoscopy: 108/184 (58.7) **Location of ectopic pregnancy (number/total (%))** Laparotomy: Ampullary: 22/23 (95.7) Cornual: 1/23 (4.3) Fimbrial: 0/23 (0)	(n=23) **Comparator** Laparoscopy (n=184)	Kuwait state: Hadi Hospital and El-Rashed Hospital. During the study period, there were 207 patients with confirmed ectopic pregnancy (145 at Hadi Hospital, 62 at El-Rashed Hospital). The patients were admitted through the emergency or outpatient department. Patients were managed by laparoscopy or laparotomy. The diagnosis of ectopic pregnancy was based on history, clinical symptoms, physical examination, a positive serum beta-hCG, and transvaginal ultrasound findings (empty uterus with or without adnexal mass). All patients had a diagnostic laparoscopy as the primary procedure to confirm the diagnosis and to evaluate the contra-lateral tube before deciding which surgical approach should be performed. The selection of operative approach was not based on any defined criteria, but depended on the availability of laparoscopic facilities and the surgical team. Once the ectopic pregnancy had been diagnosed laparoscopically, the choice of	Laparoscopy: 2/184 (1.1) Note: in one case it was not possible to achieve pneumoperitoneum due to extreme obesity, in the other case it was due to technical problems with the instruments. **Intraoperative blood loss/ml (mean (SD/SEM))** Laparotomy: 270.7 (138.4) Laparoscopy: 79.6 (96.7) p-value <0.0001 **Need for a blood transfusion (number/total (%))** Laparotomy: 6/23 (26.1)* Laparoscopy: 13/184 (7.1) P<0.01 (Note: they report that 6 patients required transfusion, but the % does not match; therefore it is unclear whether there was missing data) **Length of hospital stay/days (mean (SD))** Laparotomy: 5.25 (3.16) Laparoscopy: 2.14 (1.81) p<0.0001	laparotomy group followed up at 4 and 7 days, and the laproscopy group having follow-up appointments booked for 4-6 weeks later. **Inclusion/exclusion criteria** Poorly reported. **Small numbers in laparotomy group** Only 23 women received a laparotomy, in contrast to the 184 women that received a laparoscopy. **Skill of surgeons** The authors always performed the laparoscopies, whereas surgeons not trained in laparoscopy were those that performed the laparotomies. **Population** 40% of the EP were ruptured at the time of presentation, and over 50% of women had haemoperitoneum. **Other information** **Type of surgery (number/total (%))** Laparotomy: Linear salpingostomy: 19/23 (82.6)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	Laparoscopy: Ampullary: 177/184 (96.2) Cornual: 2/184 (1.1) Fimbrial: 5/184 (2.7) 40% of the ectopics were ruptured at the time of presentation. There was no significant difference between the sizes of EP between the two groups. There was also no significant difference between the proportion of participants with IUCD in situ, previous PID, previous ectopic pregnancy or previous laparotomy in each arm. There was no significant difference between preoperative levels of haemoglobin or hCG. **Inclusion criteria** Confirmed ectopic pregnancy **Exclusion criteria** Not reported		laparotomy or laparoscopy depended on the surgeon on call. Those not trained in operative laparoscopy proceeded to perform a laparotomy. All laparoscopic procedures were performed by the first author at Hadi Hospital and the second author at El-Rashed Hospital. Patients were counselled pre-operatively about the operative procedures, and the risks and complications of each procedure, as well as the need for follow-up. All operations were conducted under general anaesthesia with endotracheal intubation. After thorough evaluation, type of management was decided. The surgical procedure was performed and the surgical specimens were sent for histopathological examination; ectopic pregnancy was histologically confirmed in each specimen. **Laparotomy** Laparotomy was performed through a Pfannenstiel incision and standard surgical techniques (the authors report that the same laparoscopic techniques were applied). After surgery, all patients were followed up with hCG levels on	**Need for further surgery** The authors report that none of the 201 patients who had conservative surgery had persistent trophoblast after the surgery (excludes the 6 patients receiving a Salpingectomy). No further details are given.	Salpingectomy: 4/23 (17.4) Laparoscopy: Linear salpingostomy: 179/184 (97.3) Salpingectomy: 2/184 (1.1) Milking: 3/184 (1.6)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			day 4 and day 7, and then weekly until non-pregnant levels (<20 IU/l) were reached. Weekly clinical examinations and ultrasound scans were done if needed. **Laparoscopy** Laparoscopy was performed using three ports. Following establishment of pneumoperitoneum, a 10mm 00 laparoscope was introduced through an 11mm cannula in intra-umbilical incision. After confirmation of the diagnosis, and laparoscopic treatment was deemed possible, a 5mm puncture was made in the left and right lower quadrant using direct visualisation and transillumination to avoid the epigastric vessels with continuous high flow carbon dioxide insufflators. The procedure was visualised on a video monitor using a camera attached to the eyepiece of the telescope. Linear salpingostomy was performed by making a linear incision in the anti-mesenteric border of the affected tube, over the tubal swelling with point needle monopolar diathermy. The pregnancy was removed with forceps, and the		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			tube was irrigated with lactated Ringer's solution. Haemostasis was achieved with bipolar diathermy. The tubal incision was then left to heal by secondary intention. Laparoscopic total salpingostomy was performed by progressive coagulation and cutting of the mesosalpinx, starting with the fimbriated end and progressing to the proximal isthmic portion of the tube. There, it was separated from the uterus after biplar coagulation or loop-type ligation and cutting with scissors. Milking of the tube was done for patients with fimbrial ectopic pregnancy. The pregnancy was removed from the abdominal cavity via a 10mm port. Just prior to laparoscope withdrawal, the pneumoperitoneum was released and haemostasis was checked. The pelvis was irrigated with copious amounts of lactated Ringer's solution until all the blood clots were evacuated. Adhesions in the contralateral fallopian tube were freed, if present. ½ litre of Ringer's solution was left in the pelvis at the conclusion of the operation to prevent		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			adhesion formation. In the presence of haemoperitoneum, the amount of blood present was assessed by the difference between the amounts of fluid irrigated and the amounts evacuated. Post-operative management followed the normal practice in both departments. Analgesia was prescribed to the patients on demand. An outpatient follow-up appointment was arranged for 4-6 weeks after discharge from hospital. Clinical and surgical data were recorded in an investigative report form. Student's t-test, Chi square test and Fisher's exact test were used where appropriate. A p-value of <0.05 was considered significant.		

What is the effectiveness of salpingectomy compared with salpingotomy in improving outcomes in women with tubal ectopic pregnancy?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Tahseen,S., Wyldes,M., A comparative case-controlled study of laparoscopic vs laparotomy management of ectopic pregnancy: an evaluation of reproductive performance after radical vs conservative treatment of tubal ectopic pregnancy, Journal of Obstetrics and Gynaecology, 23, 189-190, 2003 **Ref Id** 69637 **Country/ies where the study was carried out** UK **Study type** Retrospective comparative observational study **Aim of the study** Not reported	**Sample size** N=150 **Characteristics** Not reported separately for salpingectomy and salpingotomy groups **Inclusion criteria** Ectopic pregnancy **Exclusion criteria** Not reported	**Interventions** Salpingectomy (n=97) Salpingotomy (n=25)	**Details** This is a retrospective study carried out in the East Birmingham Hospitals (Teaching) NHS Trust, UK. All patients operated on laparoscopically for EP during the study period were identified. A control group was selected randomly from those operated on by laparotomy. Hospital case notes were reviewed for details. An attempt was made to contact all patients regarding contraceptive use. Only one spontaneous IUP or EP was included per patient in the analysis. Subsequent fertility was analysed in relation to initial treatment method and the state of the contralateral tube.	**Results** Spontaneous intrauterine pregnancy rate (number/total (%)) Salpingectomy: 38/97 (39.2) Salpingotomy: 12/25 (48)	**Limitations** Retrospective Not reported whether women were trying to conceive Outcome of intrauterine pregnancy is not reported Unclear how fertility data was obtained Generally poor methodological reporting No baseline characteristics reported for salpingectomy vs. salpingotomy groups Unexplained missing data from 28/150 women Blinding of participants and/or those assessing outcomes is not reported. **Other information** Both laparotomies and laparoscopies were done. Follow-up was 32.7 months (SD 8.4) in the laparoscopy arm and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 1996 to 2000 **Source of funding** Not reported					34.6 months (SD 9.7) in the laparotomy arm. Averages are not reported for salpingectomy/salpingotomy groups.
Full citation Giambelli,E., Candiani,M., Natale,A., Gruft,L., De,MarinisS, Sambruni,I., Colombo,P., Busacca,M., Laparoscopic treatment of ectopic pregnancy: Analysis of 114 consecutive cases, Italian Journal of Gynaecology and Obstetrics, 8, 5-9, 1996 **Ref Id** 77300 **Country/ies where the study was carried out** Italy **Study type** Retrospective comparative observational study **Aim of the study**	**Sample size** N=114 **Characteristics** Age/years (average (range)): 32.3 (21 - 41) Gestational age/weeks (mean (range)) : 7.4 (6 - 13) <u>Site of ectopic pregnancy (number/total (%))</u> Ampullar: 100/114 (87.7) Isthmic: 10/114 (8.8) Cornual: 2/114 (1.8) Ovarian: 1/114 (0.9) Peritoneal: 1/114 (0.9) <u>Condition of tube, split by treatment type (number/total (%))</u> Unruptured: 103/114 (90.4) - Conservative: 55/103 (53.3) - Ablative: 48/103 (46.6)	**Interventions** Salpingectomy (n=59) Salpingotomy (n=55) (Note: these procedures are referred to as ablative surgery and conservative surgery in some parts of the paper)	**Details** During the study period, data was gathered from 114 consecutive patients undergoing laparoscopic surgery for ectopic pregnancy. Conservative treatment consisted of a simple, linear, longitudinal salpingotomy on the antimesenteric tubal margin by a thin diathermal tip. Enucleation of the trophoblastic tissue was performed by a suction-irrigation instrument. In some cases oxitocine had been previously injected into the tubal wall to help haemostasis and tissue asportation. No tubal suture was performed after ectopic pregnancy removal. Tissue was extracted from the abdominal cavity by an endoscopic bag. Laparoscopic salpingectomy was performed with bipolar	**Results** <u>Need for further intervention (number/total (%))</u> Salpingectomy: 0/59 (0) Salpingostomy: 4/55 (7.3) (Note: 3 received a single dose of methotrexate on days 7-10; 1 received a laparotomy on day 15. One further patient showed a very long period of slow decline of hCG but was monitored to resolution without need for a further intervention and therefore has not been included here). <u>Subsequent intrauterine pregnancy (%)</u> Salpingectomy: 62.5 Salpingostomy: 53.8 <u>Ectopic pregnancy (%)</u> Salpingectomy: 5.1 Salpingostomy: 7.8 It is unclear what the	**Limitations** Retrospective Unclear how fertility data was obtained 45% loss to follow-up for fertility outcomes (63/114 were followed up) The number of women receiving each type of surgery that desired future pregnancy is not reported, therefore denominators for future pregnancy rates cannot be calculated. Outcome of intrauterine pregnancies is not reported. Baseline characteristics not reported separately for salpingectomy/salpingostomy groups. Blinding of participants and/or those assessing outcomes is not reported. All ruptured ectopics received

