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REVIEW

Efficacy and safety of expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis

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STUDY QUESTION: Is expectant management (EM) of tubal ectopic pregnancy (EP) an effective and safe treatment strategy when compared to alternative interventions?

SUMMARY ANSWER: There is insufficient evidence to conclude EM yields a difference in the resolution of tubal EP, the avoidance of surgery or time to resolution of tubal EP when compared to intramuscular methotrexate in stable patients with β-hCG <1500 IU/l.

WHAT IS ALREADY KNOWN: The utilisation of medical and surgical management for EP is well established. EM aims to allow spontaneous resolution of the EP without intervention.

STUDY DESIGN, SIZE, AND DURATION: We performed a systematic review and meta-analysis, searching Ovid MEDLINE, Embase, PsycINFO, CINAHL, Web of Science, OpenGrey.eu, Google Scholar, cross-referencing citations and trial registries to 15 December 2019. There were no limitations placed on language or publication date. Search terms included tubal EP and EM as well as variations of these terms.

PARTICIPANTS/MATERIALS, SETTING AND METHOD: We considered studies that included patients with tubal EP, EM as a comparator, and that were randomised controlled trials (RCTs). The primary outcome was resolution of tubal EP. Secondary outcomes included avoidance of surgery and the time to resolution of EP. Two reviewers independently selected the studies, assessed bias and extracted data. Relative risk (RR) and mean difference with 95% CI were assessed using a random effects model. The certainty of evidence was scored according to Grading of Recommendations Assessment, Development and Evaluation guidelines.

MAIN RESULTS AND THE ROLE OF CHANCE: In total, 920 studies were screened. Five studies were eligible for inclusion in the systematic review. Two RCTs comparing methotrexate to EM were identified as being eligible for inclusion in meta-analysis. No RCTs comparing surgery to EM were identified. Compared with EM, there was insufficient evidence that methotrexate yields a difference on resolution of tubal EP (RR 1.04, 95% CI 0.88–1.23, $P = 0.67$; two RCTs, moderate-certainty evidence), avoiding surgery (RR 1.10, 95% CI 0.94–1.29, $P = 0.25$; two RCTs, low-certainty evidence) or the time to resolution of tubal EP (−2.56 days (favouring EM), 95% CI −7.93–2.80, $P = 0.35$; two RCTs, low-certainty evidence).

[†]These authors contributed equally to this paper and should be regarded joint first authors.

LIMITATIONS, REASONS FOR CAUTION: Only two RCTs with a total of 103 patients were eligible for inclusion in this meta-analysis. Further RCTs comparing EM to medical and surgical management are needed and these should also report adverse events. Patient preference should also be evaluated.

WIDER IMPLICATIONS OF THE FINDINGS: We found insufficient evidence of differences in terms of resolution, avoidance of surgery and time to resolution between expectant and medical management. Given the imprecision in the effect estimates as demonstrated by the wide CIs, resulting in the downgrading of certainty of evidence for all outcomes in this meta-analysis, larger RCTs comparing interventions for tubal EP are needed. Caution should be exercised when trying to decide between EM and methotrexate to treat tubal EP.

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Key word: extrauterine pregnancy / tubal ectopic pregnancy / expectant management / watchful waiting / spontaneous resolution / natural resolution / watch and wait

WHAT DOES THIS MEAN FOR PATIENTS?

This review looks at whether the expectant management (EM) of ectopic pregnancy (EP) (which is a 'watch and wait' approach without any medical intervention) is a suitable alternative to drug treatment or surgery. EP occurs when a fertilised egg implants outside of the uterus, most commonly in the Fallopian tube. It can be treated by EM, allowing the EP to resolve on its own. Other options are treatment with a drug called methotrexate or surgery to remove the EP and/or the Fallopian tube.

The advantage of EM is that it avoids the risks and side effects of methotrexate and surgery. Additionally, if a patient is treated with methotrexate, they have to wait 3 months prior to attempting to conceive again, but with EM may be able to start trying once the EP has resolved.

