National Institute for Health and Care Excellence

Draft for consultation

Termination of pregnancy

[F] Termination of pregnancy before ultrasound evidence

NICE guideline <TBC>

Evidence reviews

April 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Termination of pregnancy before ultrasound evidence

Review question

Is it safe and effective to start termination before there is ultrasound evidence of an intrauterine pregnancy?

Introduction

The aim of this review is to determine whether it is safe and effective to termination pregnancy prior to ultrasound evidence of intrauterine pregnancy.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women who have requested a surgical or medical termination of pregnancy who have had an ultrasound scan that has not shown evidence of pregnancy (i.e., there is no gestational sac on scan or there is an apparent gestation sac without a yolk sac)
Intervention	Initiation of surgical [using vacuum aspiration] or medical [using mifepristone and misoprostol] termination of pregnancy without definitive evidence of an intra-uterine pregnancy on ultrasound scan (i.e., apparent gestational sac without a yolk sac or no gestational sac).
Comparison	Initiation of surgical [vacuum aspiration] or medical [using mifepristone and misoprostol] termination of pregnancy when there is ultrasound confirmation of an intra-uterine pregnancy(i.e., presence of a gestation sac containing a yolk sac or fetal pole)
Outcome	**Critical outcomes:** • Missed diagnosis of ectopic pregnancy • Need for emergency care/hospital admission • Patient satisfaction **Important outcomes:** • Time to completion of treatment • Ongoing pregnancy • Need for repeat doses of misoprostol (mToP) • Complete termination of pregnancy without the need for surgical intervention (mToP) • Complete termination of pregnancy without the need for repeat surgical evacuation (sToP)

mToP: medical termination of pregnancy; sToP: surgical termination of pregnancy

For further details see the full review protocol in appendix A.

Clinical evidence

Included studies

Only studies conducted from 1985 onwards were considered for this review question, as mifepristone was made available in the UK in 1991 and evidence to support the use of mifepristone in practice is unlikely to be more than 5 years before its licensing in 1991. The surgical techniques used pre-1990 were also different to those used currently, however for consistency, an overall date limit of 1985 was decided, and any eligible studies on surgical termination of pregnancy published between 1985-1990 were downgraded for indirectness for this reason instead.

Three non-randomised, comparative studies were included in this evidence review. The studies compared women with or without ultrasound evidence of an intrauterine pregnancy who received medical (Bizjak 2017; Heller 2015) or surgical (Edwards 1997) termination of a pregnancy.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes
Bizjak 2017 Comparative retrospective cohort study Sweden, Austria	n=2643 Women requesting medical termination of pregnancies ≤ 49 days of gestation, based on ultrasound dating and last menstrual period.	**Medical termination:** 200mg (Sweden) or 600mg (Austria) mifepristone followed by 800micrograms (mcg) vaginal misoprostol (Sweden) or 400mcg oral misoprostol (Austria) 24 to 48 hours later. Additional oral misoprostol (400mcg) was self-administered if no vaginal bleeding had occurred after 3 hours. **Without confirmed intrauterine pregnancy (no-IUP;** defined as an empty uterine cavity or an intrauterine echogenic saclike structure without a yolk sac) **With confirmed intrauterine pregnancy (IUP;** defined as a yolk sac or a fetal structure with or without cardiac activity)	• Missed diagnosis of ectopic pregnancy • Ongoing pregnancy • Complete termination of pregnancy without the need for surgical intervention

Study and setting	Population	Intervention/ comparison	Outcomes
Edwards 1997 Comparative retrospective cohort study USA	n=1530 Women wanting an abortion of a pregnancy <6 weeks' gestation who had a positive urine pregnancy test at the clinic (sensitivity 25mIU/ml hCG).	**Surgical termination:** Cervical dilation to 7mm with Pratt dilators; handheld 60ml syringe with a rigid 7mm curved curette used to aspirate the products of conception. IV midazolam and nalbupbine and/or a cervical block also given. In women without preoperative US visualisation of the gestational sac, aspiration was followed by sharp curettage of the upper uterine cavity in the area of the tubal ostia. Immediately after the procedure, a vaginal sonogram was performed to confirm the evacuation of either the gestational sac or the decidua or both **Without confirmed intrauterine pregnancy (no-IUP;** defined as no gestational sac on vaginal US; gestational age 3^{+0} to 3^{+6} weeks) **With confirmed intrauterine pregnancy (IUP;** defined as gestational sac on vaginal US) • Gestational age 5^{+0} to 5^{+6} weeks • Gestational age 4^{+0} to 4^{+6} weeks	• Missed diagnosis of ectopic pregnancy • Ongoing pregnancy • Complete termination of pregnancy without the need for repeat surgical intervention
Heller 2015 Comparative retrospective cohort study Scotland	n=1155 Women undergoing a termination of a pregnancy which on first visit was up to 6 weeks' gestation according to ultrasound scan.	**Medical termination:** 200mg mifepristone followed by 800mcg vaginal misoprostol 24 to 48 hours later. **Without confirmed intrauterine pregnancy (no yolk sac or fetal pole on US):** • **- Meeting study protocol for ToP (no-IUP IUS;** defined as ultrasound scan showing intrauterine gestation sac 3 to 20mm that is eccentrically placed, with a visible decidual reaction; with no clinical symptoms suggestive of ectopic pregnancy [pain, bleeding] or any significant risk factors for ectopic pregnancy [sterilisation, tubal surgery, previous ectopic pregnancy] and with the last menstrual period	• Missed diagnosis of ectopic pregnancy • Ongoing pregnancy • Complete termination of pregnancy without the need for surgical intervention

Study and setting	Population	Intervention/ comparison	Outcomes
		consistent with a pregnancy of less than 6 weeks' gestation). • **- Empty uterus (no-IUP EU,** defined as no sac or fetal pole and not meeting the study protocol) **With confirmed intrauterine pregnancy (IUP;** defined as a yolk sac or a fetal pole)	

EU: empty uterus; IUP: intrauterine pregnancy; IUS: intrauterine sac; IV: intravenous; mcg: micrograms; US: ultrasound

See the full evidence tables in appendix D and forest plots in appendix E.

Quality assessment of clinical studies included in the evidence review

See the clinical evidence profile in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material 2 for details

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Evidence statements

Critical outcomes

Missed diagnosis of ectopic pregnancy

Non-RCT evidence did not detect a clinically important difference in 'the rate of missed diagnosis of ectopic pregnancy' between women whose medical termination of pregnancy was initiated before or after there was ultrasound evidence of an intrauterine pregnancy (2 observational studies, n=3796; RR= 0.26 [95% CI 0.03, 2.12]; very low quality); however there was uncertainty around the estimate.

Non-RCT evidence reported no events of 'missed diagnosis of ectopic pregnancy' in either the women whose surgical termination of pregnancy was initiated before there was ultrasound evidence of an intrauterine pregnancy or after; therefore differences between groups could not be estimated (1 observational study, n=1530; very low quality).

Need for emergency care/hospital admission

No evidence was identified to inform this outcome.

Patient satisfaction

No evidence was identified to inform this outcome.

Important outcomes

Time to completion of treatment

No evidence was identified to inform this outcome.

Ongoing pregnancy

Non-RCT evidence did not detect a clinically important difference in the ongoing pregnancy rate between women whose medical (2 observational studies, n=3785; RR= 1.06 [95% CI 0.34, 3.34]; very low quality) or surgical (1 observational study, n=1530; RR= 0.56 [95% CI 0.03, 11.59]; very low quality) termination of pregnancy was initiated before or after there was ultrasound evidence of an intrauterine pregnancy; however there was uncertainty around these estimates.