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To analyse the efficacy of laparoscopy in the treatment of ectopic pregnancy. **Study dates** January 1993 to October 1995 **Source of funding** Not reported	Ruptured: 11/114 (9.6) - Conservative: 0/11 (0) - Ablative: 11/11 (100) <u>Contralateral tube condition, split by treatment type (number/total (%))</u> Normal: 84/114 - Conservative: 44/84 (52.4) - Ablative: 40/84 (47.6) Pathologic: 30/114 (26.3) - Conservative: 11/30 (36.7) - Ablative: 19/30 (63.3) **Inclusion criteria** Treatment for ectopic pregnancy by laparoscopy **Exclusion criteria** Not reported		forceps and scissors according to the standard technique, and the tube was extracted from the abdomen with an endoscopic bag. Both types of intervention were followed by accurate washing of the peritoneal cavity and asportation of blood clots to prevent trophoblastic persistence due to surgical dissemination. The patients were discharged 24-36 hours after laparoscopy. Serum hCG was measured before treatment, and it was used as one of the criteria for judging which mode of management to perform and its efficacy. Post-treatment blood samples were taken on dats 3, 7 and 14 to diagnose persistence of trophoblastic tissue. The criteria used to evaluate the treatment were clinical conditions, hCG absolute and serial values, ultrasound, the possible monitoring period, desire for future pregnancy and patient consensus. Acute abdominal pain required urgent surgical treatment using laparoscopy or laparotomy. hCG>3000 also indicated surgery. Values	denominators are for future pregnancies. However, a total of 22 women had an intrauterine pregnancy and 2 women had another ectopic pregnancy, out of a total of 37 women who were followed up and desired a further pregnancy.	radical surgery. **Other information** All patients received laparoscopy.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			<1500 led to request for further samples and ultrasound after 24-48 hours to exclude the possibility of intrauterine pregnancy. For other values, expectant, medical or surgical treatment was indicated based on the pattern of change. A counselling session was given to the patient to evaluate her openness to a period of serum hCG monitoring and expectant or medical management acceptability. The choice of salpingectomy or salpingostomy was decided based on tubal conditions, contralateral tubal conditions, patient's age, desire for future pregnancy and other obstetric and gynaecological history (sterility, previous ectopic, PID). All the patients were informed that both kinds of procedures were possible. Persistent ectopic pregnancy was defined as the growth or plateau value of serum hCG after treatment that requires further intervention. 63 patients were followed up for 6 months after surgery,		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			of which 37 desired pregnancy.		
Full citation Parker,J., Permezel,M., Thompson,D., Review of the management of ectopic pregnancy in a major teaching hospital: Laparoscopic surgical treatment and persistent ectopic pregnancy, Australian and New Zealand Journal of Obstetrics and Gynaecology, 34, 575-579, 1994 **Ref Id** 77505 **Country/ies where the study was carried out** Australia **Study type** Retrospective comparative observational study **Aim of the study** To determine the number of patients managed by different treatment methods and to determine the incidence of persistent	**Sample size** N=203 (This is the total number of cases of ectopic pregnancy treated during the study period; however 153 were treated by salpingectomy or salpingostomy, and therefore constitute the main population of interest for this review) **Characteristics** <u>Type of treatment given (number/total)</u> <u>Laparoscopy</u> - Salpingectomy: 52/203 - Salpingostomy: 47/203 - Fimbrial expression: 4/203 - Fimbriectomy: 1/203 - Removal of tubal abortion: 4/203 - Excision peritoneal ectopic: 1/203 - Ectopic pregnancy not seen: 3/203 - Injection with methotrexate: 2/203 <u>Laparotomy</u> - Salpingectomy: 51/203 - Salpingostomy: 3/203	**Interventions** Salpingectomy (n=103) Salpingostomy (n=50)	**Details** This study was a retrospective analysis of 203 consecutive cases of ectopic pregnancy treated at the Royal Women's Hospital during the study period. 114 of these women had a laparoscopic surgical procedure. In a further 10 patients an initial laparoscopic treatment was abandoned and a laparotomy was performed due to inadequate access (adhesions, obesity), technical problems, or uncontrolled haemorrhage. The remainder of the surgically treated patients had a laparotomy, and a further 30 women received methotrexate (n=6) or expectant management (n=24). Serum beta-hCG was determined by 2 assays during the study period. An immunoradiometrc system was used from June to November 1992, and after that, a 2-site chemiluminometric immunoassay was used.	**Results** <u>Need for further intervention (number/total (%))</u> Salpingectomy: 1/103 (1.0) (Note: treated with methotrexate IMI) Salpingostomy: 6/50 (12) (Note: treated with methotrexate IMI (n=2), laparoscopic salpingectomy (n=2), laparoscopic fimbriectomy (n=1), and laparoscopic resection (n=1). A further 2 women received expectant management, however they have not been included here) Note: all cases of persistent ectopic pregnancy occurred following laparoscopic treatment.	**Limitations** Retrospective Characteristics of women at baseline are not reported - there could have been unreported differences between the arms. Unclear what drove the choice of procedure. Blinding of participants and/or those assessing outcomes is not reported. Details of surgical procedures not reported. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
ectopic pregnancy (PEP) following laparoscopic surgical treatment. **Study dates** June 1st 1992 to August 31st 1993 **Source of funding** Not reported	- Fimbrial expression: 2/203 - Removal of tubal abortion: 1/203 - Resection of ovary: 2/203 <u>Medical treatment</u> - Methotrexate orally: 3/203 - Methotrexate intramuscular injection (IMI): 3/203 <u>Expectant management:</u> 24/203 **Inclusion criteria** Treated for ectopic pregnancy **Exclusion criteria** Not reported				
Full citation Silva,P.D., Schaper,A.M., Rooney,B., Reproductive outcome after 143 laparoscopic procedures for ectopic pregnancy, Obstetrics and Gynecology, 81, 710-715, 1993 **Ref Id** 77584 **Country/ies where the**	**Sample size** N=143 (However, the true population of interest for this review question is N=86, which is the number of women attempting to conceive following a salpingectomy or salpingostomy) **Characteristics** <u>Type of operation (number/total (%))</u>	**Interventions** Salpingectomy (n=26) Salpingostomy (n=60)	**Details** A prospective database containing demographic data, clinical variables, and reproductive outcome was maintained on 143 women who had laparoscopic treatment for ectopic pregnancy during the study period. The setting for the study was a rural tertiary centre staffed by a 260-physician multispeciality group, and the tendency to sub-specialisation led to the treatment of about 90% of	**Results** <u>Subsequent intrauterine pregnancy (number/total (%))</u> <u>a. Any intrauterine pregnancy</u> Salpingectomy: 14/26 (53.8) Salpingostomy: 36/60 (60) <u>b. Live birth</u> Salpingectomy: 10/26 (38.5) Salpingostomy: 19/60 (31.7) <u>Repeat ectopic pregnancy</u>	**Limitations** Lack of intention-to-treat: patients who underwent laparoscopic salpingectomy for persistent ectopic were followed in the salpingectomy category. Blinding of participants and/or those assessing outcomes is not reported. Length of follow-up not reported. Apart from one, every case of ruptured ectopic was managed with a salpingectomy (not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out USA **Study type** Prospective comparative observational study **Aim of the study** To analyse reproductive outcome after laparoscopic procedures for ectopic pregnancy, with particular attention to laparoscopic salpingectomy **Study dates** August 1987 to August 1991 **Source of funding** Gundersen Medical Foundation	a. All ectopic pregnancies (N=143) Salpingostomy: 80/143 (55.9) Salpingectomy: 52/143 (36.4) Partial salpingectomy: 3/143 (2.1) Removal of fimbrial abortion: 5/143 (3.5) Removal of abdominal implantation: 2/143 (1.4) Salpingo-oophorectomy: 1/143 (0.7) b. Women who had or were trying to conceive (n=95) Salpingostomy: 60/95 (63.2) Salpingectomy: 26/95 (27.4) Partial salpingectomy: 2/95 (2.1) Removal of fimbrial abortion: 4/95 (4.2) Removal of abdominal implantation: 2/95 (2.1) Salpingo-oophorectomy:1/95 (1.1) Characteristics of those who had a baby or were trying to conceive a. Age/years (mean (SD) Salpingectomy: 29.3 (5.3) Salpingostomy: 28.6 (4.6) (p=0.552) b. Parity (mean (SD))		the ectopic pregnancies on one authors service. Reproductive outcome for those patients attempting pregnancy was reviewed periodically by telephone interview, letter or chart review. Laparoscopy salpingostomy used fine unipolar electrocoagulation and vasopressin. Salpingectomy used bipolar electrocoagulation and scissors. During the study period, the appearance of the opposite tube did not influence the choice of surgery type. Contralateral adhesions were lysed, but contralateral cuff salpingostomy was not performed for tubal occlusion. Patients treated with conservative procedures were followed up with weekly postoperative hCG titres to screen for persistent viable trophoblastic tissue. Salpingectomy or partial salpingectomy was performed in all cases of ruptured ectopic pregnancy, except for one patient with a small rupture site. The reproductive outcomes	(number/total (%)) Salpingectomy: 2/26 (7.7) Salpingostomy: 11/60 (18.3) Need for further intervention It is reported that 8 women that were "conservatively treated" needed further intervention (5 surgeries and 3 MTX). However, conservative surgery is not defined in the paper (therefore unclear which women would constitute the population), and no denominator is given. This outcome also has not been reported for the other "radical" arm, who were not followed up in the same way. Due to lack of information, this outcome will not be reported in the GRADE table.	reported what % of the ectopics were ruptured). Ectopics treated by salpingectomy were also significantly larger than those treated with salpingostomy. **Other information** 2 women were lost to follow-up from the women attempting conception who received a salpingostomy or salpingectomy (1 from each arm). There were significantly higher rates of any tubal damage, and damage due to adhesive disease, in the women who did not become pregnant when compared to those who did become pregnant (intrauterine pregnancies only) All women for whom reproductive outcome was assessed received a laparoscopy.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Salpingectomy: 1.04 (1.04) Salpingostomy: 0.63 (0.78) (p=0.049) c. Diameter of swelling/cm (mean (SD)) Salpingectomy: 4.0 (1.6) Salpingostomy: 2.9 (1.1) (p=0.001) d. Tubal damage (n (%) - Any Salpingectomy: 15 (57.7) Salpingostomy: 33 (55.0) (p=0.817) - Adhesive disease Salpingectomy: 15 (57.7) Salpingostomy: 29 (48.3) (p=0.425) - Previous ectopic pregnancy Salpingectomy: 1 (3.9) Salpingostomy: 5 (8.3) (p=0.453) - Tuboplasty Salpingectomy: 3 (11.5) Salpingostomy: 14 (23.3) (p=0.207) **Inclusion criteria**		of women treated by laparoscopic salpingostomy and laparoscopic salpingectomy were analysed for rates of intrauterine pregnancies, live births, miscarriages, elective abortions, and repeat ectopic pregnancies. Life table analysis was performed for intrauterine pregnancy rates. Patients who underwent laparoscopic salpingectomy for persistent ectopic were followed in the salpingectomy category. Reproductive outcome was analysed using the variables of age, parity, diameter of gestation site, evidence of prior tubal damage (i.e. contralateral adhesive disease, history of tuboplasty, or previous ectopic pregnancy), and length of follow-up. Three women treated by laparotomy were not included in the analysis of reproductive outcome (one had a ruptured intersitial pregnancy, one presented with hypovolemic shock, and one had a concomitant pelvic neoplasm). One patient with concomitant hyperstimulation was treated with methotrexate and not included, and neither were patients treated		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Receiving laparoscopic treatment for ectopic pregnancy from one of the authors **Exclusion criteria** Not directly reported, however in the analysis of reproductive outcomes, any women receiving management other than salpingectomy or salpingostomy were not included.		with removal of abdominal pregnancies, irrigation of fimbrial abortion, and partial salpingectomy. Analysis Univariate analyses of pregnancy rates by type of procedure, age, parity, size of EP, and evidence of prior tubal damage was done. Multivariate analysis was done using a backwards stepped regression.		
Full citation Tulandi,T., Guralnick,M., Treatment of tubal ectopic pregnancy by salpingotomy with or without tubal suturing and salpingectomy.[Erratum appears in Fertil Steril 1991 Jun;55(6):1213-4], Fertility and Sterility, 55, 53-55, 1991 **Ref Id** 77644 **Country/ies where the study was carried out** Canada **Study type**	**Sample size** N=58 **Characteristics** Age/years (mean (SD)) Salpingotomy without suturing: 30.3 (0.9) Salpingotomy with suturing: 31.5 (0.8) Salpingectomy: 30.5 (0.9) Gestational age/weeks (mean (SD)) Salpingotomy without suturing: 6.3 (0.3) Salpingotomy with suturing: 6.4 (0.2) Salpingectomy: 6.8 (0.2)	**Interventions** Salpingectomy (n=24) Salpingotomy (with or without tubal suturing) (n=34)	**Details** 34 women found to have an unruptured ampullary ectopic at laparotomy were randomly assigned to undergo salpingotomy without tubal suturing (n=15) or with tubal suturing (n=19). All operations were performed by the first author. The procedure was done by first injecting a solution of diluted vasopressin into the adjacent mesosalpinx and into the wall of the tube on the antemesosalpinx side of the dilated tube. A 10 - 15 mm longitudinal incision along the area of maximal distension of the tube was	**Results** Cumulative probability of intrauterine pregnancy (%) a. At 12 months Salpingectomy: 21 Salpingotomy: 32* b. At 24 months Salpingectomy: 26 Salpingotomy: 47* * calculated by the technical team by combining the data for participants who received salpingotomy with and without suturing. Cumulative probability of ectopic pregnancy (%)	**Limitations** Retrospective Method of selection of controls not reported Unclear whether participants were attempting to get pregnant Method of follow-up not reported. Their cumulative probabilities do not completely match the denominator, therefore it is likely that women have been lost to follow-up and not reported. No raw values reported. Blinding of participants and/or those assessing outcomes is not reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised controlled trial comparing salpingotomy with and without suturing, comparing them with historical controls undergoing salpingectomy. Therefore, for the purposes of this review question, it is a retrospective comparative observational study **Aim of the study** To compare reproductive performance of women after conservative treatment of ectopic pregnancy by salpingotomy with or without tubal suturing, and then to compare results with those after salpingectomy. **Study dates** Not reported **Source of funding** Not reported	Size of pregnancy/cm (range): 2 - 3 **Inclusion criteria** Unruptured ampullary ectopic pregnancy diagnosed at laparotomy **Exclusion criteria** Recurrent tubal pregnancy Ruptured tube Solitary tube		then made with the use of an insulated microdiathermy needle, and the product of conception was gently removed. Haemostasis was achieved by light application of microdiathermy needle and by ligating the vessels in the misosalpinx with 6-0 Vicryl. The tubal incision was either left open to heal by secondary intention, or approximated with 2 to 3 interrupted sutures of 6-0 Vicryl. During the procedure, peritoneal surfaces were continuously irrigated with Ringer's lactate solution. No patients received antibiotics, corticosteroids, antihistamines, or dextran. The reproductive outcome of these patients was then compared with 24 patients who underwent salpingectomy for their unruptured ampullary ectopic pregnancy. The data were analysed by the Student's t-test, ANOVA and life-table analysis.	a. At 12 months Salpingectomy: 0 Salpingotomy: 24* b. At 24 months Salpingectomy: 13 Salpingotomy: 31* * calculated by the technical team by combining the data for participants who received salpingotomy with and without suturing. All data for EP was calculated from a graph	Study dates not reported **Other information** All participants received laparotomy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mol,B.W.J., Hajenius,P.J., Engelsbel,S., Ankum,W.M., Van,derVeenF, Hemrika,D.J., Bossuyt,P.M.M., An economic evaluation of laparoscopy and open surgery in the treatment of tubal pregnancy, Acta Obstetricia et Gynecologica Scandinavica, 76, 596-600, 1997 **Ref Id** 77878 **Country/ies where the study was carried out** The Netherlands **Study type** Prospective observational study (Note: some data was collected retrospectively) **Aim of the study** To assess the impact of the introduction of laparoscopy in the	**Sample size** N=255 **Characteristics** <u>Type of surgery performed (number/total (%))</u> Radical open surgery: 118/255 (46.3) Radical laparoscopy: 39/255 (15.3) Conservative open surgery: 22/255 (8.6) Conservative laparoscopy: 76/255 (29.8) <u>Gestational age/days (mean (SD))</u> Radical open surgery: 51.8 (14.3) Radical laparoscopy: 51.1 (11.2) Conservative open surgery: 48 (9.8) Conservative laparoscopy: 48.7 (10.2) (p=0.89) <u>Presence of peritubal adhesions (number/total (%))</u> Radical open surgery: 39/118 (33.1) Radical laparoscopy: 19/39 (48.7) Conservative open surgery:	**Interventions** Radical surgery (n=157) Conservative surgery (n=98)	**Details** All patients who underwent primary surgical treatment for tubal pregnancy in the Academic Medical Center (January 1992 to December 1995) and the Onze Lieve Vrouwe Gasthuis (September 1993 to December 1995) in Amsterdam were included. Data on patients operated on prior to September 1993 was collected retrospectively; the remainder was collected prospectively. 287 patients were initially included, but 16 were excluded due to shock, 3 due to heterotopic pregnancy, and 13 due to insufficient data. Therefore, the study population was 255 patients. The diagnosis of tubal pregnancy resulted from transvaginal ultrasounds and serum hCG monitoring, with confirmation at either laparoscopy or open surgery. Four groups of patients could be distinguished: radical surgery performed by open surgery, radical surgery performed by laparoscopy, conservative surgery performed by open surgery,	**Results** <u>Need for further intervention (number of women/total (%))</u> <u>a. Overall</u> Radical: 1/157 (0.6) Conservative: 18/98 (18.4) <u>b. In those undergoing open surgery</u> Radical: 0/118 (0) Conservative: 1/22 (4.5) <u>c. In those undergoing laparoscopy</u> Radical: 1/39 (2.6) Conservative: 17/76 (22.4) (Note: 17 women received systemic MTX on an outpatient basis, 1 patient had a salpingectomy and 1 was managed expectantly. 1 woman required a second reintervention, in the form of radical open surgery, after MTX treatment failure) <u>Need for a blood transfusion (number of women/total (%))</u> <u>a. Overall</u> Radical: 10/157 (6.4) Conservative: 1/98 (1.0)	**Limitations** Part of the study data was collected retrospectively. Tubal rupture was significantly more common in those undergoing radical surgery, when compared to those undergoing conservative surgery. Radical and conservative surgery are not defined. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treatment of ectopic pregnancy on medical costs **Study dates** January 1992 to December 1995 **Source of funding** Dutch Health Insurance Council, Amstelveen	4/22 (18.2) Conservative laparoscopy: 2/76 (2.6) (p=0.17) <u>Tubal rupture (number/total (%))</u> Radical open surgery: 40/118 (33.9) Radical laparoscopy: 6/39 (15.4) Conservative open surgery: 2/22 (9.1) Conservative laparoscopy: 2/76 (2.6) (p<0.01) **Inclusion criteria** Undergoing primary surgical treatment for tubal pregnancy **Exclusion criteria** Shock Heterotopic pregnancy Insufficient data		and conservative surgery performed by laparoscopy. The choice of treatment depended on the clinical situation and the skills of the operating gynaecologist. Persistent trophoblast was defined as rising or plateauing postoperative serum hCG concentrations. This complication was treated by systemic administration of methotrexate (MTX) or by surgery, depending on the clinical situation of the patient. Costs for each procedure were calculated from the resource use recorded, and an economic analysis was performed. (Note: only outcomes relevant to this review will be recorded here). Outcomes will be reported for the overall comparison between conservative and radical surgery, and then stratified by whether the surgery was laparoscopic or open.	<u>b. In those undergoing open surgery</u> Radical: 9/118 (7.6) Conservative: 1/22 (4.5) <u>c. In those undergoing laparoscopy</u> Radical: 1/39 (2.6) Conservative: 0/76 (0) <u>Complication rate (number of women/total (%))</u> (Note: these were all in patients treated with open surgery) Radical: 2/157 (1.3) (1 case of pneumonia, 1 urinary tract infection) Conservative: 3/98 (3.1) (1 case of pneumonia, 1 urinary tract infection, 1 thrombo-embolism)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Colacurci,N., Zarcone,R., De,Franciscis P., Mele,D., Mollo,A., de,Placido G., Tubal patency after laparoscopic treatment of ectopic pregnancy, Panminerva Medica, 40, 45-47, 1998 **Ref Id** 91107 **Country/ies where the study was carried out** Italy **Study type** Retrospective comparative observational study **Aim of the study** To evaluate the operative course, tubal patency, and reproductive performance after laparoscopic treatment of ectopic pregnancy in relation to initial human chorionic gonadotrophin values and to the kind of operation. **Study dates**	**Sample size** N=45 **Characteristics** Age/years (mean) Salpingectomy: 24.5 Salpingotomy: 29.2 Gestational age/weeks (mean) Salpingectomy: 8.5 Salpingotomy: 8.0 Gestation sac diameter/cm (mean) Salpingectomy: 2.93 Salpingotomy: 3.3 (Note: the study was divided into three treatment groups, with the salpingotomy group split in to 2 by hCG > or < 10,000. These have been combined for the purposes of this review)	**Interventions** Salpingectomy (n=13) Salpingotomy (n=32)	**Details** The authors retrospectively analysed the operative course, clinical outcome and reproductive performance of 45 women with ectopic pregnancy. 32 were managed by linear salpingotomy performed on the anti-mesenteric border of the tube in the point of maximum bulge. The product of conception was flushed out of the incision using a pressurised flow from the aquadissector. The remaining 13 women underwent laparoscopic salpingectomy. The authors only analysed the patients who showed a normal pelvis and normal contralateral tube at the time of intraoperative examination. The operative time and the major complications were recorded. Hysterosalpingographic examination was performed 2-3 months after the operation, and the analysis of reproductive outcome only includes the patients with bilateral patent tubes (from the salpingotomy	**Results** Need for a blood transfusion (number/total (%)) Salpingectomy: 0/13 (0) Salpingotomy: 1/32 (3.1) Subsequent intrauterine pregnancy (number of women/total (%)) Salpingectomy: 2/11 (18.2) Salpingotomy: 10/26 (38.5) Repeat ectopic pregnancy (number of women/total (%)) Salpingectomy: 1/11 (9.1) Salpingotomy: 1/26 (3.8)	**Limitations** Retrospective Small sample size (N<50) Unclear how these patients were identified and selected Not reported whether patients were trying to conceive Length and method of follow-up is not reported Outcome of intrauterine pregnancies is not reported Blinding of those assessing outcomes is not reported No details of the salpingectomy surgical technique are given (and very little about the salpingotomy) Analysis of reproductive outcome only includes women with bilateral patent tubes from the salpingotomy arm. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported **Source of funding** Not reported	**Inclusion criteria** Ectopic pregnancy **Exclusion criteria** Not reported		arm). Statistical analysis was performed using the student's t-test, Fisher's exact test, or chi-squared as appropriate.		
Full citation Bouyer,J., Job-Spira,N., Pouly,J.L., Coste,J., Germain,E., Fernandez,H., Fertility following radical, conservative-surgical or medical treatment for tubal pregnancy: A population-based study, British Journal of Obstetrics and Gynaecology, 107, 714-721, 2000 **Ref Id** 118736 **Country/ies where the study was carried out** France **Study type** Population based study **Aim of the study** To investigate the factors	**Sample size** N=476 (Note: 36 women received medical treatment and their outcomes will not be reported here, therefore the study population of interest for this review question is N=440) **Characteristics** <u>Age/years (%)</u> <u>Radical:</u> < 25: 12 25 - 29: 24 30 - 34: 31 ≥ 35: 32 <u>Conservative:</u> < 25: 20 25 - 29: 35 30 - 34: 27 ≥ 35: 18 <u>History of infertility (%)</u> Radical: 38 Conservative: 23	**Interventions** Radical (salpingectomy) (n=178, of which 100 sought to become pregnant again) Conservative (salpingotomy) (n=262, of which 166 sought to become pregnant again)	**Details** This study is based on the Auvergne Ectopic Pregnancy Register. All women meeting the inclusion criteria were registered and prospectively followed until the age of 45 years old, to study their reproductive outcome. The completeness of the register is estimated to be 90%. In each centre, a trained investigator was in charge of case identification, follow up and data collection. The basic information collected for each woman included: sociodemographic characteristics, sexual, gynaecological, reproductive and surgical histories, conditions of conception, smoking habits, results of Chlamydia tests, characteristics of the ectopic pregnancy, and treatment procedures used.	**Results** <u>Need for further intervention (number/total (%))</u> Radical: 1/178 (0.6) (Note: repeat radical surgery) Conservative: 14/262 (5.3) (Note: 2 radical, 12 repeat conservative surgery) <u>Repeat ectopic pregnancy rate (number/total (%))</u> Radical: 10/100 (10) Conservative: 17/166 (10.2) <u>18-month cumulative rate of spontaneous intrauterine pregnancy (% (95% CI))</u> Radical: 57 (44 to 70) Conservative: 73 (65 to 80) Hazard ratio (95% CI) 0.56 (0.39 to 0.81) <u>Adjusted hazard ratios for</u>	**Limitations** Significant differences between tubal rupture, previous ectopic pregnancy and history of infertility between the groups at baseline Women underwent both laparotomy and laparoscopy, and outcomes are not reported separately Outcome of intrauterine pregnancies is not reported. Blinding of participants and/or those assessing outcomes is not reported. 9.7% of women were lost to follow-up for the fertility outcomes. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
influencing the choice of treatment for ectopic pregnancy and to compare the subsequent fertility rates of radical, conservative-surgical, or medical treatments. **Study dates** 1992 to 1996 **Source of funding** Not reported	(p=0.004) Previous miscarriage (%) Radical: 30 Conservative: 27 (p=0.57) Previous induced abortion (%) Radical: 17 Conservative: 18 (p=0.97) Previous ectopic pregnancy (%) Radical: 16 Conservative: 6 (p=0.001) Induced pregnancy (%) Radical: 9 Conservative: 6 (p=0.32) Abundant haemoperitoneum (%) Radical: 47 Conservative: 18 (p=0.001) Tubal rupture (%) Radical: 37 Conservative: 6 (p=0.001)		For every case, the women were interviewed by telephone every six months about whether they were trying to conceive again, whether they had become pregnant again, how long it took to become pregnant, obstetric outcome, time at risk of becoming pregnant, use of contraception, and medical measures related to infertility. During the study period, 835 women were registered, of which 476 women met the criteria for inclusion/exclusion. Of these, 46 (9.7%) were lost to follow-up. Subsequent fertility was therefore studied for the 291 women who attempted to conceive again at least once during the study period. Treatments were designated as 'radical' (salpingectomy), 'conservative surgical' (salpingotomy), and 'medical' (methotrexate injection) (details of women receiving medical management will not be reported here, as they are not relevant to this review question). The surgeries were performed by laparotomy or laparoscopy.	intrauterine pregnancies (95% CI) a. All women Radical: 0.72 (0.45 to 1.1) Conservative: 1 (NS) b. Women with infertility factors, previous EP, infertility/tubal surgery history, induced pregnancy, or age ≥ 35 (n=173) Radical: 0.60 (0.36 to 1.0) Conservative: 1 (NS) c. Women with no infertility factors and aged < 35 (n=118) Radical: 0.85 (0.45 to 1.6) Conservative: 1 (NS) Note: adjustments have been made for age, university educated, history of infertility, induced pregnancy, tubal rupture, normal contralateral tube, nationality (French or not) and size/type of centre.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Normal contralateral tube (%) Radical: 19 Conservative: 26 (p=0.16) **Inclusion criteria** Women aged 15 to 44 Reside permanently in Auvergne Region, France Treated either medically or surgically for ectopic pregnancy in one of the area's health centres Tubal ectopic pregnancy **Exclusion criteria** Use of contraception at the time of index ectopic pregnancy Previously undergone sterilisation or therapeutic bilateral salpingectomy (with no desire for IVF)		In some women, the initial treatment was unsuccessful, and they received another treatment. However, all analyses are performed considering only the initial treatment. Conservative surgical treatment was taken as the reference, as it is used most frequently, and considered to be the standard treatment for EP. Analysis Two reproductive outcomes were evaluated: recurrence of EP, and occurrence of spontaneous intrauterine pregnancy. Survival analysis methods were used, considering the time to pregnancy as the cumulative period during which the woman was trying to conceive until she became pregnant or was censored. Follow-up was censored if a woman began IVF. Cumulative pregnancy rates were calculated using Kaplan-Meier estimates. The curves obtained were analysed using both univariate and Cox regression analyses (to take into account confounding variables). The confounders considered were: age, educational level, nationality		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			(French origin or not), prior tubal damage, state of contralateral tube, history of infertility,and tubal rupture. The authors also evaluated the size of the treatment centre and whether it was private, public, maternity or surgical. Whether the surgery was laparotomy or laparoscopy was not taken into account, as this is not associated with future fertility. For the outcome of spontaneous intrauterine pregnancy, the whole sample was analysed. In addition, a subgroup without infertility factors, with no infertility, no history of tubal surgery, and aged younger than 35 were analysed. The authors report that this was done because this group of women would be the main target if a randomised controlled trial was designed.		
Full citation Bangsgaard,N., Lund,C.O., Ottesen,B., Nilas,L., Improved fertility following conservative surgical treatment of ectopic pregnancy, BJOG: An International Journal of	**Sample size** N=276 **Characteristics** **Age/years (mean (SD))**	**Interventions** Salpingectomy (n=68) Tubotomy (n=208) (Note: these	**Details** **Data collection** Between January 1992 and January 1999, 806 surgical interventions for ectopic pregnancy (EP) were performed at the	**Results** **Need for further intervention (n)** Salpingectomy: NR Tubotomy: 17 (Note: it is unclear whether the denominator is the 208	**Limitations** Retrospective study Variable length of follow-up, because the questionnaires were all mailed at one time. 25% of women were lost to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Obstetrics and Gynaecology, 110, 765-770, 2003 **Ref Id** 121838 **Country/ies where the study was carried out** Denmark **Study type** Retrospective cohort study **Aim of the study** To evaluate fertility after salpingectomy or tubotomy for ectopic pregnancy **Study dates** Surgeries conducted between January 1992 and January 1999 Follow-up was in June 2000 **Source of funding** Not reported	Salpingectomy: 30.1 (4.45) Tubotomy: 29.0 (3.97) (p = 0.06) **Nulliparity (number/total (%))** Salpingectomy: 33/68 (49) Tubotomy: 131/208 (63) (p < 0.05) **History of induced abortion (number/total (%))** Salpingectomy: 21/61 (38) Tubotomy: 58/208 (28) **History of miscarriage (number/total (%))** Salpingectomy: 13/68 (19) Tubotomy: 58/208 (28) **History of abdominopelvic surgery (number/total (%))** Salpingectomy: 9/68 (13) Tubotomy: 23/208 (11) **History of fertility surgery (number/total (%))** Salpingectomy: 7/68 (10) Tubotomy: 16/208 (8) **Peri-operative adhesion (number/total (%))** Salpingectomy: 30/68 (44) Tubotomy: 64/208 (31)	procedures are also referred to as "radical" and "conservative" surgery at some points in the paper)	Department of Obstetrics and Gynaecology, Hvidovre University Hospital, Denmark. The following data was obtained retrospectively from medical files: baseline demographic data, location of EP, ruptured tube, operation method, presence of adhesions, condition of contralateral salpinx, and surgical history. Subsequent fertility was elucidated using a mailed questionnaire. Questions included: desire for pregnancy, treatment for infertility, and pregnancy achieved after operation. The outcome of the pregnancy was reported as live birth, miscarriage, induced abortion or ectopic pregnancy. For those giving birth, the last menstrual date was calculated assuming delivery at 40 weeks gestation. For miscarriage or elective abortion, an average gestational age of 8 weeks was used for calculation of last menstrual date. The questionnaire was mailed in June 2000, which resulted in at least 18 months follow-up for all women.	women followed up who were attempting to conceive, or the whole study population. 9 were initially treated with MTX, of which 7 were successful and 2 had a salpingectomy, 7 initially had a salpingectomy, and 1 had a repeat salpingotomy) **Spontaneous intrauterine pregnancy rate (number/total (%))** a. Full-term birth Salpingectomy: 21/68 (30.9) Tubotomy: 88/208 (42.3) b. Any spontaneous intrauterine pregnancy Salpingectomy: 39/68 (57.4) Tubotomy: 161/208 (77.4) (Note: The outcomes were as follows: Salpingectomy: 21 full-term births, 9 miscarriages, and 1 induced abortion Tubotomy: 88 full-term birth, 36 miscarriages, 5 induced abortions, and 4 continuing pregnancies) **Repeat ectopic pregnancy rate (number/total (%))** Salpingectomy: 8/68 (11.8)	follow-up for fertility outcomes, because they did not return their questionnaires. A further 31 women had emigrated or died and were therefore uncontactable. If they are included in the loss to follow-up calculation, the loss to follow-up is 30%. There were some significant differences between the two groups at baseline (although some of these were adjusted for in the multivariate analysis). Both laparotomies and laparoscopies were performed. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(p < 0.05) **Peri-operative contralateral pathology (number/total (%))** Salpingectomy: 17/68 (25) Tubotomy: 30/208 (14) (p < 0.05) **Rupture (number/total (%))** Salpingectomy: 19/68 (28) Tubotomy: 7/208 (3) (p < 0.001) **IUCD in situ (number/total (%))** Salpingectomy: 4/68 (6) Tubotomy: 10/208 (5) **Type of surgery** **- Laparoscopy** Salpingectomy: 52/68 (76) Tubotomy: 193/208 (93) **- Laparotomy** Salpingectomy: 16/68 (23) Tubotomy: 15/208 (7) **Inclusion criteria** First, spontaneous, histologically verified tubal ectopic pregnancy Treated with salpingectomy		**Study population** Of the 651 women who underwent surgery for their first EP during that time, 46 did not meet the age criteria, 11 had previously been sterilised, 28 had other types of surgery, and 48 were not histologically verified. In 39 cases, the EP was as a result of fertility treatment, and 31 women were not available for follow-up (death/emigration). Therefore, 473 women satisfied selection criteria and were sent a questionnaire. 355 (75%) women returned the questionnaire, and of these, 79 had not attempted conception. Therefore, 276 women were included in the analysis. The characteristics of the 118 women lost to follow-up did not differ significantly from those available for analysis with respect to surgical intervention. **Analysis** The women were divided into two groups based on whether they had received radical surgery (salpingectomy) or conservative surgery	Tubotomy: 28/208 (13.5) **Hazard ratio for the occurrence of spontaneous intrauterine pregnancy (95% CI)** **- Univariate analysis:** Salpingectomy: 0.582 (0.393 to 0.861) Tubotomy: 1 **- Multivariate analysis:** Salpingectomy: 0.630 (0.421 to 0.940) Tubotomy: 1 **Hazard ratio for the occurrence of repeat ectopic pregnancy (95% CI)** **- Univariate analysis:** Salpingectomy: 0.785 (0.358 to 1.724) Tubotomy: 1 **- Multivariate analysis:** Salpingectomy: 0.782 (0.348 to 1.755) Tubotomy: 1 (Note: the multivariate analysis is adjusted for age, contralateral tube pathology and previous fertility operation)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	or linear tubotomy Aged 17 to 38 years old Actively attempting to conceive post-operatively **Exclusion criteria** Previously sterilised Bilateral salpingectomy		(tubotomy). Cumulative probabilities of spontaneous intrauterine pregnancy over time were calculated using the Kaplan-Meier estimator. The starting point for the calculations was the date of the operation. The endpoint was the date of accomplished spontaneous intrauterine pregnancy. If pregnancy was obtained through infertility treatment (28 in conservative group, 12 in radical group), the woman was censored from the analysis on the date the treatment began. The endpoint for women who did not become pregnancy was the last date of contact. Cumulative probabilities of repeated ectopic pregnancy were calculated in the same way. Cox proportional hazard regression analysis was used to compare the effect of conservative surgery with radical surgery, and to take into account potential confounding factors through multivariate analysis. The covariate factors were tested for time consistency, log linearity, and additivity before the analysis was performed. Potential confounders adjusted for in		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			the multivariate analysis were: age, contralateral tube pathology and previous fertility surgery.		
Full citation Becker,S., Solomayer,E., Hornung,R., Kurek,R., Banys,M., Aydeniz,B., Franz,H., Wallwiener,D., Fehm,T., Optimal treatment for patients with ectopic pregnancies and a history of fertility-reducing factors, Archives of Gynecology and Obstetrics, 283, 41-45, 2011 **Ref Id** 121843 **Country/ies where the study was carried out** Germany **Study type** Prospective follow-up study **Aim of the study** To evaluate the reproductive outcome after salpingotomy when compared with	**Sample size** N=261 (However, only 196 patients desired a new pregnancy and therefore constitute the main population of interest for this review question) **Characteristics** The following data is reported for the total population who were available for follow-up (N=261), and for those with a desire for pregnancy (n=196). **Age/years (median (range))** Total: 31 (19 - 43) Desiring pregnancy: 30 (19 - 42) **Nulliparity (number/total (%))** Total: 126/261 (48) Desiring pregnancy: 109/196 (56) **Presence of fertility-reducing risk factors (number/total (%))**	**Interventions** Salpingectomy (n=51) Salpingotomy (n=145)	**Details** 261 patients presenting with a subsequently confirmed ectopic pregnancy underwent routine surgical treatment. Treatment included a diagnostic laparoscopy, followed by either a laparoscopic salpingectomy, or a laparoscopic linear salpingotomy with tubal conserving removal of the EP. The decision of which surgical approach to take was left to the surgeon (done intraoperatively), and was based on the individual situation. The authors report that a large EP or ruptured EP made a salpingectomy more likely; however the decision was also based on consideration of the factors such as peritubal adhesions. Patients were recruited for prospective follow-up, following informed consent about the nature of the study. Basic information about each patient was	**Results** **Need for further intervention (number/total (%))** **Salpingectomy:** NR **Salpingotomy:** 9/183 (4.9) (Note: 4 salpingectomy, 4 treatment with MTX, 1 repeat salpingotomy) **Subsequent intrauterine pregnancy (number/total (%))** **Salpingectomy:** 25/51 (49.0) **Salpingotomy:** 122/145 (84.1) (p<0.01) (Note: there is some inconsistency in reporting, but this appears to be any IUP because the paper states that 129 women reported at least one successful delivery) **Repeat ectopic pregnancy (number/total (%))** **Salpingectomy:** 7/51 (13.7) **Salpingotomy:** 11/145 (7.6) (p=0.2)	**Limitations** Intention-to-treat analysis was not done. The 4 patients who underwent a subsequent salpingectomy for persistent ectopic pregnancy were included in the salpingectomy group. Those who underwent methotrexate treatment (n=4) or repeat salpingotomy (n=1) were included in the salpingotomy group. Baseline characteristic data is not reported separately for those undergoing salpingectomy and salpingotomy, therefore there may be unreported differences between the two populations. Median duration of follow-up is reported for whole study population, but no further details are reported (e.g. any split by type of surgery). Blinding of participants and/or those assessing outcomes is not reported. There is a discrepancy in the reporting of how many pregnancies ended in delivery, therefore only overall intrauterine