We looked through various databases and found studies that compared EM to other treatment options. We performed statistical analysis on the results of these studies, which showed that there was insufficient evidence of a difference in the success of treatment with methotrexate compared to EM. This means that caution should be exercised when trying to decide between EM and methotrexate to treat tubal EP. Other factors, such as patient preference, could be considered to guide management. There are no studies comparing EM with surgery.

Introduction

Tubal ectopic pregnancies (EPs) comprise 98% of all EPs (Lee *et al.*, 2018). It is a prevalent condition, occurring in 1–2% of all reported pregnancies in the developed world (Elson *et al.*, 2016). EP remains a significant cause of maternal morbidity and mortality, accounting for 3% of pregnancy-related deaths in the USA in 2010–2013 .

Traditionally, two management strategies for tubal EP existed: medical (i.m. methotrexate) or surgical management (salpingectomy or salpingostomy). Now, increased consideration is given to expectant management (EM), which is a 'wait and watch' strategy in which no medical or surgical treatment is given with the aim of spontaneous resolution of the EP (National Institute for Health and Care Excellence (NICE), 2019). Advances in transvaginal ultrasonography have allowed for improved and earlier identification of EPs, leading to increased awareness of the natural history of some EPs that can indeed resolve spontaneously (Dooley *et al.*, 2020). In addition, the appreciation of benefits of EM over methotrexate (e.g. avoidance of medication side effects (Alur-Gupta *et al.*, 2019), less active intervention (van den Berg *et al.*, 2020), and potential for reduced use of resources) has led to increased utilisation of EM.

The American College of Obstetricians and Gynecologists (ACOG) guidelines recommend offering EM to women that are asymptomatic, have a plateauing or decreasing serum β-hCG level and are adequately counselled and willing to accept the risks of this treatment strategy (American College of Obstetrics and Gynecology (ACOG), 2018). These risks include tubal rupture, haemorrhage and emergency surgery (American College of Obstetrics and Gynecology (ACOG), 2018). The ACOG recommendations are based on a randomised controlled trial (RCT) which was conducted on women both with EP and pregnancy of unknown location (PUL) (van Mello *et al.*, 2013) and an RCT which compared oral methotrexate to oral placebo (Korhonen *et al.*, 1996). The guideline does not state a specific serum β-hCG level cut-off for offering EM, although it mentions that if the initial serum β-hCG level is <200 IU/l, 88% of patients will have successful resolution of pregnancy (American College of Obstetrics and Gynecology (ACOG), 2018). The use of individual studies to determine guidelines results in ongoing uncertainty for optimal management. As such, we aimed to

evaluate the efficacy and safety of EM in the resolution of tubal EP through a systematic review and meta-analysis of RCTs.

Materials and methods

Our systematic review was prospectively registered with PROSPERO (CRD42020142736). The review is reported according to PRISMA guidelines (Moher *et al.*, 2009).

Information sources and search strategy

Ovid MEDLINE, Embase, PsycINFO, CINAHL, Web of Science, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, OpenGrey.eu and Google Scholar were searched from inception until December 2019. The electronic search algorithm consisted of terms relating to key concepts of 'EP', 'EM', 'watch and wait', 'spontaneous resolution', 'monitor β-hCG' and 'RCT' (Supplementary data). No limitations were placed on publication date or language; however, the search terms used were in English. Reference lists of relevant articles and related reviews were manually searched to identify papers not captured by the electronic searches. Studies were uploaded to Covidence (Veritas Health Innovation, Melbourne, Australia) for independent screening.

Eligibility criteria and study selection

All studies, published and unpublished, were considered for inclusion. Two authors (G.E.C. and T.D.) independently performed title and abstract screening using predetermined selection criteria. Full-text review of the studies that were eligible following title and abstract screening was conducted by two independent reviewers (G.E.C. and H.D.). Where disagreement occurred, the reviewers discussed and reached consensus with input from a third team member (M.L.).