Need for repeat doses of misoprostol

No evidence was identified to inform this outcome.

Complete termination of pregnancy without the need for (repeat) surgical intervention

Non-RCT evidence showed no clinically important difference in 'the rate of complete termination of pregnancy without the need for (repeat) surgical intervention' between women whose medical (2 observational studies, n=3785; RR= 1 [95% CI 0.98, 1.02]; very low quality) or surgical (1 observational study, n=1530; RR= 1 [95% CI 0.99, 1.01]; very low quality) termination of pregnancy was initiated before or after there was ultrasound evidence of an intrauterine pregnancy.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Initiating medical or surgical termination before a definitive diagnosis of pregnancy can be made on ultrasound introduces the possibility of missing an asymptomatic ectopic pregnancy. This may have serious consequences and lead to emergency care/hospital admission, potentially impacting future fertility. Missed diagnosis of ectopic pregnancy and need for emergency care/hospital admission were therefore selected as a critical outcomes. The committee also agreed to prioritise patient satisfaction as a critical outcome for decision-making as termination of pregnancy is an area where women are known to have strong preferences for prompt resolution. Time to completion of treatment was included as an important outcome because the possibility of having a termination before ultrasound evidence compared to having to wait 2 to 3 weeks until the pregnancy is visible on ultrasound is likely to further influence patient preference. The need for repeat doses of misoprostol, ongoing pregnancy and complete abortion without the need for (repeat) surgical intervention were included as important outcomes due to the impact that needing a second

appointment and intervention will have on both the woman and on available resources.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using the GRADE methodology. The quality of the evidence across all outcomes was very low, mainly due to the fact that all the included studies were observational. The majority of the outcomes were also downgraded for imprecision due to low event rates. There was no evidence for patient satisfaction, time to completion of treatment, need for repeat doses of misoprostol (for medical abortion), and need for emergency care or hospital admission.

Benefits and harms

The evidence showed that there were no clinically important differences in the rates of complete abortion without the need for (repeat) surgical intervention between women with definitive evidence of an intrauterine pregnancy on ultrasound compared to women who had an ultrasound but where an intrauterine pregnancy could not be confirmed whereas for missed diagnosis of ectopic pregnancy and ongoing pregnancy, it was unclear whether or not there was a clinically important difference.

The committee noted the evidence from the review on "What factors help or hinder the accessibility and sustainability of a safe termination of pregnancy service?" which showed that women had clear preferences not to prolong waiting times, and therefore they agreed that the recommendation should be to offer immediate treatment if that was the woman's preferred option. However, although the committee agreed that a termination of pregnancy at this stage should only be offered to women who did not have any signs or symptoms of an ectopic pregnancy and whilst the committee were aware of other evidence that shows there is a lower incidence of ectopic pregnancy in the population requesting a termination (0.8, 0.9, 5.9 /1000 in Bizjak, Heller, and Edwards respectively) compared with an overall rate of 11/1000 in the general population (NICE, 2012), nevertheless it remains a possibility and diagnosis can be delayed if symptoms are attributed to recovery following a termination. Whilst rare, the consequences of a missed ectopic pregnancy can be serious. The committee therefore agreed it was essential that women were made aware of the importance of the potential need to participate in follow-up appointments if completion of the termination could not be confirmed at the time of treatment to facilitate early intervention, the nature of the follow-up should be decided locally given the variation in nature of provider. They noted that commonly used protocols included the use of blood tests to check that serum hCG is declining, or urinary pregnancy testing to ensure this becomes negative after the procedure. If there are signs and symptoms of ectopic pregnancy (e.g., pain, bleeding) referral to an Early Pregnancy Assessment Unit (EPAU) to rule out this diagnosis should be pursued before treatment is provided.

The committee were also aware of previous national guidance from the Royal College of Obstetricians and Gynaecologists (2011) recommending that surgical procedures could be used in terminations before ultrasound evidence of pregnancy if there are appropriate safeguards, including inspection of aspirated tissue. Whilst the study included in this review did not give cause for concern, the committee agreed that in the surgical group a similar follow-up programme to those used in the medical termination group is needed where a gestation sac was not clearly identified in the aspirate in order to exclude an on-going pregnancy or missed ectopic pregnancy.

Despite the limited evidence, the committee decided to prioritise other areas addressed by the guideline for future research and therefore made no research

recommendations regarding termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee considered that there was unlikely to be a significant resource impact from the recommendations made because although providers of surgical terminations before ultrasound evidence of pregnancy will need to acquire skills in inspecting aspirated products of conception for the presence of chorionic villi and a gestational sac, and the necessary equipment to carry out this task, including ready access to ultrasound in the treatment room cases where the sac is not seen in the aspirate as well as pathways for obtaining serum hCG, staff trained in interpreting test results, and the ability to refer promptly into an EPAU where an ectopic pregnancy is suspected, these costs are likely to be balanced out by a reduction in the need for repeat visits or ultrasound or termination-related adverse events which all require additional visits and treatment because the terminations will be completed at an earlier gestational age.

References

Bizjak 2017

Bizjak, I., Fiala, C., Berggren, L., Hognert, H., Saav, I., Bring, J., Gemzell-Danielsson, K., Efficacy and safety of very early medical termination of pregnancy: a cohort study, BJOG: An International Journal of Obstetrics and Gynaecology, 124, 1993-1999, 2017

Edwards 1997

Edwards,J., Carson,S.A., New technologies permit safe abortion at less than six weeks gestation and provide timely detection of ectopic gestation, American Journal of Obstetrics and Gynaecology, 176, 1101-1106, 1997

Heller 2015

Heller, R., Cameron, S., Termination of pregnancy at very early gestation without visible yolk sac on ultrasound, Journal of Family Planning & Reproductive Health Care, 41, 90-5, 2015

NICE 2012

National Institute for Health and Care Excellence. (2012) Ectopic pregnancy and miscarriage: Diagnosis and initial management (CG154).

RCOG 2011

Royal College of Obstetricians and Gynaecologists (2011). The care of women requesting induced abortion: Evidence-based clinical guideline number 7. London: RCOG Press

Appendices

Appendix A – Review protocols

Review protocol for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

ID (to be deleted in final version)	Field (based on PRISMA-P	Content
I	Review question in SCOPE	Is it safe and effective to start termination before there is ultrasound evidence of an intrauterine pregnancy?
Ia	Review question in guideline	Is it safe and effective to start termination before there is ultrasound evidence of an intrauterine pregnancy?
II	Type of review question	Intervention
III	Objective of the review	To determine whether it is safe and effective to terminate a pregnancy prior to ultrasound evidence of intrauterine pregnancy.
IV	Eligibility criteria – population	Women who have requested a surgical or medical termination of pregnancy who have had an ultrasound scan that has not shown evidence of pregnancy (i.e., there is no gestational sac on scan or there is an apparent gestation sac without a yolk sac) Exclusions: - Studies with indirect populations will not be considered (including women who present with pain and bleeding, those experiencing early miscarriage/ spontaneous abortion, or who have been diagnosed with or are suspected to have an ectopic pregnancy
V	Eligibility criteria – intervention(s)	Initiation of surgical [using vacuum aspiration] or medical [using mifepristone and misoprostol] termination of pregnancy without definitive evidence of an intra-uterine pregnancy on ultrasound scan (i.e., apparent gestational sac without a yolk sac or no gestational sac).
VI	Eligibility criteria – comparator(s)	Initiation of surgical [vacuum aspiration] or medical [using mifepristone and misoprostol] termination of pregnancy when there is ultrasound confirmation of an intra-uterine pregnancy(i.e., presence of a gestation sac containing a yolk sac or fetal pole)
VII	Outcomes and prioritisation	**Critical outcomes:** • Missed diagnosis of ectopic pregnancy