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
salpingectomy, particularly with regards to the pre-existing presence of fertility-reducing factors. **Study dates** Not reported **Source of funding** Not reported	**- Previous abdominal surgery:** Total: 113/261 (43) Desiring pregnancy: 81/196 (41) **- Previous induced abortion:** Total: 16/261 (6) Desiring pregnancy: 8/196 (4) **- Previous miscarriage:** Total: 71/261 (27) Desiring pregnancy: 47/196 (24) **- Previous ectopic pregnancy:** Total: 49/261 (19) Desiring pregnancy: 40/196 (20) **- Previous pelvic inflammatory disease:** Total: 39/261 (15) Desiring pregnancy: 30/196 (15) **- Peritubal adhesions:** Total: 78/261 (30) Desiring pregnancy: 59/196 (30) **Type of surgery (number/total (%))** **- Salpingectomy:** Total: 78/261 (30) Desiring pregnancy: 51/196		obtained (see characteristics), and patients were then contacted over a 5-year period and interviewed about subsequent reproductive events. Information regarding desire for future pregnancy and history of subsequent pregnancies was recorded. 196 women (75%) reported an active desire for a new pregnancy following completion of treatment, and were followed up for a median of 5 years. The effect of fertility reducing factors on outcomes was also examined. Chi-squared test was used to examine the relationship between categorical factors. $p<0.05$ was considered statistically significant.	**Reproductive outcome, stratified by presence or absence of fertility-reducing factors (number/total (%))** **a. Patients with fertility-reducing factors (n=111)** **- Intrauterine pregnancy** **Salpingectomy:** 17/43 (39.5) **Salpingotomy:** 51/68 (75) ($p<0.01$) **- Ectopic pregnancy** **Salpingectomy:** 7/43 (16.3) **Salpingotomy:** 9/68 (13.2) (NS) **b. Patients without fertility-reducing factors (n=85)** **- Intrauterine pregnancy** **Salpingectomy:** 8/8 (100) **Salpingotomy:** 71/77 (92.2) (NS) **- Ectopic pregnancy** **Salpingectomy:** 0/8 (0) **Salpingotomy:** 2/77 (2.6) (NS) (Note: fertility reducing factors are listed as contralateral tube damage, history of PID, history of abdominal surgery, previous ectopic pregnancy, previous miscarriage, previous induced abortion)	pregnancy rates have been reported here. **Other information** **Time to conception** 85% of all reproductive events took place within the first 2 years after the initial EP. 10% occurred in the third year, 5% in the fourth year and 0% in the fifth year.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	(26) **- Salpingotomy:** Total: 183/261 (70) Desiring pregnancy: 145/196 (74) Note: - 111 women had at least one fertility-reducing factor, of which 43 had a salpingectomy and 68 had a salpingotomy. - 85 women had no fertility-reducing factors, of which 8 had a salpingectomy and 77 had a salpingotomy. **Inclusion criteria** Clinically proven tubal ectopic pregnancy (EP) At least 18 years old **Exclusion criteria** History of previous ectopic pregnancies Pre-operative decision to remove the tube, regardless of the intraoperative situation				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation DeCherney,A., Kase,N., The conservative surgical management of unruptured ectopic pregnancy, Obstetrics and Gynecology, 54, 451-455, 1979 **Ref Id** 121877 **Country/ies where the study was carried out** USA **Study type** Retrospective comparative observational study **Aim of the study** To evaluate conservative management of ectopic pregnancy **Study dates** 1973 to 1977 **Source of funding** Not reported	**Sample size** N=98 **Characteristics** Age/years (mean) Radical: 29.3 Conservative: 28.3 **Inclusion criteria** Ampullary ectopic pregnancy **Exclusion criteria** Tubal abortion Isthmic ectopic pregnancy Ectopic not in fallopian tube	**Interventions** Radical surgery (salpingectomy or salpingo-oophorectomy) (n=50) Conservative surgery (linear salpingostomy) (n=48)	**Details** The hospital charts of 98 women with a tubal ectopic pregnancy (EP) during the study period were reviewed. 50 had radical surgery for both ruptured and unruptured EP. Radical surgery is defined as the removal of a tube, or tube and ovary at the time of surgery. In this study, conservative treatment consisted of a linear salpingostomy. The operation was not chosen based on the severity of the condition, but was the choice of the operating physician. Radical treatment was used primarily in ruptured EP, whereas all of those treated conservatively had unruptured EP. Patients in both groups were matched for age and parity. This was achieved by selecting 48 salpingotomy patients and then finding suitable radical cases. Pairing was based on age and parity from the same year. Conservative surgical technique The tube was grasped in the area over the EP, and the	**Results** Delivery of a viable intrauterine pregnancy (number/total (%)) Radical: 21/50 (42) Conservative: 19/48 (39.6) Repeat ectopic pregnancy (number/total (%)) Radical: 6/50 (12) Conservative: 9/48 (18.8)* * This value is reported on two separate occasions in the study, however a rate of 11.6% is reported in the table	**Limitations** Retrospective Unclear how they followed up women to elucidate subsequent fertility Length of follow-up varied, and was not reported separately for the conservative and radical groups. Inconsistency of reporting for repeat EP rate in conservatively managed group Unclear whether laparotomy or laparoscopy was performed; not reported how many women had oophorectomy in addition to salpingectomy. Those with ruptured EP all had radical treatment (% rupture is not reported) Blinding of participants and/or those assessing outcomes is not reported. Unclear how cases were selected for inclusion **Other information** All patients were trying to conceive

