National Institute for Health and Care Excellence

Draft for consultation

Ectopic pregnancy and miscarriage: diagnosis and initial management

[B] Expectant versus medical management of tubal ectopic pregnancy

NICE guideline CG154 (update)

Evidence review

December 2018

Draft for Consultation

This evidence review was developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

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Expectant versus medical management

Review question

How effective is expectant management compared to medical management for tubal ectopic pregnancy?

Introduction

Management of ectopic pregnancy depends upon multiple factors including clinical presentation, haemodynamic stability, ultrasound scan features and serial serum human chorionic gonadotrophin (hCG) measurements.

Historically, surgical management was offered as the treatment of choice. This remains the case for women with haemodynamic instability, haemoperitoneum or severe pain, or for those with larger ectopic pregnancies (≥35mm), presence of a fetal heart beat or high serum hCG levels (≥5000 IU/L). Currently, women may also be offered medical management, with the use of methotrexate (an antifolate agent) if they are haemodynamically stable with confirmed diagnosis of ectopic pregnancy on ultrasound scan, no significant pelvic pain, no hemoperitoneum, no fetal heart in the ectopic pregnancy, size of ectopic pregnancy < 35mm and hCG level <5000 IU/L.

A third option is expectant management – watchful waiting and monitoring to ensure the ectopic pregnancy resolves without the need for any intervention. The aim of this review is to determine the relative effectiveness of medical and expectant management for women with an ectopic pregnancy.

Summary of the protocol

Please 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 with tubal ectopic pregnancy
Intervention	Expectant management; also known as 'conservative' or 'wait and see' (monitor hCG levels, clinical monitoring, scans)
Comparison	Medical management with methotrexate (MTX)
Outcome	**Critical outcomes:** • Maternal mortality • Resolution of tubal ectopic pregnancy (decline of serum hCG levels <20 IU/L or negative urinary pregnancy test) • Rupture rate **Important outcomes:** • Additional treatment/need for further intervention (MTX or surgery) • Future ectopic pregnancy rates • Future fertility / pregnancy rates • Patient satisfaction/ HRQoL

hCG: human chorionic gonadotrophin; HRQoL: health-related quality of life; IU/L: international units per litre; MTX: methotrexate

For full details see review protocol in Appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Please see the methods section of the 2012 guideline for further details.

Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Four randomised controlled trials (n=236) were included in this review (Jurcovic 2017, Korhonen 1996, Silva 2015, van Mello 2012), which compared expectant with medical management with methotrexate. Additional results from the study by van Mello (2012) were identified in a secondary report of the same trial (van Mello 2015) and relevant data were included in the review.

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

Excluded studies

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

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies.

Table 2: Summary of included studies

Study	Participants and inclusion criteria	Intervention	Control
Jurcovic 2017 RCT UK	N=80 women with ectopic pregnancy and serum hCG levels <1500 IU/l	Placebo, single intramuscular injection of 0.9% sodium chloride	Methotrexate, single intramuscular injection, 50 mg/m^2
Korhonen 1996 RCT Finland	N=60 women with ectopic pregnancy (<40 mm) and serum hCG levels <5000 IU/l	Placebo tablets PO x 5 days	Methotrexate, 2.5 mg/day PO x 5 days
Silva 2015 RCT Brazil	N=23 women with ectopic pregnancy (<50mm)and serum hCG levels <2000 IU/l	Placebo, single intramuscular injection of saline solution	Methotrexate, single intramuscular injection, 50 mg/m^2
van Mello 2012 RCT	N=73 women with ectopic pregnancy or pregnancy of unknown location (size not	Expectant management	Methotrexate, single intramuscular injection, 1 mg/kg

Study	Participants and inclusion criteria	Intervention	Control
The Netherlands	reported). Serum hCG levels <2000IU/l		body weight; maximum 100 mg

hCG: human chorionic gonadotropin; IU/l: international units per litre; PO: per os (by mouth); RCT: randomised controlled trial

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

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

Economic model

No economic modelling was undertaken for this review.

Evidence statements

Comparison 1. Expectant versus medical management

Critical outcomes

Resolution of ectopic pregnancy

- Very low quality evidence from four randomised controlled trials (n=236) did not demonstrate any clinically important difference in the resolution of ectopic pregnancy between those who received expectant or medical management. Subgroup analyses (by hCG levels or embryo size at presentation) provided moderate to very low quality evidence which did not detect a clinically significant difference between treatment arms.

Tubal rupture

- Low quality evidence from two randomised controlled trials (n=96) did not demonstrate any clinically important difference in tubal rupture rate between those who received expectant or medical management (no events in either group).

Important outcomes

Need for additional treatment

- . Very low quality evidence from four randomised controlled trials (n=236) did not demonstrate any clinically important difference in the need for additional treatment between those who received expectant or medical management. Subgroup analyses (by hCG levels or embryo size at presentation) provided moderate to very low quality evidence which did not detect a clinically significant difference between treatment arms.

Health-related quality of life

- Moderate to low quality evidence from a single randomised controlled trial (n=57) did not demonstrate a clinically important difference in health status (as measured by the short-form 36 [SF-36] and Rotterdam symptom checklist), depression or anxiety (as measured

by the Hospital Anxiety and Depression Scale) between those who received expectant or medical management.

Recommendations

B1. Offer expectant management as an option to women who:

- are clinically stable and pain free, **and**
- have a tubal ectopic pregnancy on transvaginal ultrasound scan measuring less than 35 mm with no visible heartbeat, **and**
- have a serum hCG level of 1,000 IU/L or less, **and**
- are able to return for follow-up.

B2. For women with an ectopic pregnancy being managed expectantly, repeat hCG levels after 48 hours:

- if the level drops by 15% or more, repeat weekly until a negative result (<20 IU/L) is obtained, or
- if hCG levels plateau or rise, review the woman's clinical condition to help decide the further management plan.

B3. Advise women that there is no significant difference in:

- the rate of ectopic pregnancies ending naturally following expectant and medical management
- the risk of tubal rupture following expectant and medical management
- the need for additional treatment following expectant and medical management
- health status, depression or anxiety scores following expectant and medical management.

B4. Advise women that the time taken for ectopic pregnancies to end and future fertility outcomes are likely to be the same with either expectant or medical management, but there is no evidence to show this.

Rationale and impact

Why the committee made the recommendations

The evidence showed no significant differences in the number of ectopic pregnancies ending naturally, the need for additional treatment, the incidence of tubal rupture or the effect on health-related quality of life between expectant management compared with medical management, so the committee recommended that expectant management could be offered to clinically stable women with small ectopic pregnancies and low hCG levels, as an alternative to medical management.

There was no evidence for the time taken for ectopic pregnancies to end naturally or the effects on future fertility but the committee agreed, based on their expertise and experience, these outcomes were likely to be the same with expectant management compared to medical management.

Impact of the recommendations on practice

These recommendations will standardise the management of ectopic pregnancy and make expectant management available for women when it is clinically appropriate. More women might have expectant management of ectopic pregnancy as a result. This may result in cost savings through a reduction in drug use and treatment of associated side effects. Local

protocols will be needed for assessment, monitoring and follow-up of women choosing expectant management.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified 3 outcomes of critical importance: maternal mortality, resolution of tubal ectopic pregnancy, and rupture rate. These 3 outcomes were selected as critical since they provide direct evidence about the effectiveness of the interventions in resolving an ectopic pregnancy without leading to adverse events. Additionally, the committee identified the need for additional treatments, future ectopic pregnancy rates, future fertility, and patient satisfaction as important outcomes.

The quality of the evidence

Four randomised controlled trials have been included in this review. The quality of the evidence was assessed according to GRADE criteria and ranged from very low to moderate quality evidence. The main reason for downgrading was imprecision – the trials had few participants, and therefore the confidence intervals for the estimates were wide. Some of the trials were also downgraded because of high to very high risk of bias. This was assessed with The Cochrane Risk of Bias Tool. The main sources of potential bias were: lack of information regarding how the randomisation was performed or concealed; or because women, clinicians and/or outcome assessors were aware of treatment allocation. Two of the trials had not registered their protocol, therefore were downgraded for high risk of reporting bias. There was no evidence available for the outcomes on maternal mortality, future ectopic rates or future fertility rates.