ID (to be deleted in final version)	Field (based on PRISMA-P	Content
		• Need for emergency care/hospital admission • Patient satisfaction **Important outcomes:** • Time to completion of treatment • Ongoing pregnancy • Need for repeat doses of misoprostol (mToP) • Complete termination of pregnancy without the need for surgical intervention (mToP) • Complete termination of pregnancy without the need for repeat surgical evacuation (sToP)
VIII	Eligibility criteria – study design	- Systematic reviews of RCTs - RCTs - If insufficient RCTs: comparative prospective cohort studies n≥100 each arm - If insufficient prospective cohort studies: comparative retrospective cohort studies n≥100 each arm
IX	Other inclusion exclusion criteria	Inclusion: - English-language
X	Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of women, where possible: Termination of pregnancy method: - Surgical - Medical Medical conditions: - Complex pre-existing medical conditions - No complex pre-existing medical conditions Type of ultrasound scan: - Vaginal (e.g., transvaginal, endovaginal) - Abdominal Definition of ultrasound evidence of no pregnancy: - Apparent gestational sac without a yolk sac versus no gestational sac
XI	Selection process – duplicate screening/selection/analysis	Dual weeding will be performed for this question Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual data extraction will not be performed for this question.

ID (to be deleted in final version)	Field (based on PRISMA-P	Content
XII	Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations,
XIII	Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Dates: from 1985 Studies conducted from 1985 onwards will be considered for this review question, as mifepristone was made available in the UK in 1991 and evidence to support the use of mifepristone in practice is unlikely to be more than 5 years before its licensing in 1991. The surgical techniques used pre-1990 were also different to those used currently, however for consistency, an overall date limit of 1985 was decided, and any eligible studies on surgical termination of pregnancy published between 1985-1990 will be downgraded for indirectness for this reason instead.
XIV	Identify if an update	Not an update
XV	Author contacts	For details please see the guideline in development web site.
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
XVII	Search strategy – for one database	For details please see appendix B
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation

ID (to be deleted in final version)	Field (based on PRISMA-P	Content
		(GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
XXII	Methods for analysis – combining studies and exploring (in)consistency	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • RoBIS for systematic reviews • Cochrane risk of bias tool for RCTs • Newcastle-Ottawa scale for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Synthesis of data: Pairwise meta-analysis will be conducted where appropriate for all other outcomes. When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter Minimally important differences: Statistical significance will be used for 'need for emergency care/hospital admission'. For the remaining outcomes, default values will be used: 0.8 and 1.25 for dichotomous outcomes (relative risks); 0.5 times SD (for the control group) for continuous outcomes.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
XXIV	Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Profession Iain Cameron in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance will undertake systematic literature searches, appraise the evidence, conduct meta-analysis and cost-effectiveness analysis where

ID (to be deleted in final version)	Field (based on PRISMA-P	Content
		appropriate, and draft the guideline in collaboration with the committee. For details please see the methods chapter.
XXVII	Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXVIII	Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXIX	Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
XXX	PROSPERO registration number	Not registered

GRADE: Grading of Recommendations Assessment, Development and Evaluation; mToP: medical termination of pregnancy; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; RCT: randomised controlled trial; RoBIS: risk of bias in systematic reviews; sToP: surgical termination of pregnancy

Appendix B – Literature search strategies

Literature search strategy for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy? The search for this topic was last run on 19th November 2018 during the re-runs for this guideline.

Database: Medline & Embase (Multifile)
Last searched on **Embase Classic+Embase** 1947 to 2018 November 16, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to November 16, 2018
Date of last search: 19th November 2018

#	Searches
1	exp abortion/ use emczd
2	exp pregnancy termination/ use emczd
3	exp Abortion, Induced/ use ppez
4	Abortion Applicants/ use ppez
5	exp Abortion, Spontaneous/ use ppez
6	exp Abortion, Criminal/ use ppez
7	Aborted fetus/ use ppez
8	fetus death/ use emczd
9	abortion.mp.
10	(abort$ or postabort$ or preabort$).tw.
11	((f?etal$ or f?etus$ or gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) and terminat$).tw.
12	((f?etal$ or f?etus$) adj loss$).tw.
13	((gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) adj3 loss$).tw.
14	(((elective$ or threaten$ or voluntar$) adj3 interrupt$) and pregnan$).tw.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	exp Ultrasonography/ use ppez
17	exp ultrasound/ use emczd
18	exp echography/ use emczd
19	(ultrasound$ or ultrasonograph$ or sonogra$ or endosonogra$).mp.
20	16 or 17 or 18 or 19
21	Gestational Sac/ use ppez
22	gestational sac/ use emczd
23	Yolk Sac/ use ppez
24	yolk sac/ use emczd
25	((yolk$ or yolc$ or gestation$) adj sac$).tw.
26	((f?etal$ or embryo$) adj3 pole$).tw.
27	*Endometrium/ use ppez
28	*endometrium/ use emczd
29	(endometr$ adj3 thick$).tw.
30	((intrauterin$ or intra-uterin$) adj3 (pregnan$ or gestation$)).tw.
31	IUP.tw.
32	(early adj gestation$).tw.
33	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

#	Searches
34	15 and 20 and 33
35	(ultrasound$ or ultrasonograph$ or sonogra$ or endosonogra$).m_titl.
36	(abortion or termination).m_titl.
37	15 and 35 and 36
38	((early or ultra-early) adj3 (abortion or termination)).m_titl.
39	15 and 38
40	34 or 37 or 39
41	remove duplicates from 40
42	limit 41 to english language
43	limit 42 to yr="1985 -Current"
44	letter/
45	editorial/
46	news/
47	exp historical article/
48	Anecdotes as Topic/
49	comment/
50	case report/
51	(letter or comment*).ti.
52	44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53	randomized controlled trial/ or random*.ti,ab.
54	52 not 53
55	animals/ not humans/
56	exp Animals, Laboratory/
57	exp Animal Experimentation/
58	exp Models, Animal/
59	exp Rodentia/
60	(rat or rats or mouse or mice).ti.
61	54 or 55 or 56 or 57 or 58 or 59 or 60
62	letter.pt. or letter/
63	note.pt.
64	editorial.pt.
65	case report/ or case study/
66	(letter or comment*).ti.
67	62 or 63 or 64 or 65 or 66
68	randomized controlled trial/ or random*.ti,ab.
69	67 not 68
70	animal/ not human/
71	nonhuman/
72	exp Animal Experiment/
73	exp Experimental Animal/
74	animal model/
75	exp Rodent/
76	(rat or rats or mouse or mice).ti.
77	69 or 70 or 71 or 72 or 73 or 74 or 75 or 76