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			antimesenteric wall was incision. The products of conception were evacuated by blunt and sharp dissection. Cautery was used to control bleeding along the edges of the tube and at the base of the site of implantation. Continuous, vigorous saline lavage was used throughout. Neither operating microscope or loupes were used, although principles of good microsurgery were followed. Closure by primary or secondary intention was accomplished with a 5-0 vicryl suture. No attempt was made at surgery to determine the patency of the contralateral tube. 80% of the cases in the conservative arm received prophylactic antibiotics, and 45% received dexamethasone and promethazine intra-abdominally every 4 hours after surgery for 12 doses. 5% of conservatively managed cases received intra-abdominal low molecular weight dextran. 15% of the radically treated group received antibiotics at some point during their course of treatment. None received dexamethasone,		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			promethazine, or low molecular weight dextran. Outcomes evaluated The groups were compared for their outcomes. Viable pregnancies and repeat EP were reported. Miscarriages were not included in the statistics. The average duration of follow-up was 2.4 years, but varied from 1 to 4 depending on when the surgery was done.		
Full citation dela,Cruz A., Cumming,D.C., Factors determining fertility after conservative or radical surgical treatment for ectopic pregnancy, Fertility and Sterility, 68, 871-874, 1997 **Ref Id** 121881 **Country/ies where the study was carried out** Canada **Study type** Retrospective comparative	**Sample size** N=90 **Characteristics** Age/years (mean (SEM)) Radical: 28.0 (0.6) Conservative: 27.7 (0.9) (NS) Gravidity (mean (SEM)) Radical: 2.1 (0.2) Conservative: 2.7 (0.3) (NS) Previous infertility (n (%)) Radical: 30 (54) Conservative: 13 (38) (NS)	**Interventions** Radical surgery (salpingectomy) (n=56) Conservative surgery (linear salpingostomy) (n=34)	**Details** A retrospective chart review was performed to identify women who had undergone surgery for ectopic pregnancy at the University of Alberta Hospital during the study period. 193 women were identified, however 103 were excluded because they did not attempt conception (n=36), had a history of previous EP (n=46), had an absent contralateral tube (n=5), were lost to follow-up (n=9), or refused to participate (n=7). A subset of 90 women who fit the inclusion criteria was then identified. Conservative surgery consisted of a linear	**Results** Intrauterine pregnancy within 3 years (number of women/total (%)) a. Term pregnancy Radical: 21/56 (37.5) Conservative: 16/34 (47.1) *RR (95% CI) 0.8 (0.49 to 1.3) b. Miscarriage Radical: 6/56 (10.7) Conservative: 7/34 (20.6) c. Any intrauterine pregnancy (term + miscarriage) Radical: 27/56 (48.2)	**Limitations** Retrospective study Details of surgical methods are not reported. Not reported whether participants had a laparoscopy or laparotomy When comparing overall data, and the data stratified by history of infertility, the number of term pregnancies reported in each group do not match - 1 term pregnancy is misclassified in one of the analyses. 9/193 (4.7%) of the original ectopic pregnancy patients were lost to follow-up. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study **Aim of the study** To examine factors determining choice of radical or conservative surgical procedure for tubal ectopic pregnancy, and evaluate subsequent pregnancy rates. **Study dates** 1987 to 1991 **Source of funding** Not reported	<u>Previous PID (n (%))</u> Radical: 26 (46) Conservative: 14 (41) <u>Past IUD use (n (%))</u> Radical: 15 (27) Conservative: 4 (12) (p=0.09) <u>Tubal adhesions (n (%))</u> Radical: 30 (54) Conservative: 14 (41) (NS) <u>Abnormal contralateral tube (n (%))</u> Radical: 24 (43) Conservative: 12 (35) (NS) <u>No risk factor (n (%))</u> Radical: 12 (21) Conservative: 11 (31) (NS) **Inclusion criteria** Undergoing surgery for a first ectopic pregnancy during the study period Subsequently attempting conception		salpingostomy. Radical surgery was defined as salpingectomy. Data obtained from the chart review included age, obstetric history, menstrual history, past infertility, history of pelvic infections, and use of IUCD. A copy of the surgical report was obtained, and when available from the chart, information about subsequent fertility was noted. The chart data, and any further information concerning subsequent reproductive history, was verified by direct contact with all patients. The main outcome measure was the occurrence of a live birth or ectopic pregnancy at 3 years of follow-up after the index ectopic pregnancy.	Conservative: 23/34 (67.6) *RR (95% CI) 0.71 (0.5 to 1.02) <u>Repeat ectopic pregnancy within 3 years (number of women/total (%))</u> Radical: 10/56 (17.9) Conservative: 4/34 (11.8) *RR (95% CI) 1.52 (0.52 to 4.46) <u>STRATIFIED ANALYSES</u> <u>Intrauterine pregnancy rate (term + miscarriage), stratified by past infertility (number of women/total (%))</u> <u>a. Past infertility (n=43)</u> Radical: 10/30 (33.3) Conservative: 7/13 (53.8) * RR (95% CI) 0.62 (0.30 to 1.26) <u>b. No past infertility (n=47)</u> Radical: 16/26 (61.5) Conservative: 17/21 (81.0) *RR (95% CI) 0.76 (0.53 to 1.10)	The % reported in the stratification above do not match those reported in the paper, because the authors used the total with/without infertility as their denominator and did not split it by type of surgery.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Traceable for follow-up **Exclusion criteria** Absent contralateral tube No attempt to conceive Lost to follow-up			Term pregnancy rate, stratified by past infertility (number of women/total (%)) a. Past infertility Radical: 8/30 (26.7) Conservative: 3/13 (23.1) *RR (95% CI) 1.16 (0.36 to 3.67) b. No past infertility Radical: 12/26 (46.2) Conservative: 14/21 (66.7) *RR (95% CI) 0.69 (0.41 to 1.16) Ectopic pregnancy rate, stratified by past infertility (number of women/total (%)) a. Past infertility Radical: 10/30 (33.3) Conservative: 3/13 (23.1) *RR (95% CI) 1.44 (0.47 to 4.40) b. No past infertility Radical: 0/26 (0) Conservative: 1/21 (4.8) *RR (95% CI) 0.27 (0.01	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				to 6.34) * calculated by the NCC technical team	
Full citation Gruft,L., Bertola,E., Luchini,L., Azzilonna,C., Bigatti,G., Parazzini,F., Determinants of reproductive prognosis after ectopic pregnancy, Human Reproduction, 9, 1333-1336, 1994 **Ref Id** 121913 **Country/ies where the study was carried out** Italy **Study type** Retrospective observational study **Aim of the study** To analyse the determinants of reproductive prognosis and ectopic pregnancy recurrence rate in a series of women who underwent conservative or radical	**Sample size** N=115 **Characteristics** <u>Age at surgery/years (n (%))</u> ≤29: 54 (47) 30-34: 41 (36) ≥35: 20 (17) <u>Contralateral tube status (n (%))</u> Intact: 49 (43) Non-intact: 19 (17) (note: missing data from 42 women, and in 5 there was an absent tube) Women analysed did not differ from those lost to follow-up for the outcomes of: age, type of surgery, and contralateral tube status. **Inclusion criteria**	**Interventions** Salpingectomy (n=71) Salpingotomy (n=44)	**Details** The medical records of 265 women who consecutively underwent surgery for ectopic pregnancy at the Obstetric and Gynaecology Clinic, Milan, between 1985 and 1990 were reviewed. Information regarding operative findings, condition of the contralateral tube, and surgical procedures were collected. All subjects who could be located were interviewed by telephone in order to obtain information on their general characteristics, reproductive outcomes, contraceptive habits, active attempts at pregnancy, and subsequent pregnancies. Information was obtained for 177 women (67%), and of these 62 reported that they had not attempted another pregnancy. Therefore, the analysis included 115 women who reported active attempts at pregnancy. Data was obtained up to October 1992. The median length of	**Results** <u>Live births (number/total (%))</u> Salpingectomy: 23/71 (32.4) Salpingotomy: 12/44 (27.3) <u>3-year cumulative live birth rate (%)</u> Salpingectomy: 38 Salpingotomy: 37 Note: it is reported that out of 70 pregnancies, 13 were ectopic, but does not report how many women this was and what type of surgery they had. However, they do report that there was no significant relationship between type of surgery and the risk of recurrent ectopic pregnancy.	**Limitations** Retrospective comparative observational study 33% of the original patients who underwent surgery for ectopic pregnancy could not be contacted Blinding not reported Variable length of follow-up. Length of follow-up is not reported separately for the salpingectomy and salpingotomy arms Baseline characteristics are not reported separately for those undergoing different types of surgery, therefore there could have been significant differences at baseline (i.e. status of other tube) **Other information** All laparotomy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
surgery for ectopic pregnancy **Study dates** 1985 to 1990 (interval when the surgeries were conducted) Follow-up data was obtained up to October 1992 **Source of funding** Not reported	Undergoing laparotomic surgery for ectopic pregnancy Attempting another pregnancy **Exclusion criteria** Not reported		follow-up was 26 months (range 2 - 83). Analysis The length of follow-up was the time of surgery to the time of the interview. The cumulative proportion of women who became pregnant or gave birth was calculated by the product-limit method, and the curves obtained were compared using the log-rank test. The odds ratios and corresponding 95% confidence intervals of a further ectopic pregnancy were calculated.		
Full citation Kuroda,K., Takeuchi,H., Kitade,M., Kikuchi,I., Shimanuki,H., Kumakiri,J., Kobayashi,Y., Kuroda,M., Takeda,S., Assessment of tubal disorder as a risk factor for repeat ectopic pregnancy after laparoscopic surgery for tubal pregnancy, Journal of Obstetrics and Gynaecology Research, 35, 520-524, 2009 **Ref Id**	**Sample size** N=83 **Characteristics** Age/years (mean (SD)) Salpingectomy: 30.3 (5.2) Salpingo(s)tomy: 30.2 (4.4) (p=0.930) Gestational age/weeks (mean (SD)) Salpingectomy: 7.1 (1.2) Salpingo(s)tomy: 6.9 (1.2) (p=0.585)	**Interventions** Salpingectomy (n=40) Linear salpingo(s)tomy (n=43)	**Details** During the study period, 180 laparoscopic surgeries were performed for tubal pregnancies, of which 163 were treated with laparoscopic linear salpingo(s)tomy or salpingectomy. The focus of this study was the post-operative pregnancy in 83 women who were monitored for at least 6 months. Tubal pregnancy management protocol	**Results** Subsequent intrauterine pregnancy (number/total (%)) Salpingectomy: 17/40 (42.5) Salpingo(s)tomy: 24/43 (55.8) Repeat ectopic pregnancy (number/total (%)) Salpingectomy: 7/40 (17.5) Salpingo(s)tomy: 4/43 (9.3)	**Limitations** Retrospective Not reported whether the participants in each arm were attempting to conceive or not. Unclear why only 83/163 women were followed up for at least 6 months. Length of follow-up in each arm is not reported. Outcome of intrauterine pregnancy is not reported. Choice of surgical procedure was affected by future fertility desires.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
121949 **Country/ies where the study was carried out** Japan **Study type** Retrospective comparative observational study **Aim of the study** To evaluate tubal disorders, including peritubal adhesions, as risk factors for repeat ectopic pregnancy after laparoscopic linear salpingo(s)tomy or salpingectomy for tubal pregnancy. **Study dates** August 1992 to December 2005 **Source of funding** Not reported	<u>Past history of ectopic pregnancy (n (%))</u> Salpingectomy: 6/40 (15.0) Salpingo(s)tomy: 4/43 (9.30 (p=0.511) **Inclusion criteria** Tubal pregnancy treated with laparoscopic linear salpingo(s)tomy or salpingectomy **Exclusion criteria** Treated with milking of the tube, peritoneal lavage, or single dose focal methotrexate (n=17) Persistent ectopic pregnancy after linear salpingo(s)tomy (n=6) Salpingectomy prior to linear salpingo(s)tomy (n=4) No tube remaining after salpingectomy (n=5)		When ectopic pregnancy was strongly suspected, and the patient's pneumocardiac condition was stable, pneumoperitoneal laparoscopy was performed. Indications for salpingo(s)tomy were a patient's desire for future conception, and a non-ruptured tubal mass less than 5 cm in greatest diameter. Salpingectomy was performed if these criteria were not satisfied. <u>Laparoscopy procedure</u> Laparoscopy was performed using the 4-puncture method with the patient under general anaesthesia with endotracheal intubation, in the lithotomy position. For linear salpingo(s)tomy, the location of the ectopic pregnancy was confirmed, and vasopressin was administered into the mesosalpinx. The tubal serosa and muscle layer were incised with scissors and the ectopic pregnancy removed with grasping forceps. Indigo carmine was infused from the uterine manipulator for the evaluation of tubal muscular damage. The tubal muscle		Blinding of participants and/or those assessing outcomes is not reported. The terms "salpingostomy" and "salpingotomy" have both been used interchangeably in this study to refer to the same procedure **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			layer and serosa were then sutured continuously with Vicryl 3-0. For salpingectomy, after examining the tubal pregnancy site, we severed the junction of the proximal tube and uterus, cut through the mesosalpinx to the ampulla of the oviduct with bipolar forceps or a LigaSure Atlas sealer, and extirpated the tube. Adhesions to the preserved tube were severed with a monopolar needle. If hydrosalpinx was present salpingostomy was performed; we identified the thin texture of hydrosalpinx on the distal side of the tube, cut with a monopolar needle, turned over the mucosa and sutured and ligated. Analysis Comparisons between the two groups were made using the Student's t-test, the Mann-Whitney test, Fishers exact test or Kruskal Wallis, with $p<0.05$ as the level of significance.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Langebrekke,A., Sornes,T., Urnes,A., Fertility outcome after treatment of tubal pregnancy by laparoscopic laser surgery, Acta Obstetricia et Gynecologica Scandinavica, 72, 547-549, 1993 **Ref Id** 121953 **Country/ies where the study was carried out** Norway **Study type** Retrospective observational study **Aim of the study** Not stated **Study dates** December 1988 to October 1990 **Source of funding**	**Sample size** N=150 (98 of these women desired a future pregnancy and hence constitute the main population of interest) **Characteristics** Desire for pregnancy (number/total) Salpingectomy: 40/76 Salpingotomy: 58/74 **Inclusion criteria** Treated for ectopic pregnancy using laparoscopy **Exclusion criteria** Not reported	**Interventions** Laparoscopic salpingectomy (n=76, of which 40 wanted to conceive) Laparoscopic linear salpingotomy (n=74, of which 58 wanted to conceive)	**Details** During the study period, 195 women were treated for an ectopic pregnancy in the Department of Obstetrics and Gynaecology of the Akershus Central Hospital, Norway. Of these, 150 were treated by operative laparoscopy and hence constitute the population of interest. Contraindications to laparoscopy were: - haemodynamic instability - interstitial pregnancy - unfamiliarity with the endoscopic approach Radical treatment was chosen for women with no desire for future fertility, and cases with a ruptured tubal pregnancy or tubal gestation of more than 5 cm in diameter. 76 cases had a laparoscopic salpingectomy. In 74 cases, treatment was conservatively performed by linear salpingotomy with carbon dioxide laser laparoscopy. During January 1992, a questionnaire was sent to all 150 patients. Information was collected on pregnancy desire and outcome, length	**Results** Spontaneous intrauterine pregnancy rate (number/total (%)) a. Pregnancy at term or > 17 weeks gestation Salpingectomy: 18/40 (45) Salpingotomy: 38/58 (65.5) b. Miscarriage Salpingectomy: 1/40 (2.5) Salpingotomy: 2/58 (3.4) c. Total spontaneous intrauterine pregnancies Salpingectomy: 19/40 (47.5) Salpingotomy: 40/58 (69.0) Repeat ectopic pregnancy (number/total (%)) Salpingectomy: 4/40 (10) Salpingotomy: 4/58 (6.9)	**Limitations** Retrospective Varying length of follow-up. The average follow-up in each group is not reported. Baseline characteristics of the study population are not reported. Details of the surgeries are not given. Blinding of participants and/or those assessing outcomes is not reported. The decision to conserve the tube was based on factors such as desire for pregnancy, past history, and condition of tubes. **Other information** All laparoscopy No loss to follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported			of pregnancy desire, infertility operations, and IVF attempts. In five cases a repeat letter was sent, and five patients were contacted by telephone. The authors obtained a response rate of 100%. The follow-up period ranged from 15 to 37 months.		
Full citation Mecke,H., Semm,K., Lehmann-Willenbrock,E., Results of operative pelviscopy in 202 cases of ectopic pregnancy, International Journal of Fertility, 34, 93-94, 1997 **Ref Id** 121982 **Country/ies where the study was carried out** Germany **Study type** Retrospective comparative observational study **Aim of the study** Not stated	**Sample size** N=202 **Characteristics** Age/years (mean (range)): 29 (19 - 45) <u>History of previous tubal surgery (number/total (%))</u> On contralateral tube: 26/202 (13) On same tube: 24/202 (12) <u>Future fertility desires (number/total (%))</u> Desire for more children: 166/202 (82.2) No desire for more children: 36/202 (17.8) **Inclusion criteria** Ectopic pregnancy treated	**Interventions** Salpingectomy (n=25) Salpingotomy (n=153) (Note: the study population includes a further 24 cases of tubal abortion in whom the tube was conserved, however they were not part of the main comparison of interest for this review question)	**Details** <u>Operative procedure</u> A 5-mm optical trocar was introduced into the abdominal cavity through an umbilical incision. A 5-mm instrument trocar was introduced through a small left lateral suprapubic incision. Once the diagnosis was confirmed, a 5-mm trocar was introduced on the right side and an 11-mm trocar in the midline suprapubically. The umbilical incision was then dilated to introduce the 11-mm operation optic. Fresh and coagulated blood was removed from the abdominal by irrigation with saline and suction, and one of the following procedures was performed:	**Results** <u>Need for further intervention (number/total (%))</u> Salpingectomy: 0/25 (0) Salpingotomy: 14/153 (9.2) (Note: re-pelviscopy or laparotomy for postoperative bleeding (n=5), infection (n=1), unexplained pain or positive pregnancy test after 10 days (n=5), laparotomy in another facility (n=1), haematosalpinx (n=2)) <u>Surgical complications (number/total (%))</u> <u>a. Infection</u> Salpingectomy: 0/25 (0) Salpingotomy: 1/153 (0.7) <u>b. Postoperative bleeding</u> Salpingectomy: 0/25 (0)	**Limitations** Retrospective Unclear why only 74/153 (48%) women had fertility outcomes reported (i.e. were the rest lost to follow-up or just not desiring pregnancy) Unclear how fertility outcomes were assessed (they were followed up for 1-6 years). Baseline characteristics not reported for salpingectomy/salpingotomy groups separately Reporting of pain also includes women with a positive pregnancy test 10 days after operation Choice of surgery was partially dependent on future fertility desires. The future fertility of those receiving a salpingectomy is not reported. Women with a tubal abortion and those treated