Benefits and harms

The evidence did not show any significant difference between expectant or medical management for ectopic pregnancy resolution, tubal rupture prevention, additional treatment requirements, or health-related quality of life. The committee therefore agreed that expectant management could be offered based on the clinical suitability of a woman, an assessment of the risks and benefits, and the preferences of the woman. The committee agreed that women who were suitable for expectant management were similar to the inclusion criteria in the clinical studies – for example those women who were clinically stable without pain, who had a small ectopic pregnancy, and who had low serum hCG levels (1000 IU/L or lower). Although the inclusion criteria of the four studies permitted women with a wider range of hCG levels to enter the trials, the committee noted that the majority of participants had relatively low levels of hCG (typically <1000 IU/l). Therefore this was reflected in the recommendations. Similarly, the two studies which reported on the size of the adnexal mass showed that most participants had an adnexal mass of <35mm. All studies in this review excluded women with an ectopic pregnancy with fetal heart activity, therefore the use of expectant or medical management in these women has not been assessed. The committee noted that their clinical experience also supported these thresholds as reasonable for the use of medical or expectant management, and reflected these in the recommendations.

Based on their clinical expertise, the committee outlined some risks and benefits that should be considered when discussing expectant management with women. The committee outlined that the main benefits of expectant management included a similar rate of resolution of ectopic pregnancy compared to medical management with methotrexate, while avoiding the side effects of methotrexate, such as nausea, anaemia, vomiting or diarrhoea, potentially mild abnormalities in liver and renal function tests, and the need to avoid pregnancy for 3 months. A disadvantage of expectant management is that women may need to be urgently

admitted into hospital if their clinical condition worsens, although this may also be the case for women who have received methotrexate.

In terms of follow-up care, serum hCG levels should be carefully monitored regardless of the treatment choice. If these plateau or rise, the women should be reviewed by a senior gynaecologist, and a discussion with the woman about other treatment options may be needed.

As there was no evidence available from this review regarding future fertility/pregnancy rates, the committee based the recommendations relating to this on their clinical knowledge and expertise. In addition, there was no evidence relating to the time for resolution of an ectopic pregnancy following medical or expectant management, but the committee were aware that the time was similar in clinical practice and so included this in their recommendations.

The committee noted that healthcare professionals counselling women with an ectopic pregnancy should be sensitive to the woman's emotions, but did not make a separate recommendation about this as it is already covered in the support and information giving section of the guideline. An ectopic pregnancy can be devastating news and some women experience the same grief as when losing a family member. The committee were also aware that some women consider medical management with methotrexate as a type of abortion and express feelings of guilt. While of course equating treatment of ectopic pregnancy to terminating a pregnancy is not accurate, offering an alternative treatment route of expectant management if clinically appropriate can help such women from an emotional perspective.

Cost effectiveness and resource use

At present there is considerable variation in practice regarding management of ectopic pregnancy. The recommendations may lead to an increase in the use of expectant management for some centres. Moving from medical management to expectant management has the potential to result in cost savings through a reduction in drug use and treatment of associated side effects.

Follow-up will be similar for women choosing expectant or medical management and early pregnancy units may need to admit women as emergencies if either management technique fails. In such cases, surgical intervention is likely to be more costly than it would have been if elective surgical management had been the initial management strategy.

Both expectant and medical management should lead to preservation of future fertility which will result in increased benefits for women, and reduce the downstream financial implications of managing fertility problems.

Other factors the committee took into account

The committee discussed a subgroup analysis conducted by Jurcovic 2017 for women with serum hCG levels between 1000 and 1500 IU/l. The study showed that, on multivariate logistic regression analyses, women with serum hCG levels in this range had an increased "failure rate" (RR 3.6, 95% CI 1.6 to 8), however there were no significant differences between treatment groups (RR 0.69, 95% CI 0.31 to 1.6). In light of this, the committee highlighted that for women with higher hCG levels, the success rate of both medical and expectant management is lower.

References

Jurkovic 2017

Jurkovic D, Memtsa M, Sawyer E, Donaldson AN, Jamil A, Schramm K, Sana Y, Otify M, Farahani L, Nunes N, Ambler G. Single-dose systemic methotrexate vs expectant

management for treatment of tubal ectopic pregnancy: a placebo-controlled randomized trial. Ultrasound in Obstetrics & Gynecology. 2017 Feb 1;49(2):171-6.

Korhonen 1996

Korhonen J, Stenman UH, Ylöstalo P. Low-dose oral methotrexate with expectant management of ectopic pregnancy. Obstetrics & Gynecology. 1996 Nov 1;88(5):775-8.

Silva 2015

Silva PM, Júnior EA, Cecchino GN, Júnior JE, Camano L. Effectiveness of expectant management versus methotrexate in tubal ectopic pregnancy: a double-blind randomized trial. Archives of gynecology and obstetrics. 2015 Apr 1;291(4):939-43.

van Mello 2015 ***(reported as part of van Mello 2012)***

van Mello NM, Mol F, Hajenius PJ, Ankum WM, Mol BW, van der Veen F, van Wely M. Randomized comparison of health-related quality of life in women with ectopic pregnancy or pregnancy of unknown location treated with systemic methotrexate or expectant management. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2015 Sep 1;192:1-5.

van Mello 2012

Van Mello NM, Mol F, Verhoeve HR, Van Wely M, Adriaanse AH, Boss EA, Dijkman AB, Bayram N, Emanuel MH, Friederich J, van der Leeuw-Harmsen L. Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? A randomized comparison. Human Reproduction. 2012 Oct 18;28(1):60-7.

1 Appendices

2 Appendix A: Review protocols

3 **Review protocol for expectant versus medical management**

Field (based on PRISMA-P)	Content
Key area in the scope	Management strategies for tubal ectopic pregnancy (expectant, medical and surgical management options).
Draft review question from the previous guideline (to be deleted in the final version)	N/A
Actual review question	How effective is expectant management compared to medical management for tubal ectopic pregnancy?
Type of review question	Intervention
Objective of the review	To determine whether expectant management should be considered as a management option for women with tubal ectopic pregnancy
Eligibility criteria – **population**/disease/condition/issue/domain	Women with tubal ectopic pregnancy
Eligibility criteria – **intervention**(s)/exposure(s)/prognostic factor(s)	Expectant management; also known as 'conservative' or 'wait and see' (monitor HCG levels, clinical monitoring, scans)
Eligibility criteria – **comparator(s)**/control or reference (gold) standard	Medical management (methotrexate [MTX])
Outcomes and prioritisation	**Critical outcomes:** • Maternal mortality • Resolution of tubal ectopic pregnancy (decline of serum hCG concentrations <20 iU/L or negative urinary pregnancy test) • Rupture rate **Important outcomes:**

Field (based on PRISMA-P)	Content
	• Additional treatment/need for further intervention (MTX or surgery) • Future ectopic pregnancy rates • Future fertility / pregnancy rates • Patient satisfaction/HRQoL
Eligibility criteria – **study design**	Only published full text papers • Systematic reviews of RCTs • RCTs • Comparative cohort studies if no RCTs Conference abstracts of RCTs will only be considered if no evidence is available from full published RCTs and are recent (i.e., in the last 2 years)
Other **exclusion criteria**	• Studies from developing countries • Non-English language reports • Women with pain and/or bleeding after the first trimester (13 or more completed weeks of pregnancy) • Women with tumours of the placenta (molar pregnancy or trophoblastic disease) after the initial diagnosis • Women with pain and/or bleeding unrelated to pregnancy • Interstitial pregnancy, abdominal pregnancy, ovarian pregnancy, cervical pregnancy, caesarean scar pregnancy • Studies with a mixed population, where women with tubal ectopic comprise <2/3 of the population

Proposed stratified, sensitivity/**sub-group analysis**, or meta-regression	**Stratified analyses:**
	• HCG at presentation:
	  ○ <500
	  ○ 501– 1000
	  ○ <=1001 – 1500

Field (based on PRISMA-P)	Content
	○ >1500 iu/L • Size at presentation ○ <35 mm ○ 35 and greater
Selection process – duplicate screening/selection/analysis	Duplicate screening/selection/analysis will not be undertaken for this review as this question was not prioritised for it. Included and excluded studies will be cross checked with the committee and with published systematic reviews when available.
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADE' will be used to assess the quality of evidence for each outcome. STAR will be used for bibliographies/citations and study sifting. Microsoft Word will be used for data extraction and quality assessment/critical appraisal
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies. <u>Key papers</u>: ○ Demirdag E, Guler I, Abay S et al. (2016) The impact of expectant management, systemic methotrexate and surgery on subsequent pregnancy outcomes in tubal ectopic pregnancy. Irish journal of medical science ○ van Mello NM, Mol F, Verhoeve HR et al. (2013) Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown

Field (based on PRISMA-P)	Content
	location and low serum hCG concentrations? A randomized comparison. Human reproduction (Oxford, England) 28:60-67. o Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy. Ultrasound.Obstet.Gynecol. 42:102-107. 25. van Mello NM, Mol F, Hajenius PJ et al. (2015) o Randomized comparison of health-related quality of life in women with ectopic pregnancy or pregnancy of unknown location treated with systemic methotrexate or expectant management. European Journal of Obstetrics, Gynecology, & Reproductive Biology 192:1-5. o Silva PM, Araujo JE, Cecchino GN et al. (2015) Effectiveness of expectant management versus methotrexate in tubal ectopic pregnancy: a double-blind randomized trial. Archives of Gynecology & Obstetrics 291:939-943. o Jurkovic D, Memtsa M, Sawyer E et al. (2016) Single dose systemic methotrexate versus expectant management for treatment of tubal ectopic pregnancy: A placebo-controlled randomised trial.]. Ultrasound Obstet Gynecol .
Identify if an update	Not an update
Author contacts	Developer: National Guideline Alliance NGA-enquiries@RCOG.ORG.UK
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B of the full guideline
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) of the full guideline.
Data items – define all variables to be collected	For clinical evidence tables (appendix D), the following data items will be collected: full reference, study ID, type of study, objective, country/ies where the study was carried out, inclusion criteria, exclusion criteria, methods, results and limitations.