#	Searches
78	61 use ppez
79	77 use emczd
80	78 or 79
81	43 and 80
82	43 not 81

Database: Cochrane Library via Wiley Online

Date of last search: 19th November 2018

#	Searches
#1	MeSH descriptor: [Abortion, Induced] explode all trees
#2	MeSH descriptor: [Abortion Applicants] explode all trees
#3	MeSH descriptor: [Abortion, Spontaneous] explode all trees
#4	MeSH descriptor: [Abortion, Criminal] explode all trees
#5	MeSH descriptor: [Aborted Fetus] explode all trees
#6	"abortion":ti,ab,kw (Word variations have been searched)
#7	(abort* or postabort* or preabort*):ti,ab,kw (Word variations have been searched)
#8	((fetal* or fetus* or foetal* or foetus* or gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) and terminat*):ti,ab,kw (Word variations have been searched)
#9	((fetal* or fetus* or foetal* or foetus*) next loss*):ti,ab,kw (Word variations have been searched)
#10	((gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) near/3 loss*):ti,ab,kw (Word variations have been searched)
#11	(((elective* or threaten* or voluntar*) near/3 interrupt*) and pregnan*):ti,ab,kw (Word variations have been searched)
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Ultrasonography] explode all trees
#14	(ultrasound* or ultrasonograph* or sonogra* or endosonogra*):ti,ab,kw (Word variations have been searched)
#15	#13 or #14
#16	MeSH descriptor: [Gestational Sac] this term only
#17	MeSH descriptor: [Yolk Sac] this term only
#18	((yolk* or yolc* or gestation*) next sac*):ti,ab,kw (Word variations have been searched)
#19	((fetal* or foetal* or embryo*) near/3 pole*):ti,ab,kw (Word variations have been searched)
#20	MeSH descriptor: [Endometrium] this term only
#21	(endometr* near/3 thick*):ti,ab,kw (Word variations have been searched)
#22	((intrauterin* or intra-uterin*) near/3 (pregnan* or gestation*)):ti,ab,kw (Word variations have been searched)
#23	IUP:ti,ab,kw (Word variations have been searched)
#24	(early next gestation*):ti,ab,kw (Word variations have been searched)
#25	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
#26	#12 and #15 and #25
#27	(ultrasound* or ultrasonograph* or sonogra* or endosonogra*):ti (Word variations have been searched)
#28	(abortion or termination):ti (Word variations have been searched)

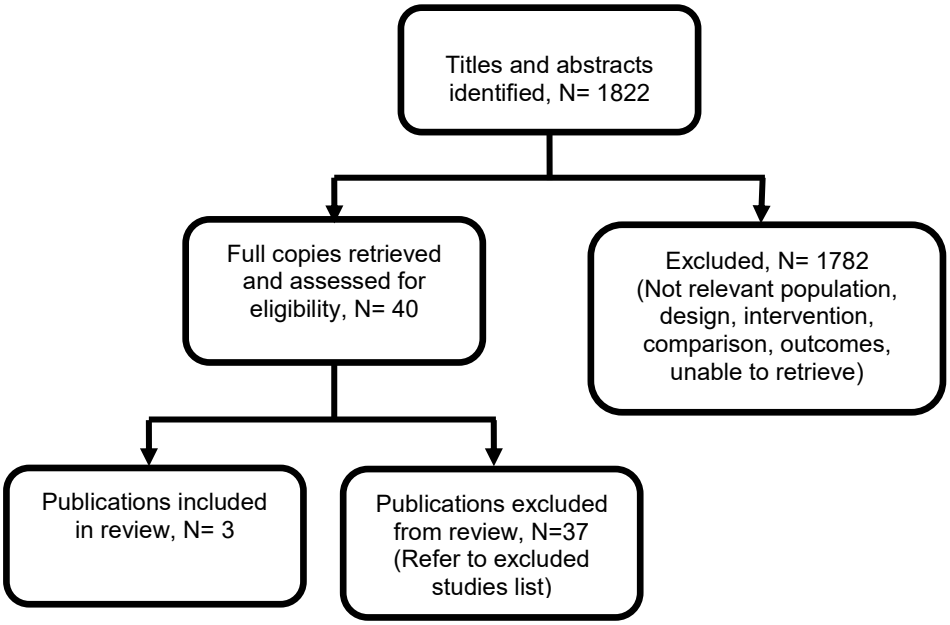
#	Searches
#29	#12 and #27 and #28
#30	#26 or #29
#31	((early or ultra-early) near/3 (abortion or termination)):ti (Word variations have been searched)
#32	#12 and #31
#33	#30 or #32

1

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Bizjak, I., Fiala, C., Berggren, L., Hognert, H., Saav, I., Bring, J., Gemzell-Danielsson, K., Efficacy and safety of very early medical termination of pregnancy: a cohort study, BJOG: An International Journal of Obstetrics and Gynaecology, 124, 1993-1999, 2017 **Ref Id** 815784 **Country/ies where the study was carried out** Sweden, Austria **Study type** Comparative retrospective cohort study **Aim of the study** "To assess the efficacy and safety of medical	**Sample size** n=2773 identified (no-IUP: n=1176; IUP: n=1597) n=2643 analysed (no-IUP: n = 1141, n=24, 10 and 1 were excluded due to incomplete records/lost to follow up, ectopic pregnancy and molar pregnancy, respectively; IUP: n = 1502, n=95 were excluded due to incomplete records. **Characteristics** No intrauterine pregnancy (no-IUP; data available from n=1107): Mean (range) age: 29.4 (15-50) years; nulliparous: n=567; ≥1 parity: n=585; smoking: n =394; empty uterine cavity / intrauterine sac like structure: n=153/988. Intrauterine pregnancy (IUP; data available from n=1455): Mean (range) age: 29.3 (14-47) years; nulliparous:	Women divided into 2 groups based on ultrasound at start of medical abortion: Without confirmed intrauterine pregnancy (no-IUP; defined as an empty uterine cavity or an intrauterine echogenic saclike structure without a yolk sac) With confirmed intrauterine pregnancy (IUP; defined as a yolk sac or a fetal structure with or without cardiac activity) **Medical termination:** 200mg (Sweden) or 600mg (Austria) mifepristone followed by 800micrograms (mcg) vaginal misoprostol (Sweden) or 400mcg oral misoprostol (Austria) 24 to 48 hours later. Additional oral misoprostol (400mcg) was self-administered if no vaginal bleeding had occurred after 3 hours. Nonsteroidal anti-inflammatory drugs, paracetamol, and opioids as needed was given for pain. **Follow-up:** No-IUP 7 days / IUP 2 to 4 weeks after mifepristone administration. Outcomes evaluated based on patient records up to 42 days after termination.	**Outcome: Missed diagnosis of ectopic pregnancy** IUP: 0/1502 No-IUP: 2/1152 (both due to not following the protocol) **Outcome: Ongoing pregnancy** IUP: 7/1502 No-IUP: 5/1141 (empty uterine cavity: 4/153; intrauterine sac like structure: 1/988) **Outcome: Complete termination of pregnancy without the need for surgical intervention** IUP: 1458/1502 No-IUP: 1120/1141 (empty uterine cavity: 143/153; intrauterine sac like structure: 977/988)	**Limitations** **Quality of study:** Risk of bias assessed using the Newcastle-Ottawa scale for cohort studies Selection 1) Representativeness of the exposed cohort a) Truly representative of the population of women undergoing medical abortion (one star) 2) Selection of the non-exposed cohort a) Drawn from the same community as the exposed cohort (one star) 3) Ascertainment of exposure a) Secure record (data drawn from hospital record) (one star) 4) Demonstration that outcome of interest was not present at start of study