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 1978 to 1987 **Source of funding** Not reported	with pelviscopy during the study period **Exclusion criteria** Not reported		Salpingectomy: If the patient had completed her family and consented, a pelviscopic salpingectomy was performed. The tube was resected with hook scissors after ligation with three endoloops and then removed through the 11-mm trocar with the spoon forceps. The tubal stump was then coagulated with the point coagulator. Tubal abortion: In the case of tubal abortion, blood and blood clots were removed using an aquapurator, and the aspirate was passed through a sieve for histological analysis. Materials located between the fimbria were removed with biopsy forceps. Salpingotomy was performed if there was any doubt concerning the complete removal of the products of conception from the tube. Salpingotomy: In cases of an intact isthmic or ampullary ectopic pregnancy, salpingotomy was performed. 20-30 ml of POR solution (ornipressin in saline) was injected into the mesosalpinx to achieve	Salpingotomy: 5/153 (3.3) Note: the women who experienced these complications are also included in those requiring further intervention. <u>Positive pregnancy test or unexplained abdominal pain 10 days later requiring diagnostic pelviscopy (number/total (%))</u> Salpingectomy: 0/25 (0) Salpingotomy: 5/153 (3.3) (Note: these are included in need for further intervention above) <u>Subsequent intrauterine pregnancy (number/total (%))</u> <u>a. Any intrauterine pregnancy</u> Salpingectomy: NR Conservative treatment: 42/74 (56.8) <u>b. Children born</u> Salpingectomy: NR Conservative treatment: 34/74 (45.9) <u>Repeat ectopic pregnancy (number/total (%))</u>	with salpingotomy are lumped together. Blinding of participants and/or those assessing outcomes is not reported. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			vasoconstriction. A longitudinal antimesenteric incision was made in the tube with the microscissors after previous coagulation of the intended incisional site. The products of conception were then removed with 11-mm spoon forceps and biopsy forceps, followed by complete cleaning of the operation site, including irrigation of the tube. Early on, the tube was left open. However, from 1982 to 1985 the wound was closed using catgut endosuture with extracorporal knotting. From 1985 onwards, only 4/0 PDS with intracorporal knotting was used, adapting only the tunica serosa and the most superficial layer of the tunica muscularis when necessary. In all cases, a full abdominal lavage using saline was done, and a Robinson drain was placed in the cul-de-sac. The total duration of the operation was around 45 minutes and patients were discharged 3-5 days later. Postoperative follow-up with hCG assay was mandatory.	Salpingectomy: NR Conservative treatment: 10/74 (13.5)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Mol,B.W.J., Matthijsse,H.C., Tinga,D.J., Huynh,T., Hajenius,P.J., Ankum,W.M., Bossuyt,P.M.M., van,derVeenF, Fertility after conservative and radical surgery for tubal pregnancy, Human Reproduction, 13, 1804-1809, 1998 **Ref Id** 121992 **Country/ies where the study was carried out** The Netherlands **Study type** Retrospective cohort study **Aim of the study** To evaluate, by life-table analysis, the effectiveness of conservative and radical surgery towards fertility outcome, and the influence of pre-existing tubal disease on such effectiveness.	**Sample size** N=135 **Characteristics** Age/years (mean (SD)) Radical: 31.4 (4.8) Conservative: 30.1 (5.6) (P=0.24) Nulliparity (n (%)) Radical: 19 (24) Conservative: 22 (39) (p=0.07) Homolateral EP in history (n (%)) Radical: 4 (5) Conservative: 0 (0) (p=0.08) Contralateral EP in history (n (%)) Radical: 3 (4) Conservative: 2 (4) (p=0.91) Previous tubal surgery (n (%)) Radical: 16 (21) Conservative: 5 (9) (p=0.07)	**Interventions** Radical surgery (salpingectomy) (n=79) Conservative surgery (salpingo(s)tomy) (n=56)	**Details** All eligible patients who underwent primary surgery for tubal pregnancy in the Academic Medical Centre, Amsterdam, and the Academic Hospital, Gronigen, during the study period were included. Tubal pregnancy was diagnosed by combined transvaginal sonography and serum hCG measurement. Data on treatment was obtained retrospectively from medical files. During the study period, 237 patients underwent surgery for tubal ectopic pregnancy. However, 6 were treated by milking or had complete expulsions, 24 had only one tube, 7 had an EP resulting from IVF, and 7 had both of the latter two criteria. Of the remaining 193 patients, 2 had a heterotopic pregnancy, 14 were lost to follow-up, and 42 patients did not try and conceive again. Therefore, 135 patients were available for analysis. Two treatment groups were defined. Radical surgery was defined as salpingectomy, and	**Results** Spontaneous intrauterine pregnancy rate (number of women/total (%)) a. Pregnancy ending in delivery Radical: 18/79 (22.8) Conservative: 22/56 (39.3) b. Any intrauterine pregnancy (Note: this includes delivery, miscarriage, elective termination, unknown outcome) Radical: 24/79 (30.4) (Note: 18 deliveries, 2 elective termination, 1 miscarriage, 3 unknown outcome) Conservative: 30/56 (53.6) (Note: 22 deliveries, 2 elective termination, 6 miscarriage) In addition, 18 women had IUP as a result of IVF (14 from radical, 4 from conservative). Ectopic pregnancy rate (number of women/total (%)) Radical: 7/79 (8.9)	**Limitations** Retrospective There were significant differences between the two groups at baseline: previous PID, homolateral tubal pathology, contralateral tubal pathology, and % receiving a laparoscopy. 14/193 (7%) of women were lost to follow-up. Unclear at what date follow-up was done, therefore length of follow-up may have differed between the groups. Blinding of participants and/or those assessing outcomes is not reported. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates January 1990 to August 1993 **Source of funding** Not reported	Previous PID (n (%)) Radical: 15 (18) Conservative: 5 (9) (p=0.04) Subfertility at time of EP (n (%)) Radical: 8 (10) Conservative: 5 (9) (p=0.82) Homolateral tubal pathology (n (%)) Radical: 40 (51) Conservative: 9 (16) (p<0.01) Contralateral tubal pathology (n (%)) Radical: 38 (48) Conservative: 15 (27) (p=0.01) Laparoscopy (n (%)) Radical: 7 (9) Conservative: 22 (39) (p<0.01) **Inclusion criteria** Primary surgery for tubal pregnancy during study period		conservative as salpingo(s)tomy. Surgery was either by laparoscopy or open surgery. Information on age, parity, previous EP, prior tubal surgery, previous PID, subfertility, surgical modality, and tubal pathology encountered at surgery was extracted from medical files. Data on subsequent fertility was obtained by reviewing medical files and, when this information was insufficient, by telephone interviews with patients. In all patients, the exact time-frame in which they were trying to conceive was registered. In the case of an IUP, follow-up ended at the estimated date of conception. An IUP was defined as an ongoing pregnancy detected by ultrasound, or the delivery of a child. The outcome of each IUP was registered. If an IUP did not occur, follow-up ended on the last day of contact. Repeat EP were also registered. Data analysis Baseline characteristics were compared using Student's t-test or chi-	Conservative: 5/56 (8.9) 3-year cumulative pregnancy rates (%) a. Spontaneous IUP Radical: 38 Conservative: 62 (P<0.001) b. Ectopic pregnancy Radical: 23 Conservative: 28 (p=0.07) Fecundity rate ratios for conservative surgery (95% CI) a. Spontaneous IUP Univariate: 2.5 (1.4 to 4.4) Multivariate: 1.9 (0.91 to 3.8) b. Repeat EP Univariate: 1.5 (0.47 to 4.7) Multivariate: 2.4 (0.57 to 11) (Note: they report that the multivariate analysis adjusted for other factors prognostic of fertility but it is unclear exactly what these are)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Complete tubal abortion Treatment by milking or nettoyage only Patients with only one tube (radical surgery would effectively sterilise these patients) Index tubal pregnancy a result of IVF and embryo transfer Heterotopic pregnancies Not trying to conceive		squared. Kaplan–Meier curves were constructed, estimating the cumulative probability of spontaneous IUP over time, which was the primary outcome measure. If an IUP was the result of IVF–embryo transfer, time to pregnancy in this patient was considered to be censored, which meant that the patient was included in the analysis until the start of IVF–embryo transfer only. The Kaplan–Meier curves were tested for statistically significant differences using the log-rank test. The effect of conservative surgery compared with radical surgery was expressed as a fecundity rate ratio (FRR) with a 95% CI, calculated through Cox proportional hazard regression analysis. Proportionality was tested visually from the Kaplan–Meier curves. To adjust the FRR of conservative surgery for other potential prognostic factors mentioned above, multivariate analysis was performed. Analysis was also stratified for tubal pathology. Two different definitions of tubal pathology were used: first, a	Stratified analysis for tubal disease and tubal pathology: 3 year absolute IUP and FRR for conservative vs. radical surgery in first 18 months (95% CI) - In patients with no history of tubal disease Radical: 18/50 (36) Conservative: 25/46 (54) FRR (95% CI) 1.4 (0.68 to 2.7) - In patients with history of homolateral tubal disease Radical: 1/2 (50) Conservative: 0/0 (0) FRR (95% CI): NR/NC - In patients with history of contralateral tubal disease Radical: 0/2 (0) Conservative: 1/2 (50) FRR (95% CI): NR/NC - In patients with history of bilateral tubal disease Radical: 5/25 (20) Conservative: 4/8 (50) FRR (95% CI) 3.1 (0.76 to 12)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			medical history of tubal pathology, i.e. previous EP, previous PID or previous tubal surgery; and second, tubal pathology detected during surgery of the index EP, i.e. presence of hydrosalpinx, peritubal adhesions or phimosis. FRRs stratified for both a history of tubal pathology (absent, homolateral, contralateral or bilateral), and tubal pathology detected at surgery (absent, homolateral, contralateral or bilateral) were calculated. Interaction between tubal pathology and treatment was assessed by Cox regression using the follow-up data collected for each patient. Three-year cumulative rates were also calculated for repeat EP. The Kaplan–Meier curves were compared using the log-rank test. In this analysis, time to EP was considered to be censored once IUP occurred. Univariate and multivariate Cox regression analysis were used to calculate FRR for repeat EP after conservative surgery compared with radical surgery.	- In patients with no tubal pathology at surgery Radical: 15/31 (48) Conservative: 26/41 (63) FRR (95% CI) 2.0 (0.87 to 4.8) - In patients with homolateral tubal pathology at surgery Radical: 3/15 (20) Conservative: 1/1 (100) FRR (95% CI): NR/NC - In patients with contralateral tubal pathology at surgery Radical: 3/8 (37.5) Conservative: 2/6 (33.3) FRR (95% CI) 0.80 (0.13 to 4.9) - In patients with bilateral tubal pathology at surgery Radical: 3/25 (12) Conservative: 1/8 (12.5) FRR (95% CI) 1.4 (0.13 to 16)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ory,S.J., Nnadi,E., Herrmann,R., O'Brien,P.S., Melton,L.J.,III, Fertility after ectopic pregnancy, Fertility and Sterility, 60, 231-235, 1993 **Ref Id** 122007 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To compare pregnancy rates after radical or conservative surgical treatment for tubal pregnancy over a 12.5 year interval (minimum of 3 years), and to assess the relative contribution of various risk factors to future fertility performance. **Study dates**	**Sample size** N=88 (however 5 of these women did not receive a salpingectomy or salpingo(s)tomy, and therefore the main population of interest is N=83) **Characteristics** Type of surgery received (number/total) Radical: 50/88 - Partial salpingectomy: 8/50 - Complete salpingectomy: 42/50 Conservative: 38/88 - Salpingo(s)tomy: 33/38 - Fimbrial expression: 5/38 Age/years (mean (SEM) Radical: 27.7 (0.7) Conservative: 26.3 (0.7) (NS) Gravidity (mean (SEM)) Radical: 2.2 (0.3) Conservative: 1.3 (0.1) (p=0.008) Prior infertility (%)	**Interventions** Radical surgery (complete or partial salpingectomy) (n=50) Salpingo(s)tomy (n=33)	**Details** In Olmsted County, the records of 188 women with a surgically confirmed EP were identified, of which 100 were eligible for the study (see inclusion criteria). The other 88 were ineligible: 47 did not attempt conception, and 41 were lost to follow-up. The fertility histories of the 100 patients were retrospectively followed from 3 to 12.5 years after the index EP. Pertinent information regarding age, gravidity, menstrual pattern, fertility history, surgical history, pelvic infections, IUCD use and subsequent fertility were obtained from their complete inpatient and outpatient medical records. Two facilities provided almost all the care for the residents of the county. Therefore, the authors report that all information was consistently available. A detailed questionnaire was sent to the 100 eligible subjects, and non-respondents were contacted by telephone. Eventually, 88 patients responded, and constitute the study	**Results** Subsequent term pregnancy within 3 years (number/total (%)) Radical: 29/50 (58) Salpingo(s)tomy: 17/33 (51.5) * RR (95% CI) 1.13 (0.75 to 1.69) Repeat ectopic pregnancy within 3 years (number/total (%)) Radical: 3/50 (6) Salpingo(s)tomy: 8/33 (24.2) * RR (95% CI) 0.25 (0.07 to 0.87) * calculated by NCC technical team Note: the following analyses include the women that received fimbrial expression, because outcomes for salpingo(s)tomy/fimbrial expression are not reported separately. Term pregnancy rate, stratified by history of infertility (number/total (%) a. With history (n=25)	**Limitations** Retrospective 53/188 (28.2%) of the original patients with a surgically confirmed ectopic pregnancy were lost to follow-up There was a significant difference between gravidity, prior infertility, and history of prior tubal surgery between the two groups. Tubal rupture was also more prevalent in the radical group. 2/50 patients in the radical arm also had an oophorectomy; their outcomes are not reported separately. Blinding of participants and/or those assessing outcomes is not reported. **Other information** All laparotomy Note: When split by specific surgery type: - Partial salpingectomy Term delivery: 2/8 (25) EP: 1/8 (12.5) - Complete salpingectomy Term delivery: 27/42 (64.2) EP: 2/42 (4.8)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
1976 to 1985 **Source of funding** Not reported	Radical: 18 Conservative: 42 (p=0.013) PID (%) Radical: 8 Conservative: 16 (NS) IUD (%) Radical: 19 Conservative: 17 (NS) Tubal adhesions (%) Radical: 2 Conservative: 11 (NS) Previous abdominal pelvic surgery (%) Radical: 8 Conservative: 8 (NS) Prior tubal surgery (%) Radical: 0 Conservative: 11 (p=0.019) History of anovulation (%) Radical: 12 Conservative: 13		population. 50 of the patients had a radical procedure, including a complete (n=42) or partial (n=8) salpingectomy, at which time the proximal segment was ligated. In addition, 2 patients in this arm also had an ipsilateral oophorectomy. 38 patients had a conservative procedure, of which 33 were salpingostomies or salpingotomies and 5 were fimbrial expressions. 8 patients in the conservative group also underwent a reparative procedure at initial laparotomy, comprising salpingolysis or ovariolysis. All patients in both groups had a remaining contralateral tube. The procedures were performed by numerous surgeons, including residents.	Radical: 1/9 (11.1) Conservative: 4/16 (25) (p=0.405) b. Without history (n=63) Radical: 28/41 (68.3) Conservative: 15/22 (68.2) (p=0.993) Ectopic pregnancy rate, stratified by history of infertility (number/total (%)) a. With history (n=25) Radical: 2/9 (22.2) Conservative: 5/16 (31.3) (p=0.629) b. Without history (n=63) Radical: 2/41 (4.9) Conservative: 3/22 (13.6) (p=0.220) (Note: unclear why a total of 4 EP are reported in the radical arm in the stratified analysis, when only 3 are reported in the overall analysis)	- Salpingo(s)tomy Term delivery: 17/33 (51.5) EP: 8/33 (24.2) - Removal of conceptus through ampulla Term delivery: 2/5 (40) EP: 0/5 (0)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	<u>No risk factor identified (%)</u> Radical: 67 Conservative: 33 (NS) **Inclusion criteria** Surgically confirmed ectopic pregnancy presenting during the study period First tubal pregnancy Treated with radical or conservative surgery at laparotomy Actively attempted conception after surgery Willing and available to participate in follow-up for at least 3 years **Exclusion criteria** Not reported				
Full citation Sherman,D., Langer,R., Sadovsky,G., Bukovsky,I., Caspi,E., Improved fertility following ectopic pregnancy, Fertility and Sterility, 37, 497-502, 1982	**Sample size** N=250 (However, fertility outcomes are only reported for 151 women who had primary EP and conservative/radical surgery, and therefore	**Interventions** Radical surgery (salpingectomy, salpingo-oophorectomy) (n=159)	**Details** During the study period, 250 ectopic pregnancies in 242 women were surgically treated. Details of age, parity, past medical history, IUCD use, diagnostic procedures, operative	**Results** <u>Subsequent intrauterine pregnancy (number/total (%))</u> <u>a. All patients</u> Radical: 75/104 (72.1) Conservative: 39/47 (83.0)	**Limitations** Retrospective Some patients received other surgical procedures than a salpingotomy or salpingectomy. Partial salpingectomy is included as a conservative surgery.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 122046 **Country/ies where the study was carried out** Israel **Study type** Retrospective comparative observational study **Aim of the study** To examine reproductive performance subsequent to operative removal of ectopic pregnancy **Study dates** January 1st 1969 to December 31st 1979 **Source of funding** Not reported	constitute the main population of interest for this review) **Characteristics** Age/years (mean (SD)): 27.8 (5.2) Gestational age/days (mean (SD)): 52.6 (17.6) Type of surgery performed (number/total (%)) Conservative: 65/250 (26) - Salpingotomy: 43/250 (17) - Milking: 14/250 (6) - Resection of ovarian pregnancy: 7/250 (3) - Partial salpingectomy: 1/250 (0.4) Radical: 159/250 (64) - Salpingectomy: 136/250 (54) - Salpingo-oophorectomy: 23/250 (9) Sterilising procedures: 26/250 (10) Adjunctive reconstructive surgery: 45/250 (18) **Inclusion criteria**	Conservative surgery (salpingotomy, milking, resection of ovarian pregnancy, partial salpingectomy) (n=65)	findings, and surgical procedures was obtained from admission records, surgery reports, and pathological files. Data regarding subsequent pregnancies, surgical operations, contraceptive measures and death were available via questionnaires sent to patients' addresses, subsequent medical records, and personal interviews. Laparoscopy was used for diagnosis in 69% of cases. In three cases of very early tubal gestation, it was initially overlooked but discovered during a second procedure. 88% of cases were operated on during the first 24 hours after admission. Conservative surgical procedures aimed at preserving the tube were carried out whenever the involved tube was not severely damaged and future fertility was desirable. Salpingotomy was the most common conservative procedure carried out. Among radically treated patients, salpingectomy was the treatment. Concomitant oophorectomy was carried out in the presence of associated ovarian	*RR (95% CI) 0.87 (0.73 to 1.04) b. In patients with either history or operative findings suggestive of coexistent sterility factors Radical: 14/32 (43.8) Conservative: 16/21 (76.2) *RR (95% CI) 0.57 (0.36 to 0.91) c. In patients with otherwise normal reproductive history and organs Radical: 61/72 (84.7) Conservative: 23/26 (88.5) *RR (95% CI) 0.96 (0.81 to 1.14) Repeat ectopic pregnancy (number/total (%)) a. All patients Radical: 6/104 (5.8) Conservative: 3/47 (6.4) *RR (95% CI) 0.90 (0.24 to 3.46) b. In patients with either history or operative findings suggestive of coexistent sterility factors	Although proportions are reported for the whole original population, they are not reported for those included in the analysis of fertility outcomes. 39/242 (16%) patients were lost to follow-up, and only 179 (77%) had adequate data available. Therefore overall missing data/loss to follow-up is high. Specific characteristics of those receiving conservative and radical surgery are not reported Includes 4% non-tubal pregnancies. 42% of cases were ruptured Outcome of pregnancies is not reported Blinding of participants and/or those assessing outcomes is not reported. **Other information** Location of ectopic (%) Tubal: 96 Ovarian: 4