Field (based on PRISMA-P)	Content
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews and meta-analyses • Cochrane risk of bias tool for randomised studies • Newcastle-Ottowa scale for cohort studies For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. Minimally important differences: Default values will be used of: 0.8 and 1.25 for relative risk of dichotomous outcomes; 0.5 times control group SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.

Field (based on PRISMA-P)	Content
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. Consider exploring publication bias for review questions where it may be more common, such as pharmacological questions, certain disease areas, etc. Describe any steps taken to mitigate against publication bias, such as examining trial registries.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 2.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered with PROSPERO

1

2

Appendix B: Literature search strategies

Review question search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	exp PREGNANCY, ECTOPIC/
2	((ectopic or extra uterine or extra?uterine or tub$ or ampullary or isthm$ or fimbrial or cornual or interstitial or abdom$ or ovar$ or cervi$) adj3 (pregnan$ or gestat$)).ti,ab.
3	(pregnan$ adj3 ((unknown or uncertain) adj (location$ or site$))).ti,ab.
4	PUL.ti,ab.
5	or/1-4
6	((expectant$ or conservative$ or natural$) adj3 (manag$ or approach$ or care$)).ti,ab.
7	WATCHFUL WAITING/
8	(watch$ adj3 wait$).ti,ab.
9	(wait$ adj3 see$).ti,ab.
10	(monitor$ adj5 (HCG or betaHCG or human chorionic gonadotropin or betahuman chorionic gonadotropin)).ti,ab.
11	(monitor$ adj5 clinical$).ti,ab.
12	(monitor$ adj10 (ultrasonograph$ or sonograph$ or ultrasound or scan$)).ti,ab.
13	or/6-12
14	METHOTREXATE/
15	(methotrexate or amethopterin or mexate).mp.
16	MXT.ti,ab.
17	or/14-16
18	((expectant$ or conservative$ or natural$) adj3 (medical$ or pharmaceutical$) adj3 (manag$ or approach$ or care$)).ti,ab.
19	5 and 13 and 17
20	5 and 18
21	or/19-20
22	limit 21 to english language
23	LETTER/
24	EDITORIAL/
25	NEWS/
26	exp HISTORICAL ARTICLE/
27	ANECDOTES AS TOPIC/
28	COMMENT/
29	CASE REPORT/
30	(letter or comment*).ti.
31	or/23-30
32	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
33	31 not 32
34	ANIMALS/ not HUMANS/
35	exp ANIMALS, LABORATORY/
36	exp ANIMAL EXPERIMENTATION/
37	exp MODELS, ANIMAL/
38	exp RODENTIA/
39	(rat or rats or mouse or mice).ti.
40	or/33-39
41	22 not 40

Databases: Embase; and Embase Classic

#	Searches
1	exp ECTOPIC PREGNANCY/
2	((ectopic or extra uterine or extra?uterine or tub$ or ampullary or isthm$ or fimbrial or cornual or interstitial or abdom$ or ovar$ or cervi$) adj3 (pregnan$ or gestat$)).ti,ab.
3	(pregnan$ adj3 ((unknown or uncertain) adj (location$ or site$))).ti,ab.

#	Searches
4	PUL.ti,ab.
5	or/1-4
6	((expectant$ or conservative$ or natural$) adj3 (manag$ or approach$ or care$)).ti,ab.
7	WATCHFUL WAITING/
8	(watch$ adj3 wait$).ti,ab.
9	(wait$ adj3 see$).ti,ab.
10	(monitor$ adj5 (HCG or betaHCG or human chorionic gonadotropin or betahuman chorionic gonadotropin)).ti,ab.
11	(monitor$ adj5 clinical$).ti,ab.
12	(monitor$ adj10 (ultrasonograph$ or sonograph$ or ultrasound or scan$)).ti,ab.
13	or/6-12
14	METHOTREXATE/
15	METHOTREXATE DERIVATIVE/
16	(methotrexate or amethopterin or mexate).mp.
17	MXT.ti,ab.
18	or/14-17
19	((expectant$ or conservative$ or natural$) adj3 (medical$ or pharmaceutical$) adj3 (manag$ or approach$ or care$)).ti,ab.
20	5 and 13 and 18
21	5 and 19
22	or/20-21
23	limit 22 to english language
24	letter.pt. or LETTER/
25	note.pt.
26	editorial.pt.
27	CASE REPORT/ or CASE STUDY/
28	(letter or comment*).ti.
29	or/24-28
30	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
31	29 not 30
32	ANIMAL/ not HUMAN/
33	NONHUMAN/
34	exp ANIMAL EXPERIMENT/
35	exp EXPERIMENTAL ANIMAL/
36	ANIMAL MODEL/
37	exp RODENT/
38	(rat or rats or mouse or mice).ti.
39	or/31-38
40	23 not 39

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

#	Searches
1	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees
2	((ectopic or extra uterine or extra*uterine or tub* or ampullary or isthm* or fimbrial or cornual or interstitial or abdom* or ovar* or cervi*) near/3 (pregnan* or gestat*)):ti,ab
3	(pregnan* near/3 ((unknown or uncertain) near/1 (location* or site*))):ti,ab
4	PUL:ti,ab
5	#1 or #2 or #3 or #4
6	((expectant* or conservative* or natural*) near/3 (manag* or approach* or care*)):ti,ab
7	MeSH descriptor: [WATCHFUL WAITING] this term only
8	(watch* near/3 wait*):ti,ab
9	(wait* near/3 see*):ti,ab
10	(monitor* near/5 (HCG or betaHCG or human chorionic gonadotropin or betahuman chorionic gonadotropin)):ti,ab
11	(monitor* near/5 clinical*):ti,ab
12	(monitor* near/10 (ultrasonograph* or sonograph* or ultrasound or scan*)):ti,ab
13	#6 or #7 or #8 or #9 or #10 or #11 or #12
14	MeSH descriptor: [METHOTREXATE] this term only
15	(methotrexate or amethopterin or mexate):ti,ab
16	MXT:ti,ab

#	Searches
17	#14 or #15 or #16
18	((expectant* or conservative* or natural*) near/3 (medical* or pharmaceutical*) near/3 (manag* or approach* or care*)):ti,ab
19	#5 and #13 and #17
20	#5 and #18
21	#19 or #20

Health economics search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	exp PREGNANCY, ECTOPIC/
23	((ectopic or extra uterine or extra?uterine or tub$ or ampullary or isthm$ or fimbrial or cornual or interstitial or abdom$ or ovar$ or cervi$) adj3 (pregnan$ or gestat$)).ti,ab.
24	(pregnan$ adj3 ((unknown or uncertain) adj (location$ or site$))).ti,ab.
25	PUL.ti,ab.
26	or/22-25
27	((expectant$ or conservative$ or natural$) adj3 (manag$ or approach$ or care$)).ti,ab.
28	WATCHFUL WAITING/
29	(watch$ adj3 wait$).ti,ab.
30	(wait$ adj3 see$).ti,ab.
31	(monitor$ adj5 (HCG or betaHCG or human chorionic gonadotropin or betahuman chorionic gonadotropin)).ti,ab.
32	(monitor$ adj5 clinical$).ti,ab.
33	(monitor$ adj10 (ultrasonograph$ or sonograph$ or ultrasound or scan$)).ti,ab.
34	or/27-33
35	METHOTREXATE/
36	(methotrexate or amethopterin or mexate).mp.
37	MXT.ti,ab.
38	or/35-37
39	((expectant$ or conservative$ or natural$) adj3 (medical$ or pharmaceutical$) adj3 (manag$ or approach$ or care$)).ti,ab.
40	26 and 34 and 38
41	26 and 39
42	or/40-41
43	limit 42 to english language
44	LETTER/
45	EDITORIAL/
46	NEWS/