Study details	Participants	Interventions	Outcomes and Results	Comments
termination of pregnancy (MTOP) when no intrauterine pregnancy (IUP) is confirmed on ultrasound.." (p. 1993) **Study dates** 2004–2014 (Austria); 2012–2015 (Gothenburg) **Source of funding** Not funded	n=744; ≥1 parity: n=758; smoking: n =536. **Inclusion criteria** Women requesting medical termination of pregnancies ≤ 49 days of gestation, based on ultrasound dating and last menstrual period. All women without confirmed intrauterine pregnancy included, whereas the women with confirmed intrauterine pregnancy were randomly selected using matched sampling (based on age, parity, and period of counselling) at a ratio between the groups of 1:1 and 1:2 in Sweden and Austria, respectively. **Exclusion criteria** Molar pregnancy, continuing miscarriage (including missed miscarriage), or ectopic pregnancy at the initial examination before the initiation of the medical termination. The authors report that "No exclusions were made for other intercurrent medical disorders or previous surgery." (p. 1994)			b) Yes, women would not be undergoing medical termination of pregnancy if pregnancy test not positive (one star) Comparability 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders a) Study controls for age (one star) b) Study controls for parity and period of counselling (one star) Outcome 1) Assessment of outcome b) Record linkage (one star) 2) Was follow-up long enough for outcomes to occur a) Yes (outcomes evaluated based on patient records up to 42 days after termination; one star) 3) Adequacy of follow-up cohorts c) follow up rate 94% (IUP) and 98% (no-IUP) and no description of those lost

Study details	Participants	Interventions	Outcomes and Results	Comments
				Overall quality High quality although only 2 stars in outcome domain **Other information** None
Full citation Edwards,J., Carson,S.A., New technologies permit safe abortion at less than six weeks' gestation and provide timely detection of ectopic gestation, American Journal of Obstetrics and Gynaecology, 176, 1101-1106, 1997 **Ref Id** 72379 **Country/ies where the study was carried out** USA **Study type** Comparative retrospective cohort study **Aim of the study**	**Sample size** n=1530 **Characteristics** Not reported **Inclusion criteria** Women wanting an abortion of a pregnancy < 6 weeks' gestation who had a positive urine pregnancy test at the clinic (sensitivity 25mIU/ml hCG). **Exclusion criteria** None reported	Women divided into 3 groups based on ultrasound at first visit: Without confirmed intrauterine pregnancy (no-IUP; defined as no gestational sac on vaginal US; gestational age 3^{+0} to 3^{+6} weeks) With confirmed intrauterine pregnancy (IUP; defined as gestational sac on vaginal US) Gestational age 5^{+0} to 5^{+6} weeks Gestational age 4^{+0} to 4^{+6} weeks **Surgical termination** Cervical dilation to 7mm with Pratt dilators; handheld 60ml syringe with a rigid 7mm curved curette used to aspirate the products of conception. IV midazolam and nalbupbine and/or a cervical block also given. In women without preoperative US visualisation of the gestational sac, aspiration was followed by sharp curettage of the upper uterine cavity in the area of the tubal ostia. Immediately after the procedure, a vaginal sonogram was performed to confirm the evacuation	**Outcome: Missed diagnosis of ectopic pregnancy** IUP: 5th week 0/915, 4th week 0/462 No-IUP: 0/153 **Outcome: Ongoing pregnancy** IUP: 5th week 1/915, 4th week 1/462 No-IUP: 0/153 **Outcome: Complete termination of pregnancy without the need for repeat surgical intervention** IUP: 5th week 914/915, 4th week 458/46 No-IUP: 153/153	**Limitations** **Quality of study:** Risk of bias assessed using the Newcastle-Ottawa scale for cohort studies Selection 1) Representativeness of the exposed cohort a) Truly representative of the population of women undergoing medical abortion (one star) 2) Selection of the non-exposed cohort a) Drawn from the same community as the exposed cohort (one star) 3) Ascertainment of exposure a) Secure record (data drawn from hospital record) (one star) 4) Demonstration that outcome of interest was

Study details	Participants	Interventions	Outcomes and Results	Comments
"The previously held dictum that elective abortion before 6 weeks' gestation carried greater risks than a later procedure was challenged by this protocol." (p. 1101) **Study dates** January 1994 - October 1995. **Source of funding** Not reported		of either the gestational sac or the decidua or both **Follow-up:** • Women with no gestational sac: 24 to 72 hours after the surgical termination for a serum 13-hCG measurement. • All women in whom, post-procedure, an appropriately sized chorionic membrane with villi was identified, to return for urine beta-hCG measurement 3 weeks later. • Serum beta-hCG was measured if the chorionic membrane and villi were identified in the curettings or if there was any doubt about the completeness of the gestational tissue (visualization of a few villi was not adequate). • "The patient was referred for further evaluation and treatment of a presumed ectopic pregnancy when no chorionic membrane was seen in the curettings and the [beta]-hCG was >1700mIU/ml. If the [beta]-hCG was <1700mIU/ml, the test was repeated in 24 to 72 hours. If the [beta]-hCG decreased by 50%, the patient was considered to have a completed abortion. If the [beta]-hCG increased or decreased <50%, the patient was referred to her gynecologist or to an emergency facility for follow-up care" (p. 1102)		not present at start of study b) Yes, women would not be undergoing termination of pregnancy if pregnancy test not positive (one star) Comparability 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders c) Study does not control for any characteristics and reports no sample or group characteristics (no stars) Outcome 1) Assessment of outcome b) Record linkage (one star) 2) Was follow-up long enough for outcomes to occur a) Yes (outcomes evaluated based on patient records; one star) 3) Adequacy of follow-up cohorts a) complete follow up - all subjects accounted for (one star)

Study details	Participants	Interventions	Outcomes and Results	Comments
				Overall quality Medium quality due to unclear comparability **Other information** None
Full citation Heller, R., Cameron, S., Termination of pregnancy at very early gestation without visible yolk sac on ultrasound, Journal of Family Planning & Reproductive Health Care, 41, 90-5, 2015 **Ref Id** 602324 **Country/ies where the study was carried out** Scotland **Study type** Comparative retrospective cohort study **Aim of the study** "to evaluate what proportion of women who presented at an early gestation, who would formerly	**Sample size** n=1155 **Characteristics** Without confirmed intrauterine pregnancy: - Meeting study protocol for ToP (no-IUP IUS): n=87 (of these 66 proceeded directly to mToP and 21 were brought back for further investigations including 1 or more serum hCGs (n=12), repeat US 1 week later (n=6) or both (n=3). - Empty uterus (no-IUP EU): n=38 (of these 9 proceeded directly to mToP, 23 were brought back for further investigations including 1 or more serum hCGs, repeat US 1 week later or both, 5 received medical management of miscarriage and 1 was successfully treated for ectopic pregnancy) With confirmed intrauterine pregnancy (IUP): n=1017 (+	Women divided into 3 groups based on ultrasound at first visit: Without confirmed intrauterine pregnancy (no yolk sac or fetal pole on US): - Meeting study protocol for ToP (no-IUP IUS; defined as ultrasound scan showing intrauterine gestation sac 3 to 20mm that is eccentrically placed, with a visible decidual reaction; with no clinical symptoms suggestive of ectopic pregnancy (pain, bleeding) or any significant risk factors for ectopic pregnancy (sterilisation, tubal surgery, previous ectopic pregnancy) and with the last menstrual period consistent with a pregnancy of less than 6 weeks' gestation). - Empty uterus (no-IUP EU, defined as no sac or fetal pole and not meeting the study protocol) With confirmed intrauterine pregnancy (IUP; defined as a yolk sac or a fetal pole) **Medical termination:** 200mg mifepristone followed by 800mcg vaginal misoprostol 24 to 48 hours later.	**Outcome: Missed diagnosis of ectopic pregnancy** IUP: 2/1017 No-IUP IUS: 0/87 No-IUP EU: 0/38 **Outcome: Ongoing pregnancy** IUP: 0/1017 No-IUP IUS: 0/87 No-IUP EU: 0/38 **Outcome: Complete termination of pregnancy without the need for surgical intervention** IUP: 1015/1017 No-IUP IUS: 87/87 No-IUP EU: 36/38	**Limitations** **Quality of study:** Risk of bias assessed using the Newcastle-Ottawa scale for cohort studies Selection 1) Representativeness of the exposed cohort a) Truly representative of the population of women undergoing medical abortion (one star) 2) Selection of the non-exposed cohort a) Drawn from the same community as the exposed cohort (one star) 3) Ascertainment of exposure a) Secure record (data drawn from hospital record) (one star) 4) Demonstration that outcome of interest was not present at start of study