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Ectopic pregnancy **Exclusion criteria** Not reported		pathology. Reconstructive procedures (lysis of adhesions and/or tuboplasty) were combined with either radical or surgical operations in 45 patients who desired future pregnancy. Additional measures directed towards the prevention of post-operative scar formation included gentle tissue handling, saline irrigations, use of fine non-absorbable sutures, blood-clot removal, and intra-abdominal instillation of a solution containing steroids, antibiotics and antihistamines. Post-operative care included chemotherapy with antibiotics, steroids and enzymatic drugs, and hydrotubations. Twenty six sterilising procedures were carried out, seven of which were in repeat ectopic pregnancy cases. Follow-up Of the 242 patients under study, 39 (16%) were lost to follow-up. One patient died 2 weeks post-operatively in another hospital of probable massive pulmonary embolism. 23 underwent	Radical: 3/32 (9.4) Conservative: 1/21 (4.8) *RR (95% CI) 1.97 (0.22 to 17.68) c. In patients with otherwise normal reproductive history and organs Radical: 3/72 (4.2) Conservative: 2/26 (7.7) *RR (95% CI) 0.54 (0.10 to 3.06) * Calculated by the technical team	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			sterilising operations. Adequate data was available for 179 patients, of which 25 used contraception. Therefore, reproductive performance was evaluated in the remaining 154 patients, who were followed for a mean time of 4.18 (SD 2.8) years, with a range of 3 months to 11 years. 70% were followed for more than 2 years. The reproductive outcomes of 151 patients with a primary ectopic pregnancy (3 patients with two previous EP were excluded) are reported below. The authors report that there was no statistically significant difference in length of follow-up between the two arms.		
Full citation Tuomivaara,L., Kauppila,A., Radical or conservative surgery for ectopic pregnancy? A follow-up study of fertility of 323 patients, Fertility and Sterility, 50, 580-583, 1988 **Ref Id** 122086 **Country/ies where the**	**Sample size** N=323 **Characteristics** Characteristics are not reported separately for salpingectomy and conservative surgery arms. <u>Type of surgery received (number/total (%))</u>	**Interventions** Salpingectomy (n=237) Conservative surgery (n=86)	**Details** During the study period, 523 patients underwent surgery for ectopic pregnancy. The majority of patients had radical operations, due to tubal rupture and/or a grossly normal contralateral tube. If the patients had suffered from infertility or the tube was not ruptured, conservative surgery was	**Results** <u>Subsequent intrauterine pregnancy (number of women/total (%))</u> <u>a. In all women</u> Salpingectomy: 170/237 (71.7) Conservative surgery: 59/86 (68.6) (Note: tubal resection (28),	**Limitations** Retrospective 14% loss to follow-up for fertility outcomes. No characteristics are reported to illustrate comparability of treatment groups, therefore there could be unreported differences at baseline No surgical details are reported -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Finland **Study type** Retrospective comparative observational study **Aim of the study** To evaluate the subsequent fertility of 323 patients who desired pregnancy, by paying special attention to the type of surgical management, state of the tubes at operation, and parity. **Study dates** 1973 to 1982 (point at which operations occurred) **Source of funding** Not reported	Salpingectomy: 237/323 (73.4) Conservative surgery: 86/323 (26.6) - Tubal resection: 40/86 (46.5) - Tubal section: 20/86 (23.3) - Ovum expression: 20/86 (23.3) - No manipulation: 6/86 (7.0) **Inclusion criteria** Desiring pregnancy after an operation for ectopic pregnancy **Exclusion criteria** Not reported		chosen. A questionnaire was sent to each patient to analyse subsequent fertility. The questionnaire had questions on: fertility after operation, time from surgery to first pregnancy, clinical course of pregnancy, infertility, and contraception methods. The mean follow-up time was 5.1 years (range 1 - 11). 450/523 (86%) of patients returned the questionnaire, of which 127 did not wish to become pregnant. Therefore, the outcomes of 323 women who desired pregnancy were analysed using chi-squared test.	tubal section (14), ovum expression (12), no manipulation (5)) <u>b. Excluding women who had "no manipulation"</u> Salpingectomy: 170/237 (71.7) Tubal resection/section or ovum expression: 54/80 (67.5) <u>Repeat ectopic pregnancy (number of women/total (%))</u> <u>a. In all women</u> Salpingectomy: 25/237 (10.5) Conservative surgery: 10/86 (11.6) (Note: tubal resection (3), tubal section (2), ovum expression (5), no manipulation (0)) <u>b. Excluding women who had "no manipulation"</u> Salpingectomy: 25/237 (10.5) Tubal resection/section or ovum expression: 10/80 (12.5) (Note: % do not exactly match those stated in the paper, because the authors	unclear whether women in the conservative arm are receiving a surgery type relevant to this review question Length of follow-up is not reported separately for the two arms. Outcome of pregnancy is not reported in a way that permits analysis (very small bar graph) Lack of blinding **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				calculate number of ectopics as a proportion of total pregnancies, not women) Live birth rate (number of women/total (%)) a. In women with an affected contralateral tube Salpingectomy: 13/30 (43.3) Conservative surgery: 14/19 (73.7) b. In women with an intact contralateral tube The authors report that there was no significant difference in fertility with respect to operation method, but raw numbers are not given.	
Full citation Turan,V., Fertility outcomes subsequent to treatment of tubal ectopic pregnancy in younger Turkish women, Journal of Pediatric and Adolescent Gynecology, 24, 251-255, 2011 **Ref Id** 155383 **Country/ies where the**	**Sample size** N = 133 (However, 34 patients underwent treatment with methotrexate and therefore the true population of interest for this review is N = 99) **Characteristics** **Age/years (mean±SD)** Salpingectomy: 25.3±3.8 Salpingostomy: 25.7±3.6	**Interventions** Salpingectomy (n = 62) Salpingostomy (n = 37)	**Details** The records of 219 women hospitalised for tubal ectopic pregnancy during the study period were reviewed. 81 women were excluded as per the exclusion criteria. Patients were called and asked whether they had an intrauterine pregnancy up to 24 months, and for how long a period they waited to conceive. 9 patients (7 from the salpingectomy group and 2 from the	**Results** **Subsequent intrauterine pregnancy (n/total (%))** Salpingectomy: 33/55 (60) Salpingostomy: 23/35 (65.7) (p = 0.942) **Repeat ectopic pregnancy (n/total (%))** Salpingectomy: 2/55 (3.6) Salpingostomy: 6/35 (17.1) (p = 0.091)	**Limitations** Retrospective 9/99 (9%) of patients were lost to follow-up Study population only includes women 18-28 years old with concerns about infertility, and therefore does not exactly match the population of interest for this review. There is inconsistency in the reported rates within the paper: in the table it reports that there were

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out Turkey **Study type** Retrospective comparative observational study **Aim of the study** To determine intrauterine pregnancy rates and mean time to future pregnancy that are experienced following tubal ectopic pregnancy **Study dates** January 1998 to September 2008 **Source of funding** None stated	**<u>Type of surgery performed (n/total)</u>** Salpingectomy: - Laparotomy: 23/62 - Laparoscopy: 39/62 Salpingostomy: - Laparotomy: 15/37 - Laparoscopy: 22/37 **Inclusion criteria** Tubal ectopic pregnancy Aged 18-28 Concerns about infertility **Exclusion criteria** Unwillingness for pregnancy and using a contraceptive method Previous pelvic or tubal surgery Pregnancy following IVF Extratubal ectopic pregnancy Aged over 28		salpingostomy group) could not be reached. The Pearson chi-squared test was used to compare rates of ectopic and intrauterine pregnancies between the groups.		23 intrauterine pregnancies in the salpingostomy group and 33 in the salpingectomy group; however, in the flow chart it reports 22 and 34 respectively. The technical team have reported the values which most closely match the % reported in the text of the results. Outcome of the pregnancy is not reported **Other information**

Should anti-D rhesus prophylaxis be given to women with a threatened miscarriage, miscarriage or ectopic pregnancy in the first trimester?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Visscher,R.D., Visscher,H.C., Do Rh-negative women with an early spontaneous abortion need Rh immune prophylaxis?, American Journal of Obstetrics and Gynecology, 113, 158-165, 1972 **Ref Id** 126397 **Country/ies where the study was carried out** USA **Study type** Two part study: 1. double blind trial of Rhogam vs. placebo 2. case series, following women without intervention	**Sample size** N=57 (Note: 48 women participated in the double-blind part of the study; 9 participated in the second part of the study, without intervention) **Characteristics** Gestational age/weeks (range): 8 - 24 No further details are given, apart from that the majority were between 8 and 16 weeks gestation, by dates. <u>Type of miscarriage, split by intervention received (number/total (%))</u> Complete miscarriage - Rhogam: 5/19 - Placebo: 4/29 - No intervention: 0/9 Incomplete miscarriage with curettage - Rhogam: 14/19 - Placebo: 25/29	**Interventions** Rhogam (300 micrograms) (n=19) Placebo (homologous gamma globulin) (n=29) No intervention (n=9)	**Details** All women admitted to Grand Rapids hospitals with a diagnosis of miscarriage were interviewed by a registered nurse, who obtained the patient's obstetric history and miscarriage information, explained the project and gained consent. The nurse also drew the blood samples and gave all injections. Women matching the inclusion criteria were included in the study, which had two parts. During the study period, 1084 women were admitted with a diagnosis of miscarriage, of which 65 were Rh- and non-sensitised, and 57 consented to participate. The first part of the study was a double blind study comparing anti-D administration and placebo, in which 48 women participated. Coded ampules contained either 300 micrograms of Rh immune globulin (supplied as RhoGAM by the Ortho Research Foundation) or 1 ml of homologous gamma globulin with no demonstrable Rh (D) antibody. Women were then injected intramuscularly with the	**Results** STUDY PART 1: TRIAL OF RHOGAM VS. PLACEBO <u>Evidence of sensitisation (number/total (%))</u> <u>a. At 6 months</u> Rhogam: 0/19 Placebo: 0/29 (Note: 12 of the 19 who received Rhogam had evidence of passive antibody from the treatment, but this had disappeared by 6 months after injection) <u>b. In a later Rh+ pregnancy</u> Rhogam: 0/3 (0) Placebo: 0/6 (0) STUDY PART 2: FOLLOW-UP OF PATIENTS WITH NO INTERVENTION <u>Evidence of sensitisation (number/total (%))</u> a. At 6 months: 0/9 (0) b. In a later Rh+ pregnancy: 0/2 (0)	**Limitations** Method of randomisation not reported. Unclear that treatment allocation would be concealed and blinding maintained, if one ampule contained 300 micrograms of anti-D and the other contained 1 ml of gamma globulin. Small sample size in both parts of the trial, and particularly for follow-up of later pregnancies. An unknown proportion of women had gestational ages outside the scope of the guideline. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine the risk of sensitisation after miscarriage **Study dates** July 1968 to March 1971 **Source of funding** Supported by a grant from the John A. Hartford Foundation Inc., New York, through the Blodgett Memorial Hospital Research Department.	- No intervention: 9/9 **Inclusion criteria** Diagnosis of miscarriage, confirmed by either: - Histopathologic confirmation of the products of conception by a pathologist or obstetrician, or - A reliable history of vaginal bleeding and cramping associated with the passing of products of conception occurring in a woman who had missed at least one menstrual period and had a prior diagnosis of pregnancy established by pelvic examination or lab test Rh- and not immunised to any of the blood group antigens, as determined by the absence of immune antibodies in their sera at the time of miscarriage Rh+ fathers **Exclusion criteria** Not reported		contents of one of the randomly selected coded ampules, within 72 hours after a spontaneous complete miscarriage or a surgical completion of an incomplete miscarriage. The results of the double blind study were evaluated after 2 years, and as there was no evidence of isoimmunisation, it was terminated. During the second part of the study, 9 women were followed as controls, with no one receiving any injection. All 9 had received a D&C for incomplete miscarriage. <u>Follow-up</u> All 57 women were followed up for 6 months. Sera was obtained at 3 and 6 months from all patients, and screened for the presence of atypical antibodies. Subsequent pregnancies were then studied for clinical and serological evidence of Rh isoimmunisation. Samples from pre-injection and follow-up samples were labelled, frozen and stored for future reference and to confirm any primary immune response. All sera were screened for atypical antibodies in two ways. The initial screen was performed with the Indirect Coombs test. At		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			3 month intervals, all frozen stored sample were evaluated with an enzyme-Coombs screening procedure. The screening cells were incubated for 15 minutes at 37 degrees in 1% solution of trypsin in buffer. The 4% cell suspension was washed three times with saline and reconstituted to its original volume with buffered saline. The screening with the trypsinised cells was conducted in the same manner as non-trypsinised cells. The technique increases sensitivity 10 times.		
Full citation Simonovits,I., Bajtai,G., Kellner,R., Kerenyl,M., Rucz,L., Szilvas,R., Takacs,S., Immunization of RhO(D)-negative secundigravidae whose first pregnancy was terminated by induced abortion, Haematologia, 8, 291-298, 1974 **Ref Id** 126740 **Country/ies where the study was carried out**	**Sample size** N=397 (however 156 of these had a pregnancy that ended in delivery and did not receive anti-D. Their outcomes are reported in another included study. Therefore, the population of interest for this review is N=241) **Characteristics** <u>Outcome of second pregnancy</u> <u>a. In those who received anti-D after first abortion</u> Induced abortion: 53/96	**Interventions** Some women received 50 micrograms of anti-D IgG after the first induced abortion (n=96) Some women did not receive any prophylaxis after the first induced abortion (n=301)	**Details** The study reports data from women in their second pregnancy, split into two groups: - Women who received 50 micrograms of anti-D following a first trimester abortion in their first pregnancy - Women who were not protected after the first abortion, and whose second pregnancy terminated in induced abortion, miscarriage, or delivery during the study period The serological tests were made immediately after the obstetric event and then three to six months later. All the women were reported to be negative for	**Results** <u>Rates of immunisation at the end of the second pregnancy (number/total (%))</u> a. in women who were given anti-D following their induced abortion: 1/96 (1.0) (Note: this woman delivered a baby at the end of her second pregnancy; therefore it is likely that she became immunised during the pregnancy. The evidence of sensitisation was from a positive papain-treated RBC test at the end of the second pregnancy. ICT result is not reported. This woman had also tested negative using ICT and papain-treated RBC about 6 months before birth)	**Limitations** Women were sensitised after an induced abortion, and therefore are not our exact population of interest. Unclear if the fathers were Rh+ and therefore whether they were actually at risk of sensitisation The sensitisation in the woman who received anti-D is likely to have occurred during the second pregnancy - she tested negative in February and May of the year that she became pregnant and gave birth (November). **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Hungary **Study type** Prospective, observational study **Aim of the study** To clarify the frequency of antibody formation during the second pregnancy in women whose first pregnancy was interrupted in the first trimester. **Study dates** 1971 to 1973 **Source of funding** None stated	(55.2) Miscarriage: 3/96 (3.1) Delivery: 39/96 (40.6) b. In women who did not received anti-D after first abortion Induced abortion: 121/301 (40.2) Miscarriage: 24/301 (8.0) Delivery; 156/301 (51.8) **Inclusion criteria** Rh-D negative Secundigravidae Previous pregnancy ended by first trimester induced abortion **Exclusion criteria** Not reported		immunisation before their first abortion. No further methodological details are given.	b. in women who were not given anti-D following their induced abortion: 2/145 (1.4) (Note: out of those sensitised, 1 woman had a miscarriage and 1 woman had an induced abortion in their second pregnancy. The former had a positive test result using papain-treated RBC (1:256) and ICT (1:128). The latter had received an intramuscular blood injection in childhood, and no details are given regarding her particular test results)	This study population overlaps with the population of Simonovits et al. 1980. Therefore, outcomes in women who were not protected and whose pregnancies ended in delivery will not be reported in this study, as they are reported elsewhere.
Full citation Katz,J., Marcus,R.G., Incidence of Rh immunization following abortion: possible detection of lymphocyte priming to Rh antigen, American Journal of Obstetrics and Gynecology, 117,	**Sample size** Prospective study: N=36 Retrospective study: N=208 (however only 25 of them had a previous abortion, and therefore are the population of interest for this review)	**Interventions** N/A	**Details** Prospective study 36 patients were investigated following curettage for a miscarriage of less than 20 weeks gestation. Kleihauer fetal cell counts were performed within 48 hours of the surgery, and tests for rosette immunocyto	**Results** PROSPECTIVE STUDY Presence of Rh antibody at 5 months after miscarriage (number/total (%)) All patients: 1/36 (2.8) Primigravidas only: 0/17 (0)	**Limitations** Prospective study - Miscarriage was up to 20 weeks; therefore some are outside the scope of this guideline - Study was conducted in South Africa and no characteristics of the population are reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
261-267, 1973 **Ref Id** 126795 **Country/ies where the study was carried out** South Africa **Study type** This paper reports both a prospective and a retrospective study **Aim of the study** Not stated **Study dates** 1968 to 1971 (for retrospective study) **Source of funding** Atomic Energy Board South African Medical Research Council	**Characteristics** Of the 36 patients included in the prospective study, 17 were primigravidas and 19 were multigravidas. 24 of them were known to have Rh+ husbands. **Inclusion criteria** Prospective study: - Rh negative - Suffered miscarriage of a pregnancy less than 20 weeks gestation - Required uterine curettage Retrospective study: - Rh negative primipara **Exclusion criteria** None stated		adherence and the presence of plaque-forming cells (PFC) were carried out between day 6 and day 14 after the miscarriage. At the same time, Rh antibody was tested for and in 35 women, this test was repeated 5 - 6 months later. <u>Retrospective study</u> The findings of all Rh-negative primiparas admitted to the Queen Victoria Maternity Hospital over a 3 year period were examined. A total of 208 patients were identified, and split into those who were immunised (i.e. had the Rh antibody) and those who were not immunised. It was then reported whether or not the women had experienced a previous abortion. Results below will be reported out of those women who had a previous abortion. <u>Tests used</u> Rosette immunocytoadherence and the plaque-forming cell technique were used to test for the presence of fetal cells, but that is not an outcome of interest for this review; therefore the methods will not be described further. Rh antibody was tested for using the indirect Coombs' test, enzyme treated cells (Lows papainised cells, ficin and	Multigravidas only: 1/19 (5.3) (Note: this woman had a weak antibody titre on admission and then a titre of 1:4 at 5 months. 2 further women had a positive result using the rosette immunocyte adherence test) RETROSPECTIVE STUDY (primiparous women only) <u>Presence of Rh antibody in women with previous abortion/miscarriage:</u> 5/25 (20%) (Note: it is unclear whether the women could have been sensitised in the current pregnancy. However, in 2 patients the authors state that there is definite evidence of immunisation following abortion/miscarriage: in one patient, the infant born after a primigravida abortion was Rh-negative, and in the other patient, her obstetric history was of three previous abortions.) <u>Neonatal outcomes in sensitised women:</u> - Positive direct Coombs test: 2/3 (66.7%) (note: results of the test are not reported for 2 of the infants born to sensitised women; therefore the denominator is 3) - Hyperbilirubinemia/hydropic infant: 3/4 (75%)	- Unclear which technique was used to test for the presence of antibodies, because the use of ICT, Low's papainised cells and other techniques is reported in the methods - Small sample size, N=36 Retrospective study - Retrospective - Unclear whether the previous abortion occurred in the first trimester. - In three of the sensitised patients, it cannot be proved that the sensitisation was definitely a result of the abortion/miscarriage, rather than in the current pregnancy - Unclear if the previous "abortion" was an abortion or a miscarriage; therefore it could be outside the scope of the guideline - Not reported whether the fathers were Rh+ and hence whether the women were actually at risk of sensitisation - Study was conducted in South Africa and no characteristics of the population are reported - Unclear which technique was used to test for the presence of antibodies, because the use of ICT, Low's papainised cells and other techniques is reported in the methods