#	Searches
47	exp HISTORICAL ARTICLE/
48	ANECDOTES AS TOPIC/
49	COMMENT/
50	CASE REPORT/
51	(letter or comment*).ti.
52	or/44-51
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	or/54-60
62	43 not 61
63	21 and 62

Databases: Embase; and Embase Classic

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	exp ECTOPIC PREGNANCY/
19	((ectopic or extra uterine or extra?uterine or tub$ or ampullary or isthm$ or fimbrial or cornual or interstitial or abdom$ or ovar$ or cervi$) adj3 (pregnan$ or gestat$)).ti,ab.
20	(pregnan$ adj3 ((unknown or uncertain) adj (location$ or site$))).ti,ab.
21	PUL.ti,ab.
22	or/18-21
23	((expectant$ or conservative$ or natural$) adj3 (manag$ or approach$ or care$)).ti,ab.
24	WATCHFUL WAITING/
25	(watch$ adj3 wait$).ti,ab.
26	(wait$ adj3 see$).ti,ab.
27	(monitor$ adj5 (HCG or betaHCG or human chorionic gonadotropin or betahuman chorionic gonadotropin)).ti,ab.
28	(monitor$ adj5 clinical$).ti,ab.
29	(monitor$ adj10 (ultrasonograph$ or sonograph$ or ultrasound or scan$)).ti,ab.
30	or/23-29
31	METHOTREXATE/
32	METHOTREXATE DERIVATIVE/
33	(methotrexate or amethopterin or mexate).mp.
34	MXT.ti,ab.
35	or/31-34
36	((expectant$ or conservative$ or natural$) adj3 (medical$ or pharmaceutical$) adj3 (manag$ or approach$ or care$)).ti,ab.
37	22 and 30 and 35
38	22 and 36
39	or/37-38

#	Searches
40	limit 39 to english language
41	letter.pt. or LETTER/
42	note.pt.
43	editorial.pt.
44	CASE REPORT/ or CASE STUDY/
45	(letter or comment*).ti.
46	or/41-45
47	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
48	46 not 47
49	ANIMAL/ not HUMAN/
50	NONHUMAN/
51	exp ANIMAL EXPERIMENT/
52	exp EXPERIMENTAL ANIMAL/
53	ANIMAL MODEL/
54	exp RODENT/
55	(rat or rats or mouse or mice).ti.
56	or/48-55
57	40 not 56
58	17 and 57

Database: Cochrane Central Register of Controlled Trials

#	Searches
1	MeSH descriptor: [ECONOMICS] this term only
2	MeSH descriptor: [VALUE OF LIFE] this term only
3	MeSH descriptor: [COSTS AND COST ANALYSIS] explode all trees
4	MeSH descriptor: [ECONOMICS, HOSPITAL] explode all trees
5	MeSH descriptor: [ECONOMICS, MEDICAL] explode all trees
6	MeSH descriptor: [RESOURCE ALLOCATION] explode all trees
7	MeSH descriptor: [ECONOMICS, NURSING] this term only
8	MeSH descriptor: [ECONOMICS, PHARMACEUTICAL] this term only
9	MeSH descriptor: [FEES AND CHARGES] explode all trees
10	MeSH descriptor: [BUDGETS] explode all trees
11	budget*:ti,ab
12	cost*:ti,ab
13	(economic* or pharmaco?economic*):ti,ab
14	(price* or pricing*):ti,ab
15	(financ* or fee or fees or expenditure* or saving*):ti,ab
16	(value near/2 (money or monetary)):ti,ab
17	resourc* allocat*:ti,ab
18	(fund or funds or funding* or funded):ti,ab
19	(ration or rations or rationing* or rationed):ti,ab
20	#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 or #15 or #16 or #17 or #18 or #19
21	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees
22	((ectopic or extra uterine or extra*uterine or tub* or ampullary or isthm* or fimbrial or cornual or interstitial or abdom* or ovar* or cervi*) near/3 (pregnan* or gestat*)):ti,ab
23	(pregnan* near/3 ((unknown or uncertain) near/1 (location* or site*))):ti,ab
24	PUL:ti,ab
25	#21 or #22 or #23 or #24
26	((expectant* or conservative* or natural*) near/3 (manag* or approach* or care*)):ti,ab
27	MeSH descriptor: [WATCHFUL WAITING] this term only
28	(watch* near/3 wait*):ti,ab
29	(wait* near/3 see*):ti,ab
30	(monitor* near/5 (HCG or betaHCG or human chorionic gonadotropin or betahuman chorionic gonadotropin)):ti,ab
31	(monitor* near/5 clinical*):ti,ab
32	(monitor* near/10 (ultrasonograph* or sonograph* or ultrasound or scan*)):ti,ab
33	#26 or #27 or #28 or #29 or #30 or #31 or #32
34	MeSH descriptor: [METHOTREXATE] this term only
35	(methotrexate or amethopterin or mexate):ti,ab
36	MXT:ti,ab
37	#34 or #35 or #36

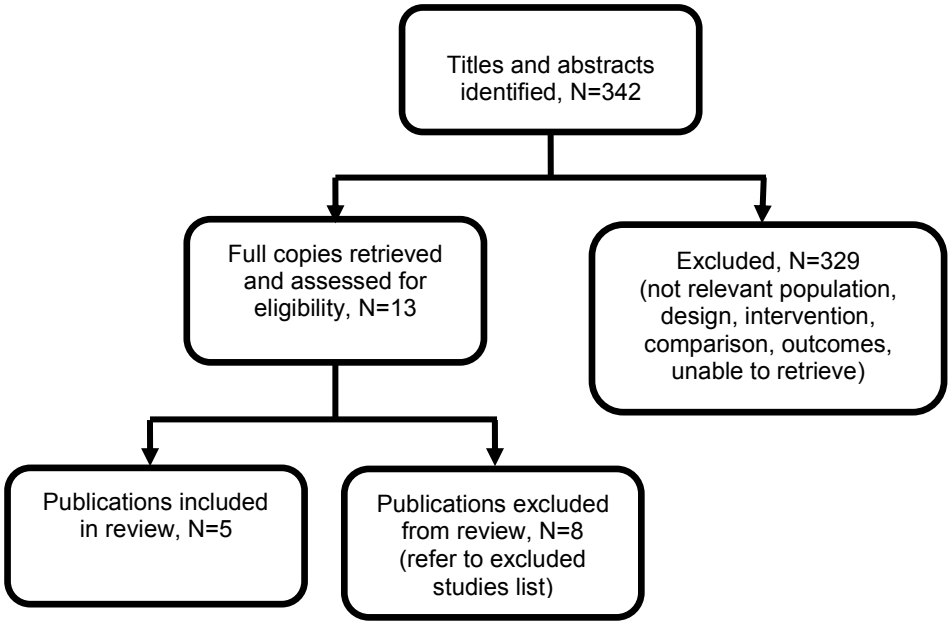
#	Searches
38	((expectant* or conservative* or natural*) near/3 (medical* or pharmaceutical*) near/3 (manag* or approach* or care*)):ti,ab
39	#25 and #33 and #37
40	#25 and #38
41	#39 or #40
42	#20 and #41

Databases: Health Technology Assessment; and NHS Economic Evaluation Database

#	Searches
1	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees
2	((ectopic or extra uterine or extra*uterine or tub* or ampullary or isthm* or fimbrial or cornual or interstitial or abdom* or ovar* or cervi*) near/3 (pregnan* or gestat*)):ti,ab
3	(pregnan* near/3 ((unknown or uncertain) near/1 (location* or site*))):ti,ab
4	PUL:ti,ab
5	#1 or #2 or #3 or #4
6	((expectant* or conservative* or natural*) near/3 (manag* or approach* or care*)):ti,ab
7	MeSH descriptor: [WATCHFUL WAITING] this term only
8	(watch* near/3 wait*):ti,ab
9	(wait* near/3 see*):ti,ab
10	(monitor* near/5 (HCG or betaHCG or human chorionic gonadotropin or betahuman chorionic gonadotropin)):ti,ab
11	(monitor* near/5 clinical*):ti,ab
12	(monitor* near/10 (ultrasonograph* or sonograph* or ultrasound or scan*)):ti,ab
13	#6 or #7 or #8 or #9 or #10 or #11 or #12
14	MeSH descriptor: [METHOTREXATE] this term only
15	(methotrexate or amethopterin or mexate):ti,ab
16	MXT:ti,ab
17	#14 or #15 or #16
18	((expectant* or conservative* or natural*) near/3 (medical* or pharmaceutical*) near/3 (manag* or approach* or care*)):ti,ab
19	#5 and #13 and #17
20	#5 and #18
21	#19 or #20

Appendix C: Clinical evidence study selection

Figure 1: Flow diagram of clinical article selection for expectant versus medical management review



Appendix D: Clinical evidence tables

<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>Full citation
Jurkovic, D., Memtsa, M., Sawyer, E., Donaldson, A. N., Jamil, A., Schramm, K., Sana, Y., Otify, M., Farahani, L., Nunes, N., Ambler, G., Ross, J. A., Single-dose systemic methotrexate vs expectant management for treatment of tubal ectopic pregnancy: a placebo-controlled randomized trial, Ultrasound in Obstetrics & Gynecology, 49, 171-176, 2017
Ref Id
659875

Country/ies where the study was carried out
UK.