Study details	Participants	Interventions	Outcomes and Results	Comments
have had to delay treatment until ultrasound evidence of a yolk sac was present, were able to be treated without the need for further visits or investigations." (p. 91) **Study dates** January 2011 to December 2012 **Source of funding** Not reported	13 women who underwent surgical ToP) Not further reported. **Inclusion criteria** Women undergoing a termination of a pregnancy which on first visit was up to 6 weeks' gestation according to ultrasound scan. **Exclusion criteria** Women who continued with their pregnancy.	**Follow-up:** Not reported		b) Yes, women would not be undergoing medical termination of pregnancy if pregnancy test not positive (one star) Comparability 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders c) Study does not control for any characteristics and reports no sample or group characteristics (no stars) Outcome 1) Assessment of outcome b) Record linkage (one star) 2) Was follow-up long enough for outcomes to occur a) Yes (outcomes evaluated based on patient records; one star) 3) Adequacy of follow-up cohorts a) complete follow up - all subjects accounted for (one star) Overall quality

Study details	Participants	Interventions	Outcomes and Results	Comments
				Medium quality due to unclear comparability **Other information** None

EU: empty uterus: hCG: human chorionic gonadotropin; IUP: intrauterine pregnancy; IUS: intrauterine sac; IV: intravenous; mcg: micrograms; MTOP: medical termination of pregnancy; TOP: termination of pregnancy; US: ultrasound

Appendix E – Forest plots

Forest plots for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

Figure 2: Missed diagnosis of ectopic pregnancy

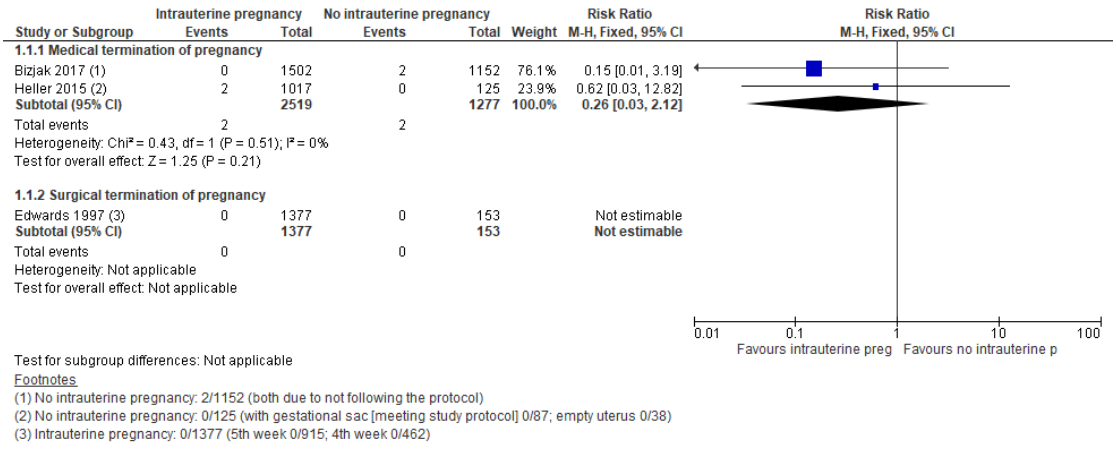


Figure 3: Ongoing pregnancy

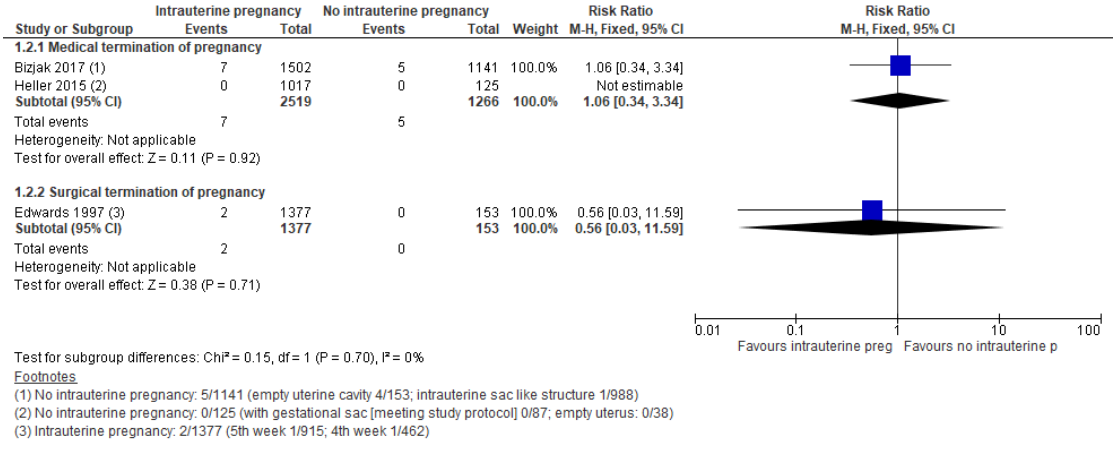
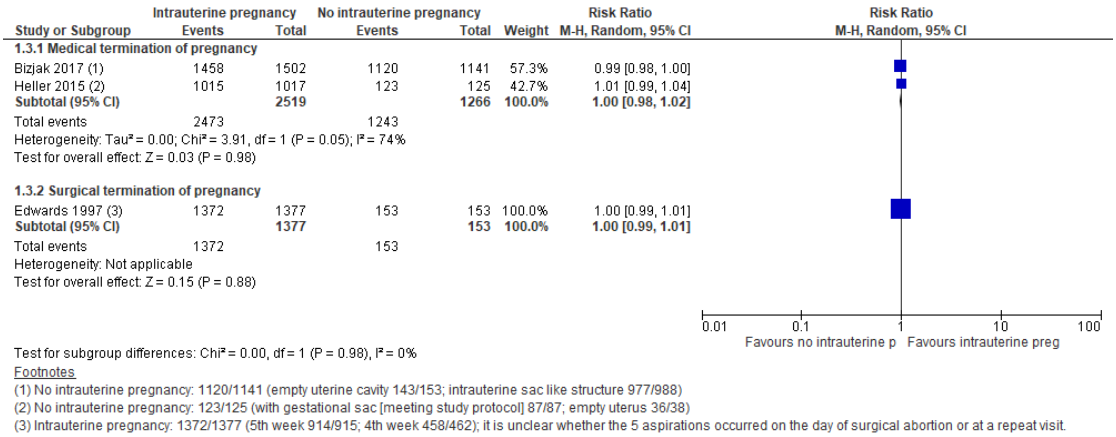


Figure 4: Complete termination of pregnancy without the need for (repeat) surgical intervention



Please note although a random effects model has been used for this analysis due to the high heterogeneity in the medical termination subgroup, this has no influence on the estimate and 95% CI for the surgical termination subgroup which is identical to that observed when using a fixed effects model.