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			trypsinised cells), albumin and saline agglutination tests.	(note: one woman delivered a stillborn hydropic infant; the other two had exchange transfusions performed)	- Small sample size, N=25 **Other information**
Full citation Simonovits,I., Timar,I., Bajtai,G., Rate of Rh immunization after induced abortion, Vox Sanguinis, 38, 161-164, 1980 **Ref Id** 127379 **Country/ies where the study was carried out** Hungary **Study type** Prospective case series **Aim of the study** Not stated **Study dates** January 1st 1971 to	**Sample size** N=386 **Characteristics** Not reported **Inclusion criteria** Rh D- Second pregnancy, when the first pregnancy had been medically interrupted Gave birth to a Rh D+ child at the end of the second pregnancy **Exclusion criteria** None stated	**Interventions** None	**Details** This study includes pregnant women who were referred to be screened for Rh immunisation. This study only includes Rh- secundigravidae whose first pregnancy was medically interrupted and who gave birth to an Rh+ child at the end of her second pregnancy. There were 386 women in the study period. The authors considered that if antibodies were detectable with papain-treated red blood cells during the first 3 months of the second pregnancy, that this was likely to be a result of immunisation after the abortion. The women who became positive at the end of the second pregnancy were considered to be exhibiting a secondary immunisation, however the authors state that it is possible that the women became immunised during their second pregnancy. No further methodological details are given.	**Results** <u>Detection of antibodies during second pregnancy (number/total (%))</u> <u>a. By the 2nd to 3rd month of pregnancy</u> Indirect Coombs test: 3/386 (0.8) Papain-teated RBC: 6/386 (1.6) (Note: 2 women who were positive using papain-treated RBC were negative using the indirect Coombs test and 1 had a questionable or unknown result, represented only as a ? in the table) <u>b.By the 8th to 9th month of pregnancy</u> Indirect Coombs' test: 10/386 (2.6) Papain-treated RBC: 12/386 (3.1) (Note: the values for 8-9 months include those who were positive earlier. 1 patients pregnancy ended in miscarriage before the 8-9 month point, but she was positive for antibodies using both tests at 2-3 months and therefore has been included by the authors in those who were positive by 8-9 months. One	**Limitations** Women are having an induced abortion and therefore are not exactly the population of interest for this review Women could have become sensitised during their second pregnancy Unclear at what point during the first pregnancy the abortion occurred and what method was used to terminate the pregnancy These are a discrete sub-group of the population of interest, in that they had to have had a second Rh+ pregnancy to be included. No demographic characteristics are reported for this population. **Other information** This population includes some women from another included study (Simonovits et al., 1974).

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
June 30th 1979 **Source of funding** Not reported				patient who tested positive using papainised cells tested negative using ICT and one had no result listed)	Their outcomes are reported here and will be excluded from the other study.
Full citation Gavin,P.S., Rhesus sensitization in abortion, Obstetrics and Gynecology, 39, 37-40, 1972 **Ref Id** 127567 **Country/ies where the study was carried out** USA **Study type** Clinical trial (not randomised) **Aim of the study** Not stated **Study dates** November 1st 1969 to August 15th 1970	**Sample size** N=57 **Characteristics** Gestational age/weeks (number/total) 4-5 - Rhogam: 0/21 - Placebo: 1/36 6-7 - Rhogam: 0/21 - Placebo: 2/36 8-9 - Rhogam: 7/21 - Placebo: 14/36 10-11 - Rhogam: 4/21 - Placebo: 8/36 12-13 - Rhogam: 4/21 - Placebo: 4/36 14-15 - Rhogam: 3/21 - Placebo: 4/36	**Interventions** Rhogam (n=21) Placebo (n=36)	**Details** During the study period, 491 underwent therapeutic abortions and 180 women were treated for an incomplete miscarriage. Of these, 57 were found to be eligible, as they were Rh- and indirect Coombs test negative at the time of the abortion. Out of these 57, 3 refused to participate, 9 were lost to follow-up and 1 was found to have a Rh- husband. Therefore, the remaining 44 patients were combined with 13 patients identified in the same manner from a different facility. All participants were given Rhogam or a placebo in a double-blind manner within 72 hours after the abortion. The patients returned for a follow-up indirect Coombs test and paternal genotype after 4 months. Paternal genotypes were obtained in 50% of the couples, resulting in the elimination of one, as previously stated.	**Results** Incidence of sensitisations at 4 months using indirect Coombs' test (number/total (%)) Rhogam: 0/21 (0) Placebo: 2/36 (5.6) Further information regarding sensitisations in placebo arm **Patient 1:** 18 years old, Gravida 1, Para 0 Received therapeutic abortion by suction curettage at 81 days after onset of LMP. Uterine size was noted to be 11 weeks gestation. **Patient 2:** 17 years old, Gravida 1, Para 0 Received therapeutic abortion by suction curettage at 76 days after onset of LMP. Uterine size was noted to be 10-11 weeks.	**Limitations** 13/57 (22.8%) of women had a gestational age of over 13 weeks and therefore are outside the scope of the guideline. The sensitisations were not in this group though. 33/57 (58%) women were presenting for a therapeutic abortion, and therefore are outside the scope of this guideline. Not randomised, and method of treatment allocation is not described. Method of blinding not reported. 9/57 were lost to follow-up and excluded. They were then replaced with women from another facility. Dose of Rhogam not stated **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Supported in part by the Ortho Research Foundation and the Kaiser Foundation Hospital	16-17 - Rhogam: 1/21 - Placebo: 1/36 18-19 - Rhogam: 1/21 - Placebo: 1/36 20+ - Rhogam: 1/21 - Placebo: 1/36 <u>Primigravida (number/total (%))</u> Rhogam: 6/21 (28.6) Placebo: 12/36 (33.3%) <u>Method of abortion (number/total)</u> **Spontaneous** **-** Rhogam: 5/21 - Placebo: 5/36 **Spontaneous and D&C** - Rhogam: 5/21 - Placebo: 9/36 **Suction** - Rhogam: 8/21 - Placebo: 16/36 **Saline infusion** - Rhogam: 1/21 - Placebo: 0/36 **D&C** - Rhogam: 2/21				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	- Placebo: 4/36 **Hysterotomy** - Rhogam: 0/21 - Placebo: 1/36 **Ectopic** - Rhogam: 0/21 - Placebo: 1/36 **Inclusion criteria** Therapeutic abortion, or surgical treatment of miscarriage Rh- and indirect Coombs test negative at time of procedure **Exclusion criteria** Rh- husband				
Full citation Murray,S., Barron,S.L., McNay,R.A., Transplacental haemorrhage after abortion, Lancet, 1, 631-634, 1970 **Ref Id** 128000 **Country/ies where**	**Sample size** N=483 This is the entire study population; however only 25 were followed-up for analysis of sensitisation, therefore they constitute the population of interest for this review.	**Interventions** No intervention	**Details** During the study period, 483 patients were admitted for therapeutic abortion or miscarriage. Clinical details were recorded on a serially numbered form and blood samples were labelled only with the serial number, so that fetal cell counts were carried out blind. Blood was collected before admission where possible, and	**Results** <u>Rate of sensitisation at six months after abortion, using different techniques (number/total (%))</u> a. Indirect Coombs' test: 1/23 (4.3) b. Low's papain: 2/23 (8.7) c. Papainised cells: 3/23 (13.0) All of these three sensitised women tested negative for transplacental	**Limitations** Over 80% of the whole study population were presenting for induced abortion, not miscarriage. Out of the 23 in whom sensitisation was evaluated, the proportion is unknown. Small sample size (only 25/483 women were followed up) An unknown proportion of women had a gestational age

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
the study was carried out UK **Study type** Prospective case series **Aim of the study** To compare the frequency of transplacental haemorrhage in spontaneous and therapeutic abortion. **Study dates** November 1968 to June 1969 **Source of funding** United Newcastle upon Tyne Hospitals and Newcastle Regional Hospital Board	**Characteristics** <u>Type of procedure (number/total (%))</u> Miscarriage: 91/483 (18.8) Induced abortion: 392/483 (81.2) - Suction curettage: 243/392 (62.0) - Intra-amniotic saline: 73/392 (18.6) - Abdominal hysterotomy: 58/392 (14.8) - Other induced: 18/392 (4.6) **Inclusion criteria** Admission for therapeutic abortion or miscarriage **Exclusion criteria** Not reported		Rh antibody tests were done for Rh- patients. At least three samples (taken immediately before and after evacuation of the uterus, and 6-48 hours later before discharge) were examined for fetal cells. The Kleihauer technique was used for fetal cell detection. To collect direct evidence about the risk of Rh isoimmunisation, all Rh- patients were asked to have another blood specimen examined after six months, to look for Rh antibodies. Many women were reluctant to cooperate. <u>Surgical procedures</u> Women underwent either: - Suction curettage: Vacuum aspiration with the Kerslake curette. This was generally followed by gentle exploration of the uterine cavity with a blunt curette or ovum forceps. - Intra-amniotic saline solution: injected into the amniotic sac after aspiration of clear liquor, and then the uterine cavity was generally emptied using a vacuum curette - Abdominal hysterotomy: in 44/58 cases this was combined with tubal ligation - Other: 8 patients had a conventional D&C and 10 had either a hysterectomy or a	haemorrhage. The details of the cases were as follows: Patient A: Received an abdominal hysterotomy at 18 weeks gestation, and was known to be negative at time of surgery. Tested positive with papainised cells technique only. Para 3, gravida 4. Patient B: Received suction curettage at 10 weeks gestation, but was not tested for antibodies at surgery. Tested positive using Low's papain and papainised cells techniques. Para 2, gravida 3. Patient C: Received suction curettage at 12 weeks gestation, and was known to be negative at time of surgery. Tested positive using all three techniques. Para 3, gravida 4.	outside the scope of the guideline. Characteristics of the study population are not reported. Blood groups of the fathers are not reported; therefore it is unclear whether these women were actually at risk or not **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			variety of techniques The choice of which operation to use was largely decided based on the length of gestation; therefore those at under 14 weeks were more often terminated by suction curettage. Gestation length was measured from the last recorded menstrual period. Follow-up Blood samples for 25 Rh-patients were examined for Rh antibodies six months after the procedure. A sensitive enzyme technique using papainised cells was used, as well as indirect antiglobulin and Low's papain techniques. In two patients, antibodies were known to have been present at the time of surgery; therefore these were excluded. The remainder of the study population were only investigated for trans placental haemorrhage at the time of surgery, and were not followed up. Therefore, rates of sensitisation are not reported, and they do not constitute the main population of interest for this review question.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Walsh,J.J., Lewis,B.V., Transplacental haemorrhage due to termination of pregnancy, Journal of Obstetrics and Gynaecology of the British Commonwealth, 77, 133-136, 1970 **Ref Id** 128002 **Country/ies where the study was carried out** UK **Study type** Prospective case series **Aim of the study** Not reported **Study dates** Not reported	**Sample size** N=200 (however only 18 of these women had antibody measurements and therefore constitute the population of interest for this review) **Characteristics** **<u>Type of abortion (number/total)</u>** D&C: 29/200 Vacuum aspiration: 102/200 Hysterectomy: 19/200 Hysterotomy: 24/200 Intra-amniotic injection of glucose solution: 26/200 **Inclusion criteria** Women undergoing termination of pregnancy **Exclusion criteria** Not reported	**Interventions** N/A	**Details** This study includes 200 women who were admitted for vaginal or abdominal termination of pregnancy. Specimens of venous blood were collected at the point at which the patients were admitted. The blood group was determined, and any Rh negative women were checked for the presence of antibodies. The presence of fetal cells was detected using an acid elution technique. Thin and uniform blood films were examined for fetal cells. Vaginal termination was performed by cervical dilatation followed by curettage or vacuum aspiration. Abdominal termination was performed by hysterotomy or intra-amniotic injections of 50% glucose solution with penicillin cover. In a selected group of patients (those with uterine pathology such as fibroids or those undergoing sterilisation who also suffered from menstrual dysfunction) termination was performed by hysterectomy. 18 Rh - women had antibody tests at 6 months, using papain and Coombs technique.	**Results** Presence of incomplete anti-D at six months: 1/18 (5.6%) (Note: this was a multiparous woman whose titre rose from 1:1 immediately prior to termination to 1:256 Coombs after six months)	**Limitations** Small sample size Women are having termination of pregnancy and therefore are not the exact population of interest Gestational age at which abortion was performed is not reported Characteristics of the study population are not reported Not reported whether the fathers were Rh+ and therefore whether the women were at risk of sensitisation **Other information** The paper also reports another case, who was not part of their study population. The patient was admitted in labour at 35 weeks and delivered a hydropic infant. The blood transfusion service had detected antibodies at a titre of 1:1000 albumin and the hospital lab detected anti-D antibody at 1:128 albumin and Coombs in serum collected one week prior to delivery. The patient was on her second