Study type
RCT.

Aim of the study
To assess the effectiveness of methotrexate compared to placebo.

Study dates
August 2005 to Jun 2014.

Source of funding
Not reported.</td>
<td>Sample size
N=80 at randomisation
(N=38 randomised to placebo and N=42 randomised to methotrexate).

Characteristics
<table>
<tr><th></th><th>Placebo (N=38)</th><th>Methotrexate (N=38)</th></tr>
<tr><td>Maternal age, mean years (SD)</td><td>30 (6.7)</td><td>29 (6.9)</td></tr>
<tr><td>Gestational age, mean weeks (SD)</td><td>7 (2.1)</td><td>6.9 (1.6)</td></tr>
<tr><td>Primigravid, n (%)</td><td>21 (55)</td><td>22 (52)</td></tr>
<tr><td>Parity, median (IQR)</td><td>0 (0-1)</td><td>0 (0-1)</td></tr>
<tr><td>Previous miscarriage, n (%)</td><td>9 (24)</td><td>10 (24)</td></tr>
<tr><td>Previous ectopic pregnancy, n (%)</td><td>4 (11)</td><td>3 (7)</td></tr>
<tr><td>Serum hCG (IU/L) at baseline, median (IQR)</td><td>405 (189-784)</td><td>465 (238-914)</td></tr>
</table>
</td>
<td>Interventions
Placebo: single intramuscular injection of 0.9% sodium chloride
Methotrexate: single intramuscular injection, 50 mg/m2
Medication was given within 24 h of the initial visit.
Follow-up visits occurred on day 4, when serum hCG levels were measured and day 7, when hCG levels and liver and renal function tests were checked.
Women were advised to avoid sexual intercourse, alcohol, aspirin, non-steroidal anti-inflammatory drugs, and UV exposure.
Women were advised to increase their fluid intake and informed of the</td>
<td>Details
Computer-generated randomisation was performed. Trial investigators and patients were blinded to treatment allocation. The arms of the study were matched in terms of age, ethnicity, obstetric history, pregnancy characteristics and serum levels of hCG and progesterone. Trial medication was kept in a sealed opaque bag and distributed by the same provider. The medication was administered by personnel not related to the trial.
Analysis was ITT; it was estimated that 35 patients in each arm would be</td>
<td>Results
Resolution of ectopic pregnancy (defined as resolution of clinical symptoms and decline in hCG concentration <20 IU/L or a negative pregnancy test without the need for additional medical intervention)
Placebo group: 29/38
MTX group: 34/41

Additional treatment needed (surgery)
Placebo group: 9/38
MTX group: 7/41</td>
<td>Limitations
Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias
Random sequence generation: low risk (computer-generated randomisation was performed)
Allocation concealment: low risk (patients and investigators were unaware of treatment allocation, randomisation list retained by third party)
Blinding of participants and personnel: low risk (double blind)
Blinding of outcome assessment: unclear risk (not mentioned whether the outcome assessors were blinded)
Blinding (performance bias and detection bias): low risk (see details above)
Incomplete outcome data: low risk (low drop-out rate [N=1])
Selective reporting: low risk (outcomes reported match with those in the study protocol http://www.isrctn.com/ISRCTN95698259)

Other information</td>
</tr>
</table>

	<table><tr><td>Serum progesterone (nmol/L) at baseline, median (IQR)</td><td>14 (7-28)</td><td>18 (8-28)</td></tr><tr><td>US findings: gestational sac, n (%)</td><td>12 (32)</td><td>23 (55)</td></tr><tr><td>US findings: inhomogenous solid mass, n (%)</td><td>26 (68)</td><td>19 (45)</td></tr><tr><td>Size at presentation (mm), mean (SD)</td><td>13 (7.2)</td><td>11.4 (6.9)</td></tr></table> **Inclusion criteria** Haemodynamically stable women with a tubal ectopic pregnancy diagnosed through ultrasound; no previous history of hepatic, renal or pulmonary disease; absence of embryonic heart beat or haemoperitoneum on the US scan; normal full blood count and liver and renal function tests; and serum hCG< 1500 IU/L at baseline. **Exclusion criteria** Not reported.		common side effects of MTX.	needed to guarantee a power of 80% to detect a reduction in surgical intervention rates from 40% to 12%. Treatment was classified as unsuccessful if women were offered surgery (hCG levels had increased by >15% on 2 consecutive visits or women had abdominal pain with evidence of haemoperitoneum on US).		
Full citation Korhonen,J., Stenman,U.H., Ylostalo,P., Low-dose oral methotrexate with expectant management of ectopic pregnancy, Obstetrics and Gynecology, 88, 775-778, 1996 Ref Id 65331	**Sample size** N=60 (N=30 randomised to placebo and N=30 randomised to methotrexate). Characteristics <table><tr><td></td><td>Placebo (N=30)</td><td>Methotrexate (N=30)</td></tr></table>		**Interventions** Placebo: placebo tablets PO x 5 days Methotrexate: 2.5 mg/day PO x 5 days Follow-up visits occurred on days 2, where hCG levels were measured (if	**Details** Randomisation was performed with a table of random numbers. The trial was double blind, conducted in a single centre. It was estimated that	**Results** Resolution of ectopic pregnancy (defined as decline in hCG concentration <5 IU/L) Placebo group: 23/30 MTX group: 23/30	**Limitations** Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: low risk (table of random numbers was used)

Full citation	Sample size	Interventions	Details	Results	Limitations
Country/ies where the study was carried out Finland **Study type** RCT. **Aim of the study** To assess the recovery times and need for surgery in women with ectopic pregnancy. **Study dates** Not reported. **Source of funding** Not reported.	<table><tr><td>Maternal age, mean, years (SD)</td><td>31.7 (4.4)</td><td>31.8 (5.2)</td></tr><tr><td>Gestational age, mean, days (SD)</td><td>49.1 (8.3)</td><td>52.3 (10.2)</td></tr><tr><td>Gravidity, median (IQR)</td><td>2 (1-6)</td><td>2 (1-6)</td></tr><tr><td>Parity, median (IQR)</td><td>0.5 (0-3)</td><td>0.5 (0-3)</td></tr></table> **Inclusion criteria** Women with an ectopic pregnancy (<40 mm) and serum hCG<5000 IU/l, absent or mild abdominal pain. **Exclusion criteria** Women with an increase of serum hCG >50% in 2 days.	these had increased more than 30 to 50%, women were asked to return for transvaginal sonography), at 4 to 6 days, and 11 to 13 days, when serum hCG levels, serum glutamic oxaloacetate transaminase, red blood cell count, white blood cell count, and platelet counts were determined and transvaginal sonography was determined. Thereafter, expectant management was continued with individual monitoring at 1-3 week intervals. Women were informed about the common side effects of MTX, advised to avoid alcohol intake during the first 5 days, and limit sexual intercourse to a minimum.	N=58 had 80% power to detect a difference of 30% between arms. Treatment was classified as unsuccessful if women were offered laparoscopy (hCG levels increased or plateaued, or women developed abdominal pain, intra-abdominal haemorrhage, or if an adnexal mass was visible by transvaginal sonography).	Additional treatment needed (laparoscopy) Placebo group: 7/30 MTX group: 7/30	Allocation concealment: low risk (codes with the allocations were opened at the end of the treatment) Blinding of participants and personnel: low risk (double blind) Blinding of outcome assessment: low risk (double blind) Blinding (performance bias and detection bias): low risk (see details above) Incomplete outcome data: low risk (low drop-out rate [N=2; reasons were provided]) Selective reporting: high risk (protocol does not appear to have been published) **Other information** Intervention (oral methotrexate) does not reflect current practice in the UK, where IM methotrexate is administered.