Appendix F – GRADE tables

GRADE tables for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

Table 3: Clinical evidence profile: Termination of pregnancy before and after there is ultrasound evidence of an intrauterine pregnancy

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intrauterine pregnancy	No intrauterine pregnancy	Relative (95% CI)	Absolute	Quality	Importance
Missed diagnosis of ectopic pregnancy - Medical termination of pregnancy (follow-up 7-42 days)												
2 (Bizjak 2017; Heller 2015)	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	2/2519 (0.08%)	2/1277 (0.16%)	RR 0.26 (0.03 to 2.12)	1 fewer per 1000 (from 2 fewer to 2 more)	VERY LOW	CRITICAL
Missed diagnosis of ectopic pregnancy - Surgical termination of pregnancy (follow-up 1-3 days)												
1 (Edwards 1997)	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	0/1377 (0%)	0/153 (0%)	Not estimable	Not estimable	VERY LOW	CRITICAL
Ongoing pregnancy - Medical termination of pregnancy (follow-up 7-42 days)												
2 (Bizjak 2017; Heller 2015)	Observational studies	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[1]	None	7/2519 (0.28%)	5/1266 (0.39%)	RR 1.06 (0.34 to 3.34)	0 more per 1000 (from 3 fewer to 9 more)	VERY LOW	IMPORTANT
Ongoing pregnancy - Surgical termination of pregnancy (follow-up 1-3 days)												
1 (Edwards 1997)	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[1]	None	2/1377 (0.15%)	0/153 (0%)	RR 0.56 (0.03 to 11.59)	Not estimable	VERY LOW	IMPORTANT
Complete termination of pregnancy without the need surgical intervention - Medical termination of pregnancy (follow-up 7-42 days)												
2 (Bizjak 2017;	Observational studies	No serious	Serious[4]	No serious indirectness	No serious imprecision	None	2473/2519 (98.2%)	1243/1266 (98.2%)	RR 1 (0.98 to 1.02)	0 fewer per 1000 (from 20	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intrauterine pregnancy**	**No intrauterine pregnancy**	**Relative (95% CI)**	**Absolute**		
Heller 2015)		risk of bias								fewer to 20 more)		
Complete termination of pregnancy without the need for repeat surgical intervention - Surgical termination of pregnancy (follow-up 1-3 days)												
1 (Edwards 1997)	Observational studies	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1372/1377 (99.6%)	153/153 (100%)	RR 1 (0.99 to 1.01)	0 fewer per 1000 (from 10 fewer to 10 more)	VERY LOW	IMPORTANT

CI: confidence interval; MID: minimal important difference; RR: relative risk

[1] *The 95% CI crosses two MIDs.*

[2] *Risk of bias assessed using the Newcastle-Ottawa scale for cohort studies and the overall quality of this study was medium quality due to unclear comparability.*

[3] *The study is not powered to for this outcome. No events observed.*

[4] *I^2 = 74%.*

Appendix G – Economic evidence study selection

Economic evidence for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

No economic evidence was identified which was applicable to this review question.

Appendix H – Economic evidence tables

Economic evidence tables for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

No economic evidence was identified which was applicable to this review question.

Appendix I – Health economic evidence profiles

Economic evidence profiles for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

No economic evidence was identified which was applicable to this review question.

Appendix J – Health economic analysis

Economic analysis for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

Clinical studies

Study	Reason for Exclusion
Dean, G., Colarossi, L., Porsch, L., Betancourt, G., Jacobs, A., Paul, M., The sensitivity of manual versus electric vacuum aspiration in detecting completed abortion at less than 6 weeks of gestation, Contraception, 86 (3), 296, 2012	Abstract of Dean 2015, which is excluded
Dean, G., Colarossi, L., Porsch, L., Betancourt, G., Jacobs, A., Paul, M. E., Manual compared with electric vacuum aspiration for abortion at less than 6 weeks of gestation: a randomized controlled trial, Obstetrics & GynecologyObstet Gynecol, 125, 1121-9, 2015	Analyses not in PICO
Edward,J., Creinin,M.D., Early abortion: Surgical and medical options, Current Problems in Obstetrics, Gynecology and Fertility, #20, 6-32, 1997	Same data as included Edwards 1997 study, which although it includes fewer women includes more study and outcome information
Fiala, C., Is there a lower gestational limit for abortion?, European Journal of Contraception and Reproductive Health Care, 17, S161, 2012	Published as abstract only, not enough information available to ascertain relevance
Gao,P., Wang,P., Clinical observation on termination of early pregnancy of 213 cases after caesarean section with repeated use of mifepristone and misoprostol, Journal of reproduction and contraception, 10, 227-233, 1999	Population/analyses not in PICO
Gbolade, B., Ultrasound-guided surgical termination of pregnancy at less than 7 completed weeks, European Journal of Contraception and Reproductive Health Care, 1), S108, 2014	Published as abstract only, not enough information available to ascertain relevance
Goldstein,S.R., Danon,M., Watson,C., An updated protocol for abortion surveillance with ultrasound and immediate pathology, Obstetrics and Gynecology, 83, 55-58, 1994	Analyses not in PICO; N = 26 had no sac on US, but had non-diagnostic endometrial findings
Goldstone, P., Michelson, J., Williamson, E., Effectiveness of early medical abortion using low-dose mifepristone and buccal misoprostol in women with no defined intrauterine gestational sac, Contraception, 87, 855-8, 2013	Non-randomised study; N<100 in one of the comparison groups.
Heller, R., Cameron, S., Outcomes of very early medical termination of pregnancy at <=6 weeks of gestation, BJOG: An International Journal of Obstetrics and Gynaecology, 2), 11, 2012	Published as abstract only, not enough information available to ascertain relevance
Jain, J. K., Dutton, C., Harwood, B., Meckstroth, K. R., Mishell Jr, D. R., Godfrey, E. M., Stanwood, N. L., Termination of early pregnancy with vaginal misoprostol alone was not as effective as mifepristone plus misoprostol, Evidence-based Obstetrics and Gynecology, 5, 18-19, 2003	Published as abstract only, not enough information available to ascertain relevance, but "If the gestational sac was still present by ultrasonography on day 4," implies that the population is not in PICO