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported					pregnancy, and the first one had been terminated in another centre by hysterotomy at 14 weeks. There was no history of blood transfusion. This patient has not been reported as a case here, as she was not part of the study population.
Full citation Murray,S., Barron,S.L., Rhesus isoimmunization after abortion, British Medical Journal, 3, 90-92, 1971 **Ref Id** 128117 **Country/ies where the study was carried out** UK **Study type** Prospective case series **Aim of the study** Not stated	**Sample size** N=177 (However, only 96 were successfully followed up and therefore constitute the main population of interest for this review question) **Characteristics** Parity (number/total (%)) **Nulliparous:** 83/177 (46.9%) Of these, 48 were successfully followed up **Multiparous:** 94/177 (53.1%) Of these, 48 were followed up Length of gestation/weeks (number/total (%)) **Up to 12 weeks:** - Followed-up: 44/96 (45.8) - Defaulted: 45/81 (55.5)	**Interventions** N/A	**Details** 177 women were admitted to hospital for a therapeutic abortion or for curettage following a miscarriage. Samples were collected, where possible, before and after the operation to test for transplacental haemorrhage using the Kleihauer technique. Rh-antibody tests were performed with the indirect Coombs test and Low's papain technique, as well as by a sensitive enzyme technique using papainised cells. Wherever possible, blood samples were collected before the operation for such antibody tests, and an attempt was made to obtain a follow-up sample six months after the operation. The maximum effort for follow-up was concentrated on women with their first pregnancy, who would provide the most reliable evidence of primary immunisation. Most patients	**Results** Incidence of post-operative immunisation at approx. 6 months (number/total (%)) a. Using indirect Coombs test 2/96 (2.1%) [Note: One patient was at 12 weeks gestation and the other patient's gestational age was not known. Both received a suction curettage. Both had tested nil for antibodies pre-operatively] b. Using enzyme-treated cells 9/96 (9.4%) [Note: This includes one patient who was not tested pre-operatively but was known to be free of antibodies after her last delivery. 4 were at a gestational age of 12 weeks or less, and 4 were at least 13 weeks. 3 received I.A. saline, 5 had a suction curettage and 1 had a hysterotomy]	**Limitations** Out of the original series of 177 women, 81/177 (45.6%) defaulted and had no post-operative specimen obtained. Method of follow-up is not reported. 10 of the 96 patients followed up had not been tested before the operation, including one of the patients who tested positive using the cellular method. Indirectness of population - includes an unknown proportion of therapeutic abortions. It is unclear whether the sensitised patients were having a surgical termination, or a surgery for an incomplete miscarriage. Only 44/96 women had a gestational age of up to 12 weeks. The remainder had a gestational age of at least 13

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported **Source of funding** Research grant given jointly by the United Newcastle Hospitals and the Newcastle Regional Hospital Board	**13 weeks:** - Followed-up: 40/96 (41.7) - Defaulted: 31/81 (38.3) **Not known:** - Followed-up: 12/96 (12.5) - Defaulted: 5/81 (6.2) Those who were lost to follow-up had higher proportion of early gestations (12 weeks or less) among their primigravidae. Also, 17/81 defaulters had an abdominal hysterotomy, whereas only 10/96 of those followed-up had the operation. <u>Method of termination (number/total)</u> Spontaneous: 11/96 Suction curettage: 54/96 Abdominal hysterotomy: 10/96 Intra-amniotic saline: 18/96 Other methods: 1/96 Not known: 2/96 **Inclusion criteria** Rh-negative women Admitted to hospital for therapeutic abortion or for curettage following		were followed-up between six and nine months after the procedure, however a few were longer than this, with the longest interval being 14 months. Out of the 96 patients successfully followed-up, 86 had been tested before the operation and been found to be free of antibodies.		weeks or an unknown gestational age Blood groups of the fathers are not reported; therefore it is unclear whether these women are actually at risk of sensitisation. **Other information** 6 out of those immunised were reported to have no evidence of transplacental haemorrhage. 1 had <0.1 ml, 1 had 0.1 ml, and 1 had no Kleihauer test performed. The authors report that transplacental haemorrhage, as detected by the Kleihauer technique, was of no value in predicting development of anti-D. <u>Number of women with Rh antibodies detected, related to amount of transplacental haemorrhage</u> None: 6/51 < 0.1 ml: 1/13 0.1 ml: 1/7 No Kleihauer-Betke test performed: 1/26

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	miscarriage **Exclusion criteria** Not reported				

What is the appropriate dose of anti-D that should be administered to women with a threatened miscarriage, miscarriage or ectopic pregnancy in the first trimester?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Stewart,F.H., Burnhill,M.S., Bozorgi,N., Reduced dose of Rh immunoglobulin following first trimester pregnancy termination, Obstetrics and Gynecology, 51, 318-322, 1978 **Ref Id** 127399 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To evaluate the efficacy and safety of a reduced dose (50 micrograms) of Rh D immune globulin for prevention of Rh sensitisation following first trimester vacuum	**Sample size** N=1027 **Characteristics** Age/years (mean (range)): 22.5 (14 - 44) Gestation/weeks (mean (range)): 8.27 (4 - 13) Nulliparous (%): 75 Interval between abortion and routine follow-up/days: 205 days (Note: the 9 who were contacted through special follow-up were contacted at an average of 339 days) Subjects completing follow-up did not differ significantly from those lost to follow-up with respect to: age, weight or race. However, those lost to follow-up reported higher gravidity (2.02 vs. 1.68), higher parity (0.56 vs. 0.39), and higher frequency of previous abortions (0.34 vs. 0.23). **Inclusion criteria**	**Interventions** 50 microgram dose of Rh immune globulin (n=931, of which 691 completed follow-up) 300 microgram dose of Rh immune globulin (n=96, of which 64 completed follow-up)	**Details** Subjects eligible for the study (see inclusion criteria) were recruited from three centres providing first trimester abortion services. Evaluation for the study at the time of abortion included: medical history (obstetric history and history of previous blood transfusions), determination of ABO and Rh type, and screening for atypical blood group antibodies. A preoperative serum specimen was obtained and frozen. Immediately following the procedure, a specimen was obtained for the Kleihauer-Betke test. 1052 subjects undergoing abortion were initially recruited, but 25 were excluded for the following reasons: positive antibody titre prior to operation (n=2), error in Rh typing (n=20), lost forms (n=1), other error in medication or laboratory procedures (n=2). Subjects were randomly assigned to receive either 50 or 300 micrograms of Rh immune globulin intramuscularly, immediately following the abortion (intervals reported were 15 minutes to 4 hours, with the exception of one woman who received it 24 hours	**Results** <u>Presence of Rh D antibodies at 6 months follow-up (number/total)</u> 50 micrograms: 0/691 300 micrograms: 0/64 (Note: One patient from the 50 microgram group had a positive antibody test using automated screening; however retesting of her pre-injection specimen demonstrated a positive result, therefore she was excluded. In addition, one patient who received 300 micrograms was found to have anti-K at follow-up) <u>Adverse reactions (number/total (%))</u> 50 microgram: 1/931 (0.1) 300 microgram: 0/96 (0) (Note: the patient experienced nausea, dizziness, hypotension with BP of 70/40 mmHg, and bradycardia of 64 bpm)	**Limitations** Method of randomisation not stated Loss to follow-up was 26.5% Study does not report what test was used to detect antibodies (e.g. indirect Coombs' test or other) Characteristics of the study groups are not reported separately. Women are undergoing elective abortion, and therefore are not the precise population of interest Paternal blood groups are not reported, and therefore it is not clear whether all these women were actually at risk of sensitisation **Other information** <u>Postoperative</u>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
abortion. **Study dates** November 1974 to March 1976 (follow-up extended to January 1977) **Source of funding** None stated	Undergoing vacuum abortion at 12 weeks gestation or less Rh- and D^u negative Preoperative screening negative for atypical blood group antibodies Capable of understanding the meaning and possible risks of study participation, and willing to give informed consent Willing to return for follow-up evaluation 4-6 months after abortion **Exclusion criteria** Not stated		later). At the time of follow-up evaluation, a history for the intervening period was taken (pregnancy and blood transfusions), and serum was tested for the presence of atypical blood group antibodies: at room temperature, in high protein after 30 minutes incubation at 37 degrees, and by the antihuman globulin technique. A sample of the subjects lost to routine follow-up was identified and targeted for intensive follow-up tracing efforts (all patients registered during December 1975 and January 1976). This was conducted to assess whether there were systematic differences between those lost to follow-up and those completing the study. 40 of these patients could be identified. Statistical comparisons between subjects lost to follow-up and those completing the study were performed. Of the initial 1027 participants, 746 completed follow-up screening through the routine study protocol, and an additional 9 were screened through the intensive follow-up programme. Therefore, in total, 755 subjects completed screening.		Kleihauer-Betke test values: percent of fetal RBC in maternal peripheral smear (number/total (%)) 1.1: 1/900 (0.1) Less than 1: 15/900 (1.7) Less than 0.1: 26/900 (2.9) Rare, occasional, or positive: 6/900 (0.7) Negative: 852/900 (94.7)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hensleigh,P.A., Leslie,W., Dixon,E., Hall,E., Kitay,D.Z., Jackson,J.E., Reduced dose of Rho(D) immune globulin following induced first-trimester abortion, American Journal of Obstetrics and Gynecology, 129, 413-416, 1977 **Ref Id** 127400 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To present clinical data concerning the effectiveness of reduced doses of Rh (D) immune globulin in Rh-negative women undergoing induced abortion by suction curettage during the first 12 weeks of	**Sample size** N=187 **Characteristics** Gestational age/weeks (n) 5 weeks: 3 6 weeks: 8 7 weeks: 15 8 weeks: 27 9 weeks: 11 10 weeks: 27 11 weeks: 23 12 weeks: 13 13 weeks: 3 14 weeks: 4 Note: these figures are estimations from a bar chart provided by the authors Gravidity (range): 1 - 10 **Inclusion criteria** Undergoing elective termination in two hospital-based abortion centres Rh negative with no evidence of atypical antibodies No history or evidence of hypersensitivity to human immuno-globulin, and had never	**Interventions** Rh_o(D) immune globulin in one of three doses: - 73 micrograms - 155 micrograms - 499 micrograms	**Details** Patients enrolled in this study were volunteers giving informed consent and undergoing elective termination by suction curettage. 187 patients were enrolled, and following the surgery, their medical history was recorded. Length of gestation was calculated from the first day of the LMP. If the physician found the uterine size to differ by any more than a week from the stage estimated using LMP, the results of the physical exam were used. The Rh D human immune globulin used (Gamulin) contained 499 micrograms of antibody per dose. Dilutions of this were prepared to contain 155 micrograms per dose and 73 micrograms per dose. The resulting single-dose vials were double blind labelled according to a randomised code. Patients from one centre (Kansas) received 499 and 155 micrograms in a ratio of 1:4. Patients in the other centre (Georgia) received 499, 155 and 73 micrograms in a ratio of 2:4:4. One vial of Rh D immune globulin was administered intramuscularly after cross matching with a 1:1000 dilution of the RhD immune globulin lot. Most patients received the dose within 24 hours of the abortion, but two received it between 24 and 48	**Results** Incidence of sensitisation (number/total (%)) 73 micrograms: 0/8 155 micrograms: 0/83 499 micrograms: 0/25 (Note: the authors report that no sensitisations occurred, but do not report the exact denominators for each arm of the trial. Therefore, the technical team have used the latest known denominators as a proxy) Positive passive antibody titres (number/total (%)) a. at 48 hours 73 micrograms: 5/10 (50) 155 micrograms: 58/91 (63.7) 499 micrograms: 23/25 (92) b. at 6 weeks 73 micrograms: 0/10 (0) 155 micrograms: 4/88 (4.5) 499 micrograms: 18/24 (75) c. at 4 months 73 micrograms: 0/10 (0) 155 micrograms: 1/77 (1.3) 499 micrograms: 0/23 (0) d. at 6 months	**Limitations** Women are undergoing termination of pregnancy, and therefore are not the exact population of interest Method of randomisation is not reported 7/187 (3.7%) patients were at or above 13 weeks gestation; therefore outside the scope of the guideline. 28% of patients were lost to follow-up Paternal blood group is not reported, and therefore it is not clear whether all these patients were at risk. Characteristics of the study groups are not reported, so there may have been unreported differences between the arms. **Other information** Kleihauer-Betke test results: number of fetal

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pregnancy **Study dates** Not reported **Source of funding** None reported	been transfused with Rho(D)- or D^u- positive blood Received no blood or blood products in the period of gestation under study **Exclusion criteria** Not reported		hours after the surgery. All treatment was performed on a double blind basis. Fresh maternal blood smears were prepared to determine fetal-maternal haemorrhage using the Kleihauer-Betke stain. Quantitation involved recording the number of fetal cells per 1000 maternal cells. All patients were observed for local or systemic reactions for about 3 hours following anti D injection. Maternal serum was obtained 2 days, six weeks, four months and six months after treatment. It was frozen and sent to Dow Chemical Company's lab, where Rho (D) antibody titres were measured using standard antiglobulin titration. Serum samples from a given patient were titrated simultaneously with the same reagents and Rho (D) test cells. The highest dilution of serum showing agglutination was read as the end point and the result was expressed as the reciprocal of this dilution. The eventual disappearance of passive (exogenous) antibody and the continued absence of active (endogenous) antibody were taken as signs that sensitisation had not occurred. However, only 134 patients were available for follow-up.	73 micrograms: 0/8 (0) 155 micrograms: 1/83 (1.2) 499 micrograms: 0/25 (0) The patient who had positive titres at 4 and 6 months had a small fetomaternal leak with two fetal cells per 1000. Her antibody titre was reported as 1 at 48 hours, <1 at six weeks and 1 at four months. The authors state that since the titres only differ by one tube in the dilution series, they are within the expected test variation and therefore do not strictly indicate reappearance of antibody. At the time of the four month follow-up, the patient was pregnant again and 13 days later she was evaluated in another clinic and found to have no antibodies. At that time she underwent another induced abortion and received a standard dose of Rh immune globulin. Therefore, the presence of antibodies at six months is consistent with the presence of passive antibodies from the second treatment. A final titre at 12 months was negative and proved that she was not sensitised to Rh D antigen.	<u>cells per 1000 maternal cells (% of dosage group)</u> **0 cells** - 155: 73 - 499: 70 **1 cell** - 155: 9 - 499: 5 **2 cells** - 155: 8 - 499: 15 **3 cells** - 155: 2 - 499: 5 **4 cells** - 155: 10 - 499: 5 **6 cells** - 155: 4 - 499: 1 Note: Only 95 women had satisfactory stains. These are estimations of % from a bar chart; no information is provided for the 73 micrograms group, due to the low number of women with satisfactory stains.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Adverse reactions There were no cases of systemic or local adverse drug reactions.	
Full citation Keith,L., Bozorgi,N., Small dose anti-Rh therapy after first trimester abortion, International Journal of Gynaecology and Obstetrics, 15, 235-237, 1977 **Ref Id** 127676 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** Not stated **Study dates**	**Sample size** N=400 (However only 315 returned for follow-up antibody screening; no details are reported about the 85 that were lost to follow-up) **Characteristics** All patients tested negative for antibodies prior to the porcedure, with the exception of 3 patients in the 50 micrograms arm, for whom no information was available. Uterine size / menstrual weeks gestation (number/total) <7 50 micrograms: 16/298 300 micrograms: 1/17 7 50 micrograms: 36/298 300 micrograms: 3/17 8 50 micrograms: 91/298 300 micrograms: 5/17	**Interventions** 50 micrograms of anti-D [MICRhoGAM] (n=298) 300 micrograms of anti-D [RhoGAM] (n=17)	**Details** Rh- women were selected from patients at a private, outpatient abortion service. Eligible patients gave informed consent, and those who declined to participate were given the standard dose of 300 micrograms. 400 women agreed to participate, and were randomised to received either 50 or 300 micrograms of RhoGAM (anti-D). 315 of them returned for antibody assessment at 6 months. Patients were assigned using numerical codes which were only opened when all blood samples had been taken. The difference in sample sizes between the two arms is because 300 micrograms had already been demonstrated to be effective.	**Results** Detection of antibodies at 6 months (number/total (%)) 50 micrograms: 0/298 (0) 300 micrograms: 0/17 (0) (Note: for three women in the 50 microgram group, information about antibodies present prior to prophylaxis was not available) Adverse reactions There were no adverse reactions in either arm, although information was not available for 11 women in the 50 micrograms arm and 2 in the 300 micrograms arm.	**Limitations** Women are undergoing elective abortion and therefore are not the precise population of interest. Paternal blood groups are not reported and therefore, it is unclear whether these women are actually at any risk of sensitisation 85/400 (21%) were lost to follow-up. Characteristics of those lost to follow-up, even with regards to what intervention they were randomised to, are not reported Big difference in sample size between the two arms, and their randomisation ratio is not reported. Therefore, there could have been differential loss to follow-up

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported **Source of funding** None stated	9 50 micrograms: 60/298 300 micrograms: 6/17 10 50 micrograms: 42/298 300 micrograms: 1/17 11 50 micrograms: 32/298 300 micrograms: 1/17 12 50 micrograms: 15/298 300 micrograms: 0/17 >12 50 micrograms: 0/298 300 micrograms: 0/17 No information available 50 micrograms: 6/298 300 micrograms: 0/17 Age / years (number/total) Under 20 50 micrograms: 101/298 300 micrograms: 3/17 20 - 29 50 micrograms: 163/298 300 micrograms: 12/17 30 - 39 50 micrograms: 31/298 300 micrograms: 2/17				Method of randomisation is not reported. Antibody test used for screening at 6 months is not reported No details of the treatment that women received for their abortion are reported (therefore it is unclear if they received surgery or medical management) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	40 - 49 50 micrograms: 2/298 300 micrograms: 0/17 No information available 50 micrograms: 1/298 300 micrograms: 0/17 Gravida (number/total) 1 50 micrograms: 198/298 300 micrograms: 8/17 2 50 micrograms: 59/298 300 micrograms: 4/17 3 50 micrograms: 24/298 300 micrograms: 3/17 4 50 micrograms: 6/298 300 micrograms: 2/17 5 50 micrograms: 8/298 300 micrograms: 0/17 6 50 micrograms: 2/298 300 micrograms: 0/17 No information available 50 micrograms: 1/298 300 micrograms: 0/17 Parity (number/total)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	0 50 micrograms: 251/298 300 micrograms: 12/17 1 50 micrograms: 22/298 300 micrograms: 2/17 2 50 micrograms: 16/298 300 micrograms: 3/17 3 50 micrograms: 4/298 300 micrograms: 0/17 4 50 micrograms: 4/298 300 micrograms: 0/17 No information available 50 micrograms: 1/298 300 micrograms: 0/17				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Rh negative patients at a private outpatient abortion service Agreed to accept randomisation and to return 6 months later for antibody determination **Exclusion criteria** Not reported				