Silva, P. M., Araujo Junior, E., Cecchino, G. N., Elito Junior, J., Camano, L., Effectiveness of expectant management versus methotrexate in tubal ectopic pregnancy: a double-blind randomized trial, Archives of Gynecology & Obstetrics, 291, 939-43, 2015 Ref Id 660110 **Country/ies where the study was carried out** Brazil **Study type** RCT **Aim of the study** To assess the effectiveness of MTX versus placebo in women with tubal ectopic pregnancy. **Study dates** September 2011 to January 2013. **Source of funding** Not reported.	N=23 (N=13 randomised to placebo and N=10 randomised to MTX). **Characteristics** <table><tr><td></td><td>Placebo (N=13)</td><td>Methotrexate (N=10)</td></tr><tr><td>Maternal age, mean, years (SD)</td><td>28 (6.8)</td><td>27.8 (4.8)</td></tr><tr><td>Number of pregnancies, mean (SD)</td><td>2.2 (1)</td><td>1.9 (1)</td></tr><tr><td>Parity, mean (SD)</td><td>0.8 (0.8)</td><td>0.6 (0.7)</td></tr><tr><td>Previous ectopic pregnancy, n (%)</td><td>1 (7)</td><td>1 (10)</td></tr><tr><td>Serum hCG (IU/l) at baseline, mean (SD)</td><td>794 (868)</td><td>883 (729)</td></tr><tr><td>Size at presentation (mm), mean (SD)</td><td>25.8(9.7)</td><td>28.3 (8.2)</td></tr></table> **Inclusion criteria** Haemodynamically stable women with a tubal ectopic pregnancy visible on transvaginal ultrasound; tubal mass< 0.5 cm; serum hCG <2000 IU/L at baseline; and declining titres of hCG 48h prior to treatment. **Exclusion criteria** Pregnancies of unknown location; non-tubal ectopic pregnancy; embryonic cardiac activity; signs of tubal rupture and women for whom MTX was contraindicated.	Placebo: single intramuscular injection of saline solution Methotrexate: single intramuscular injection, 50 mg/m2 Follow-up visits occurred on day 4, where serum hCG levels were measured, and on day 7, where blood type, Rhesus factors, complete blood count, aspartate aminotransferase, alanine aminotransferase, urea and creatinine were checked.	Women were randomised and trial investigators and patients blinded to treatment allocation. Treatment was classified as unsuccessful if hCG titres did not fall by at least 15% between the 4th and 7th days after treatment.	Resolution of ectopic pregnancy (defined as negative titres of hCG concentrations, <5mIU/mL) Placebo group: 12/13 MTX group: 9/10 Additional treatment needed (surgery) Placebo group: 1/13 MTX group: 1/10 Tubal rupture Placebo group: 0/13 MTX group: 0/10	Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: unclear risk (randomisation methods have not been reported) Allocation concealment: unclear risk (no details have been provided) Blinding of participants and personnel: low risk (double blinded) Blinding of outcome assessment: unclear risk (not mentioned whether the outcome assessors were blinded) Blinding (performance bias and detection bias): low risk (see details above) Incomplete outcome data: low risk (no drop outs have been reported) Selective reporting: high risk (protocol does not appear to have been published) **Other information**
Full citation van Mello, N. M., Mol, F., Hajenius, P. J., Ankum, W. M., Mol, B. W.,	**Sample size** See van Mello 2012	**Interventions** See van Mello 2012	**Details** See van Mello 2012	**Results** See van Mello 2012	**Limitations** See van Mello 2012

van der Veen, F., van Wely, M., Randomized comparison of health-related quality of life in women with ectopic pregnancy or pregnancy of unknown location treated with systemic methotrexate or expectant management, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 192, 1-5, 2015 Ref Id 660241 **Country/ies where the study was carried out** See van Mello 2012 **Study type** See van Mello 2012 **Aim of the study** See van Mello 2012 **Study dates** See van Mello 2012 **Source of funding** See van Mello 2012	**Characteristics** See van Mello 2012 **Inclusion criteria** See van Mello 2012 **Exclusion criteria** See van Mello 2012				**Other information**
Full citation van Mello, N. M., Mol, F., Verhoeve, H. R., van Wely, M., Adriaanse, A. H., Boss, E. A., Dijkman, A. B., Bayram, N., Emanuel, M. H., Friederich, J., van der Leeuw-Harmsen, L., Lips, J. P., Van Kessel, M. A., Ankum, W. M., van der Veen, F., Mol, B. W., Hajenius, P. J., Methotrexate or	**Sample size** N=73 (N=32 randomised to expectant management and N=41 randomised to MTX). Characteristics Expectant management (N=32) Methotrexate (N=41)	**Interventions** Expectant management: did not receive any specific intervention Methotrexate: single intramuscular injection, 1 mg/kg body weight; maximum 100 mg	**Details** A web-based block randomisation program stratified by hospital and serum hCG concentration (<1000 versus 1000 to 2000 IU/l).	**Results** Resolution of ectopic pregnancy Expectant management group: 19/32 MTX group: 31/41 Rupture rate	**Limitations** Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: low risk (web-based block randomisation)

expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? A randomized comparison, Human Reproduction, 28, 60-7, 2012
Ref Id
377301

Country/ies where the study was carried out
The Netherlands

Study type
RCT

Aim of the study
To assess whether expectant management is an alternative to MTX in women with low and plateauing hCG concentrations.

Study dates
April 2007 to January 2012.

Source of funding
Supported by a grant from the Netherlands Organization for Health Research and Development.

Maternal age, mean, years (SD)	33.1 (5.6)	32.9 (5.7)
Gestational age, mean, weeks (SD)	7.7 (2.6)	6.7 (2)
Primigravid, n (%)	13 (41)	12 (29)
Parity, mean (SD)	0.5 (0.8)	0.7 (0.9)
Previous miscarriage, mean (SD)	0.6 (1)	0.5 (1.3)
Previous ectopic pregnancy, n (%)	2 (6)	5 (13)
Serum hCG (IU/L) at baseline, mean (SD)	708 (376)	535 (500)
Serum progesterone (nmol/L) at baseline, mean (SD)	10 (37)	8 (21)
US findings: ectopic mass, n (%)	7 (21.8)	8 (19.5)
US findings: PUL, n (%)	25 (78.1)	33 (80.4)

Inclusion criteria
Haemodynamically stable women with either

MTX was given within 24 h of their initial visit. Follow-up visits occurred weekly and on day 7, where serum hCG serum concentrations and progesterone were measured. At day 7, in the MTX group, liver and renal function were checked and full blood count was carried out. In those given MTX, repeated doses were given (maximum of 3) if serum hCG concentrations did not fall by at least 15% in the weekly follow up.
Women who received MTX were advised to avoid sexual intercourse. They were also informed about the side effects of alcohol, aspirin, antibiotics, and non-steroidal anti-inflammatory drugs. Women were advised to increase their fluid intake, use appropriate buccal

For 80% power to detect a 30% difference in treatment success at the 5% level, 72 women were required for the study.
Treatment was classified as unsuccessful in the MTX group if more than 4 MTX injections were required (surgical intervention was indicated).
Treatment was unsuccessful in the expectant management group if women became haemodynamically unstable or had clinical signs of tubal rupture (surgical intervention was indicated).

Expectant management: 0/32
MTX group: 0/41

Further treatment needed (further doses of MTX/commence MTX treatment/ salpingectomy)
Expectant management: 13/32
MTX group: 10/41

Health related quality of life outcomes (data from van Mello 2015)
Mean (SD) difference between baseline and 4 week scores. Higher scores indicate a lower quality of life.
SF-36 Physical component scale
Expectant management: 4 (6.3)
MTX group: 3 (6.3)
SF-36 Mental component scale
Expectant management: 9 (8.4)
MTX group: 10 (9.1)
RSCL physical symptoms
Expectant management: -7 (5.6)
MTX group: -6 (9.1)
HADS depression
Expectant management: -1.2 (2.4)
MTX group:-2.3 (3)

Allocation concealment: low risk (patients and investigators were unaware of allocation system)
Blinding of participants and personnel: high risk (not blinded)
Blinding of outcome assessment: high risk (not blinded)
Blinding (performance bias and detection bias): high risk (see details above)
Incomplete outcome data: low risk
Selective reporting: low risk (outcomes reported match with those in the study protocol http://www.biomedcentral.com/1472-6874/8/10)