Study	Reason for Exclusion
Jain, J. K., Meckstroth, K. R., Mishell Jr, D. R., Early pregnancy termination with intravaginally administered sodium chloride solution-moistened misoprostol tablets: Historical comparison with mifepristone and oral misoprostol, American Journal of Obstetrics and Gynecology, 181, 1386-1391, 1999	Population/analyses not in PICO
Kapp, N., Baldwin, M. K., Rodriguez, M. I., Efficacy of medical abortion prior to 6 gestational weeks: a systematic review, 97, 90-99, 2018	Comparison/analyses not in PICO
Kara,F., Dogan,N.U., Bati,S., Demir,S., Durduran,Y., Celik,C., Early surgical abortion: safe and effective, European Journal of Contraception and Reproductive Health Care, 18, 120-126, 2013	Population/analyses not in PICO
Li, C. L., Chen, D. J., Song, L. P., Wang, Y., Zhang, Z. F., Liu, M. X., Chen, W. L., Effectiveness and Safety of Lower Doses of Mifepristone Combined With Misoprostol for the Termination of Ultra-Early Pregnancy: A Dose-Ranging Randomized Controlled Trial, 22, 706-711, 2015	Comparison not in PICO
Li, C. L., Song, L. P., Tang, S. Y., Zhou, L. J. G. Y. K., He, H., Mo, X. T., Liao, Y. M., Efficacy, Safety, and Acceptability of Low-Dose Mifepristone and Self-Administered Misoprostol for Ultra-Early Medical Abortion: A Randomized Controlled Trial, Reproductive Sciences, 24, 731-737, 2017	Comparison not in PICO
Lichtenberg, E. S., Paul, M., Surgical abortion prior to 7 weeks of gestation, Contraception, 88, 7-17, 2013	Guideline that appears based on narrative, not systematic, review of the evidence.
Lohr,P.A., Reeves,M.F., Creinin,M.D., A comparison of transabdominal and transvaginal ultrasonography for determination of gestational age and clinical outcomes in women undergoing early medical abortion, Contraception, 81, 240-244, 2010	Population/comparison/analyses not in PICO
Lyerly, A. D., Little, M. O., Harm Reduction Protocols for Early Abortion: A Middle Way?, Obstetrics & GynecologyObstet Gynecol, 131, 619-620, 2018	Editorial
Macisaac,L., Darney,P., Early surgical abortion: An alternative to and backup for medical abortion, American Journal of Obstetrics and Gynecology, 183, S76-S83, 2000	Narrative review
Mikkelsen, A. L., Felding, C., The value of peroperative ultrasound examination in first trimester legally induced abortion, Clinical and Experimental Obstetrics and Gynecology, 21, 150-152, 1994	Population not in PICO
Paul,M.E., Mitchell,C.M., Rogers,A.J., Fox,M.C., Lackie,E.G., Early surgical abortion: efficacy and safety, American Journal of Obstetrics and Gynecology, 187, 407-411, 2002	Population not in PICO
Reeves, M. F., Monmaney, J. A., Creinin, M. D., Predictors of uterine evacuation following early medical abortion with mifepristone and misoprostol, Contraception, 93, 119-25, 2016	Population/analyses not in PICO
Rodrigues, A., Coutinho, I., Bombas, T., Moura, P., Do Ceu Almeida, M., Safety and efficacy of outpatient mifepristone-misoprostol medical abortion through 76 days of gestational age-Portuguese experience in a tertiary hospital, European Journal of Contraception and Reproductive Health Care, 21, 59, 2016	Published as abstract only, not enough information available to ascertain relevance
Saxena, B. N., Datey, S., Gaur, L. N., Gupta, N. K., Mehta, S., Roy, M., Saxena, N. C., Vishwanath, P., Baveja, R., Buckshee, K., Ghosh, A., Hazra, M. N., Krishna, U., Premila, S., Rajaram, P., Zaveri, K., A multicentre clinical trial with RU 486 followed by 9-methylene-PGE2 vaginal gel for termination of early pregnancy: A dose-finding study, Contraception, 49, 87-88, 1994	Intervention not in PICO

Study	Reason for Exclusion
Schaff,E.A., Fielding,S.L., Eisinger,S., Stadalius,L., Mifepristone and misoprostol for early abortion when no gestational sac is present, Contraception, 63, 251-254, 2001	Non-comparative study
Shand,C., Rose,S.B., Simmons,A., Sparrow,M.J., Introduction of early medical abortion in New Zealand: an audit of the first 67 cases, Australian and New Zealand Journal of Obstetrics and Gynaecology, 45, 316-320, 2005	Population/analyses not in PICO
Sivin, I., Trussell, J., Lichtenberg, E. S., Fjerstad, M., Cleland, K., Cullins, V., Unexpected heaping in reported gestational age for women undergoing medical abortion, Contraception, 80, 287-291, 2009	Analyses not in PICO
Song, L. P., Tang, S. Y., Li, C. L., Zhou, L. J. G. Y. K., Mo, X. T., Early medical abortion with self-administered low-dose mifepristone in combination with misoprostol, Journal of Obstetrics and Gynaecology Research., 2018	Comparison not in PICO
Spitz,I.M., Bardin,C.W., Benton,L., Robbins,A., Early pregnancy termination with mifepristone and misoprostol in the United States, New England Journal of Medicine, 338, 1241-1247, 1998	Population/analyses not in PICO
Tang, O. S., Chan, C. C. W., Ng, E. H. Y., Lee, S. W. H., Ho, P. C., Hamoda, H., Ashok, P. W., Templeton, A., Sublingual misoprostol was as efficacious as vaginal for early termination of pregnancy but had more side effects, Evidence-based Obstetrics and Gynecology, 6, 74-75, 2004	Published as abstract only, not enough information available to ascertain relevance, but main analyses not in PICO
Ulmann, A., Silvestre, L., Chemama, L., Rezvani, Y., Renault, M., Aguillaume, C. J., Baulieu, E. E., Medical termination of early pregnancy with mifepristone (RU 486) followed by a prostaglandin analogue. Study in 16,369 women, Acta Obstetricia et Gynecologica Scandinavica, 71, 278-283, 1992	Intervention not in PICO: Mifepristone not used with misoprostol
Vayssiere, C., Gaudineau, A., Attali, L., Bettahar, K., Eyraud, S., Faucher, P., Fournet, P., Hassoun, D., Hatchuel, M., Jamin, C., Letombe, B., Linet, T., Msika Razon, M., Ohanessian, A., Segain, H., Vigoureux, S., Winer, N., Wylomanski, S., Agostini, A., Induced abortion: Guidelines for clinical practice - Text of the Guidelines (short text), Journal de gynecologie obstetrique ET biologie de la reproduction, 45, 1596-1603, 2016	Guideline. Full text in French
Vayssiere, C., Gaudineau, A., Attali, L., Bettahar, K., Eyraud, S., Faucher, P., Fournet, P., Hassoun, D., Hatchuel, M., Jamin, C., Letombe, B., Linet, T., Msika Razon, M., Ohanessian, A., Segain, H., Vigoureux, S., Winer, N., Wylomanski, S., Agostini, A., Elective abortion: Clinical practice guidelines from the French College of Gynecologists and Obstetricians (CNGOF), European Journal of Obstetrics Gynecology and Reproductive Biology, 222, 95-101, 2018	Guideline
Verma, M. L., Singh, U., Singh, N., Shankhwar, P., Srivastava, D., Efficacy of misoprostol administration 24 hours after mifepristone for termination of early pregnancy, Indian Journal of Medical Sciences, 65, 511-517, 2011	Population/analyses not in PICO
Von Hertzen, H., Honkanen, H., Piaggio, G., Bartfai, G., Erdenetungalag, R., Gemzell-Danielsson, K., Gopalan, S., Horga, M., Jerve, F., Mittal, S., Ngoc, N. T. N., Peregoudov, A., Prasad, R. N. V., Pretnar-Darovec, A., Shah, R. S., Song, S., Tang, O. S., Wu, S. C., WHO multinational study of three misoprostol regimens after mifepristone for early medical abortion. I: Efficacy, 110, 808-818, 2003	Population not in PICO

Study	Reason for Exclusion
World Health Organisation Task Force on Post-ovulatory Methods of Fertility, Regulation, Special Programme of Research, Development, Research, Training, World Health, Organisation, Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial, BJOG: An International Journal of Obstetrics & Gynaecology, 107, 524-30, 2000	Population not in PICO (none of them received an ultrasound scan at study entry); analyses not in PICO
Zikopoulos, K. A., Papanikolaou, E. G., Kalantaridou, S. N., Tsanadis, G. D., Plachouras, N. I., Dalkalitsis, N. A., Paraskevaidis, E. A., Early pregnancy termination with vaginal misoprostol before and after 42 days gestation, Human Reproduction, 17, 3079-3083, 2002	Intervention not in PICO

CI: confidence interval: EMA: early medical abortion; IUGS: intrauterine gestational sac; PICO: population, intervention, comparison and outcome

Economic studies

No economic evidence was identified for this review. See supplementary material 2 for further information.

Appendix L – Research recommendations

Research recommendations for question: Is it safe and effective to start termination of pregnancy before there is ultrasound evidence of an intrauterine pregnancy?

No research recommendations were made for this review question.