Other information

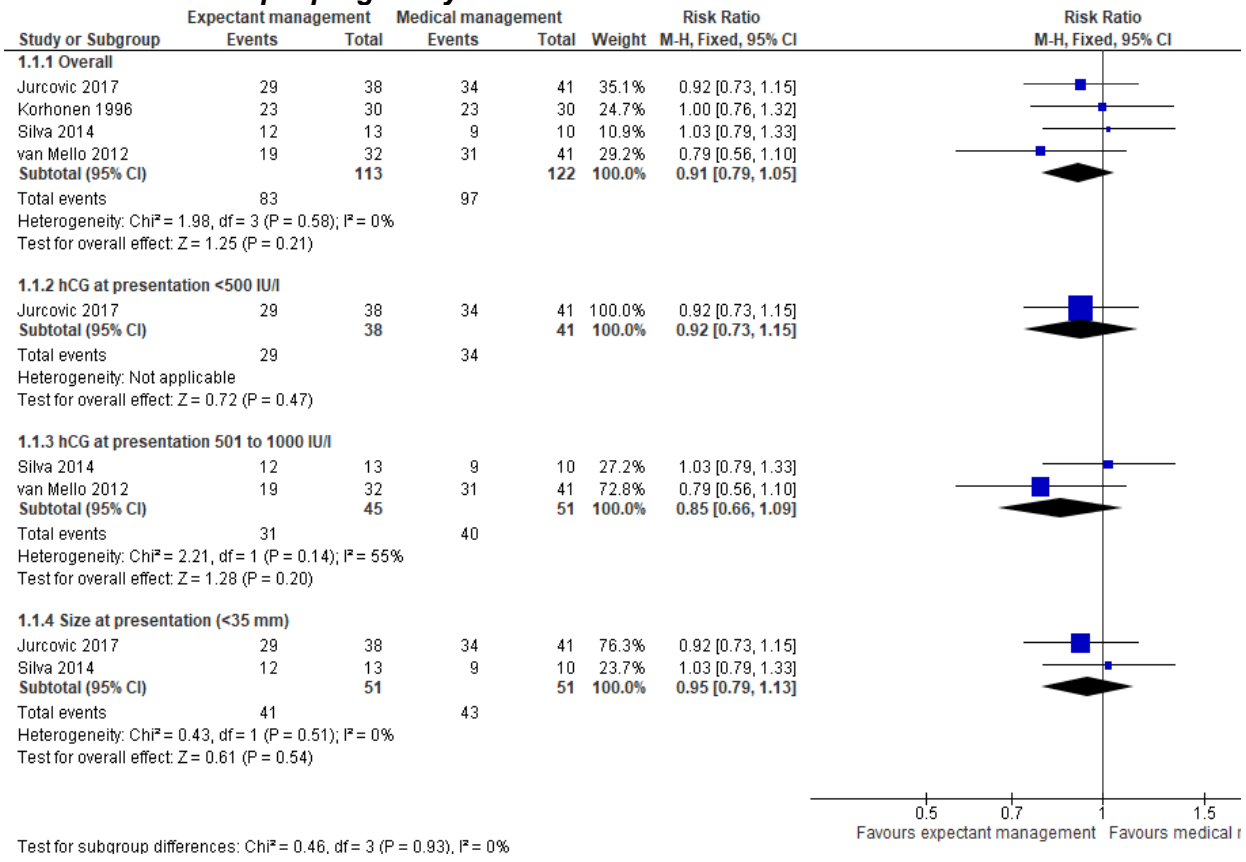
	a tubal ectopic pregnancy visible through transvaginal sonography (an ectopic ring, or an ectopic mass and/or fluid in the pouch of Douglas) and plateauing serum hCG concentrations < 1500 IU/L at baseline or pregnancy of unknown location and a plateauing serum hCG concentration <2000 IU/l A plateauing hCG level was defined as a <50% rise, or a fall between day 0 (first suspicion of an ectopic pregnancy) and day 4. **Exclusion criteria** Women < 18 years old; women in whom MTX was contraindicated; women with a viable ectopic pregnancy; signs of tubal rupture and/or active intra-abdominal bleeding.	hygiene, avoid UV exposure and informed of the common side effects of MTX.		HADS anxiety Expectant management: -3.1 (2.7) MTX group: -3.5 (3.4)	

Appendix E: Forest plots

Comparison 1: Expectant versus medical management

Critical outcomes

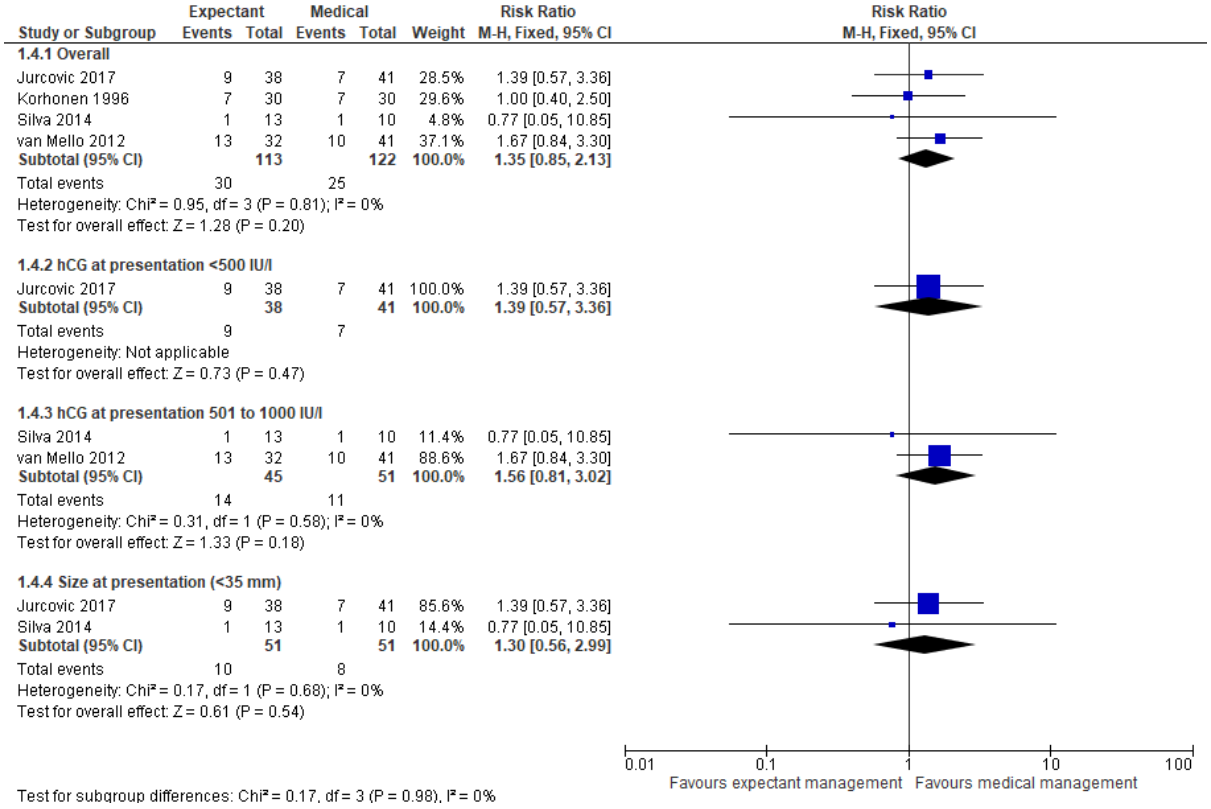
Resolution of ectopic pregnancy



Note: The subgroup analysis for hCG 501-1000IU/L was noted to have I^2= 55%, therefore a random effects model was considered. However, the same subgroup analysis for the 'reversed' outcome (need for additional intervention) was identified as 0%. Therefore the moderate heterogeneity was noted, but a random effects model was not used for this analysis.

Important outcomes

Additional treatment needed



Appendix F:GRADE tables

Table 3: Clinical evidence profile: Expectant versus medical management of ectopic pregnancy

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Expectant management	Medical management	Relative (95% CI)	Absolute	Quality	Importance
Resolution of ectopic pregnancy - Overall												
4 (Jurkovic 2017, Korhonen 1996, Silva 2014, van Mello 2012)	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	83/113 (73.5%)	97/122 (79.5%)	RR 0.91 (0.79 to 1.05)	72 fewer per 1000 (from 167 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
Resolution of ectopic pregnancy - hCG at presentation <500 IU/l												
1 (Jurkovic 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	29/38 (76.3%)	34/41 (82.9%)	RR 0.92 (0.73 to 1.15)	66 fewer per 1000 (from 224 fewer to 124 more)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of ectopic pregnancy - hCG at presentation 501 to 1000 IU/l												
2 (Silva 2014, van Mello 2012)	Randomised trials	Very serious[3]	Serious[4]	No serious indirectness	Serious[2]	None	31/45 (68.9%)	40/51 (78.4%)	RR 0.85 (0.66 to 1.09)	118 fewer per 1000 (from 267 fewer to 71 more)	⊕OOO VERY LOW	CRITICAL
Resolution of ectopic pregnancy - Size at presentation (<35 mm)												
2 (Jurkovic 2017, Silva 2014)	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Serious[2]	None	41/51 (80.4%)	43/51 (84.3%)	RR 0.95 (0.79 to 1.13)	42 fewer per 1000 (from 177 fewer to 110 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Expectant management	Medical management	Relative (95% CI)	Absolute	Quality	Importance
Tubal rupture												
2 (Silva 2014, van Mello 2012)	Randomised trials	Very serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0/45 (0%)	0/51 (0%)	No events were reported	No events were reported	⊕⊕OO LOW	CRITICAL
Additional treatment needed - Overall												
4 (Jurkovic 2017, Korhonen 1996, Silva 2014, van Mello 2012)	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Serious[6]	None	30/113 (26.5%)	25/122 (20.5%)	RR 1.35 (0.85 to 2.13)	72 more per 1000 (from 31 fewer to 232 more)	⊕OOO VERY LOW	IMPORTANT
Additional treatment needed - hCG at presentation <500 IU/l												
1 (Jurkovic 2017)	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[7]	None	9/38 (23.7%)	7/41 (17.1%)	RR 1.39 (0.57 to 3.36)	67 more per 1000 (from 73 fewer to 403 more)	⊕⊕OO LOW	IMPORTANT
Additional treatment needed - hCG at presentation 501 to 1000 IU/l												
2 (Silva 2014, van Mello 2012)	Randomised trials	Very serious[3]	No serious inconsistency	No serious indirectness	Serious[6]	None	14/45 (31.1%)	11/51 (21.6%)	RR 1.56 (0.81 to 3.02)	121 more per 1000 (from 41 fewer to 436 more)	⊕OOO VERY LOW	IMPORTANT
Additional treatment needed - Size at presentation (<35 mm)												
2 (Jurkovic 2017, Silva 2014)	Randomised trials	Serious[5]	No serious inconsistency	No serious indirectness	Very serious[7]	None	10/51 (19.6%)	8/51 (15.7%)	RR 1.3 (0.56 to 2.99)	47 more per 1000 (from 69 fewer to 312 more)	⊕OOO VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Expectant management	Medical management	Relative (95% CI)	Absolute	Quality	Importance
HRQoL (change from baseline to 4 weeks) - Physical component scale (SF-36) (Better indicated by lower values)												
1 (van Mello 2012)	Randomised trials	Serious[8]	No serious inconsistency	No serious indirectness	No serious imprecision	None	28	29	-	MD 1 higher (2.27 lower to 4.27 higher)	⊕⊕⊕O MODERATE	IMPORTANT
HRQoL (change from baseline to 4 weeks) - Mental component scale (SF-36) (Better indicated by lower values)												
1 (van Mello 2012)	Randomised trials	Serious[8]	No serious inconsistency	No serious indirectness	No serious imprecision	None	28	29	-	MD 1 lower (5.54 lower to 3.54 higher)	⊕⊕⊕O MODERATE	IMPORTANT
HRQoL (change from baseline to 4 weeks) - Physical symptoms (RSCL) (Better indicated by lower values)												
1 (van Mello 2012)	Randomised trials	Serious[8]	No serious inconsistency	No serious indirectness	No serious imprecision	None	21	26	-	MD 1 lower (5.24 lower to 3.24 higher)	⊕⊕⊕O MODERATE	IMPORTANT
HRQoL (change from baseline to 4 weeks) - Depression (HADS) (Better indicated by lower values)												
1 (van Mello 2012)	Randomised trials	Serious[8]	No serious inconsistency	No serious indirectness	Serious[9]	None	23	28	-	MD 1.1 higher (0.38 lower to 2.58 higher)	⊕⊕OO LOW	IMPORTANT
HRQoL (change from baseline to 4 weeks) - Anxiety (HADS) (Better indicated by lower values)												
1 (van Mello 2012)	Randomised trials	Serious[8]	No serious inconsistency	No serious indirectness	No serious imprecision	None	24	28	-	MD 0.4 higher (1.26 lower to 2.06 higher)	⊕⊕⊕O MODERATE	IMPORTANT

CI: confidence interval; IU/l: international units per litre; MD: mean difference; MID: minimally important difference; mm: millimetres; RR: risk ratio; SF-36: The 36-item Short Form Health Survey
[1] The quality of the evidence was downgraded by 2 levels because of high risk of selective reporting for one study; unclear risk of random sequence generation, unclear risk of allocation concealment, unclear risk of blinding of outcome assessors, and high risk of selective reporting for one study, and participants and personnel not blinded to treatment allocation for one study

[2] The quality of the evidence was downgraded by 1 level because the 95% CI crossed 1 default MID (0.8)
[3] The quality of the evidence was downgraded by 2 levels because of unclear risk of random sequence generation, unclear risk of allocation concealment, unclear risk of blinding of outcome assessors, and high risk of selective reporting for one study, and participants and personnel not blinded to treatment allocation for one study
[4] The quality of the evidence was downgraded by 1 level because the I-square=55%
[5] The quality of the evidence was downgraded by 1 level because of an unclear risk of random sequence generation, unclear risk of allocation concealment, unclear risk of blinding of outcome assessors, and high risk of selective reporting for one study
[6] The quality of the evidence was downgraded by 1 level because the 95% CI crossed 1 default MID (1.25)
[7] The quality of the evidence was downgraded by 2 levels because the 95% CI crossed 2 default MIDs (0.8 and 1.25)
[8] The quality of the evidence was downgraded by 1 level because the participants and personnel were not blinded to treatment allocation
[9] The quality of the evidence was downgraded by 1 level because the 95% CI crossed 1 default MID (4.3 x +/- 0.5= +/-2.15)

Appendix G: Economic evidence study selection

Figure 2: Flow diagram of economic evidence study selection

Appendix H: Economic evidence tables

No economic evidence was identified for this review question.

Appendix I: Health economic evidence profiles

No economic evidence was identified for this review question.

Appendix J: Health economic analysis

No health economic analysis was conducted for this review question.

Appendix K: Excluded studies

Clinical studies

Study	Reason for Exclusion
Casikar, Ishwari, Lu, Chuan, Reid, Shannon, Bignardi, Tommaso, Mongelli, Max, Morris, Alastair, Wild, Richard, Condous, George, Methotrexate vs placebo in early tubal ectopic pregnancy: a multi- centre double-blind randomised trial, Reviews on recent clinical trials, 7, 238-43, 2012	Not available
Cecchino, G. N., Araujo Jr, E., Elito Jr, J., Methotrexate for ectopic pregnancy: When and how, Archives of Gynecology and Obstetrics, 290, 417-423, 2014	Narrative review
Demirdag, E., Guler, I., Abay, S., Oguz, Y., Erdem, M., Erdem, A., The impact of expectant management, systemic methotrexate and surgery on subsequent pregnancy outcomes in tubal ectopic pregnancy, Irish Journal of Medical Science, 186, 387-392, 2017	Retrospective cohort study
Hajenius, P. J., Mol, F., Mol, B. W. J., Bossuyt, P. M. M., Ankum, W. M., Van Der Veen, F., Interventions for tubal ectopic pregnancy, Cochrane Database of Systematic Reviews, (1) (no pagination), 2007	No relevant comparisons have been covered (single versus double dose of MTX and surgery)
Mol, F., Mol, B. W., Ankum, W. M., van der Veen, F., Hajenius, P. J., Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis, Human Reproduction Update, 14, 309-19, 2008	No relevant comparisons have been covered (single versus double dose of MTX and surgery)
van Mello, N. M., Mol, F., Adriaanse, A. H., Boss, E. A., Dijkman, A. B., Doornbos, J. P. R., Emanuel, M. H., Friederich, J., van der Leeuw-Harmsen, L., Lips, J. P., van Santbrink, E. J. P., Verhoeve, H. R., Visser, H., Ankum, W. M., van der Veen, F., Mol, B. W., Hajenius, P. J., The METEX study: Methotrexate versus expectant management in women with ectopic pregnancy: A randomised controlled trial, BMC Women's Health, 8, 10, 2008	Study protocol
Varma,R., Gupta,J., Tubal ectopic pregnancy, Clinical Evidence, 2012, 2012., -, 2012	No relevant comparisons have been covered (single versus double dose of MTX and surgery)
Wekker, M. Z., Mol, F., VanWely, M., Ankum, W. M., Mol, B. W., Van Der Veen, F., Hajenius, P. J., Van Mello, N. M., Randomised comparison of fertility outcome in women with ectopic pregnancy or pregnancy of unknown location treated with systemic methotrexate or expectant management, Human Reproduction, 28, 2013	Conference abstract

Economic studies

No economic evidence was identified for this review question.

Appendix L: Research recommendations

No research recommendations were made for this review question.