The inclusion criteria selected were patients with an ultrasound diagnosis of EP without intrauterine pregnancy (ICD-10-CM O00.90), EM as an intervention for EP (including placebo i.m. injections) and studies that were conducted as RCTs. The exclusion criteria were studies including patients with intrauterine pregnancy, studies in which EM is not one of the interventions, inappropriate comparison interventions (e.g. oral methotrexate) based on accepted standard of care and quasi-randomised and non-randomised trials. No specific ultrasound criteria for EP (e.g. embryo, yolk sac) (Barnhart *et al.*, 2011) were required for inclusion of studies in this review beyond their own centre-specific classification of EP.

Data extraction

Two reviewers (G.E.C. and H.D.) independently extracted the data from each study. Where disagreement occurred, the reviewers discussed and reached consensus with input from a third team member (M.L.). Data extracted included study characteristics and outcome data. Where data were missing or unclear, the authors were contacted for more information. If no response was received after 3 weeks, this was counted as no response.

Outcome measures

The primary outcome measured was resolution of EP. This was defined as an undetectable serum β-hCG level (<20 IU/l) or a negative urine pregnancy test. The intervention was deemed successful if the EP resolved without further treatment or surgery. Secondary outcomes included whether surgery was avoided, adverse events, time to resolution of EP, fertility outcomes (repeat EP, tubal patency, live birth rate, clinical intrauterine pregnancy rate) and patient preferences and experience.

Assessment of methodological quality

Each study was assessed independently by two authors (G.E.C. and M.L.). The Cochrane Risk of Bias 2 tool (Sterne *et al.*, 2019) was utilised for the risk of bias assessment. Each bias category was characterised as either low risk of bias, some concerns or high risk of bias.

The certainty of evidence for each outcome analysed with a meta-analysis was summarised and scored according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (Guyatt *et al.*, 2009) independently by G.E.C. and M.L. Where disagreement occurred, the reviewers discussed and reached consensus with input from a third team member (M.A.).

GRADEpro and Cochrane methods (GRADEpro GDT, 2015) were utilised to prepare a summary of findings table (see Results section), which presents the overall quality of the body of evidence for the main review outcomes (the resolution of EP, the avoidance of surgery and time to resolution).

Statistical analysis

Data were analysed using Comprehensive Meta-Analysis software (Version 3; provided by Biostat, Englewood, NJ, USA) . A random effects model was used, which assumes there is a degree of clinical heterogeneity between studies. For dichotomous outcomes, we report relative risk (RRs) and 95% CIs, while for continuous outcomes where the same scale was used, mean difference and 95% CIs were reported. When necessary, data reported using median and interquartile ranges were transformed into mean and SD (Wan *et al.*, 2014).

Cochrane's Q and I^2 statistic were used to quantify statistical heterogeneity between studies.

Sub-group analysis was planned in the PROSPERO protocol for the groups of medical management versus EM and surgical management versus EM. However, no studies comparing surgical management to EM were included in this meta-analysis; therefore, no sub-group analyses were performed. Sensitivity analysis was performed with the inclusion of the data from van Mello *et al.* (2013) in addition to the two studies eligible for inclusion in the meta-analysis.

Results

Study selection

A total of 920 articles were identified by implementing the search strategy in the selected databases. No studies were identified by manual review. Following removal of duplicates, title and abstract screening, and full-text screening, four RCTs (van Mello *et al.*, 2013, 2015;

Silva et al., 2015; Jurkovic et al., 2017) and one abstract presentation (Wekker et al., 2013) remained eligible for inclusion in the systematic review. The PRISMA flowchart of study selection is depicted in Fig. 1.

Included studies

Study design and setting

Two studies included patients with exclusively tubal EP. One was a multi-centre RCT conducted in teaching hospitals in the UK (Jurkovic et al., 2017) and the other was a single-centre study conducted in Brazil (Silva et al., 2015). A third multi-centre RCT from the Netherlands included women with EP or PUL, with no distinction in the data between these two conditions (EP and PUL) for outcomes (van Mello et al., 2013). This RCT formed the basis for van Mello et al. (2015) and the abstract presentations (Wekker et al., 2013; van Mello et al., 2015). The authors were contacted in order to obtain data relating specifically to participants with EP. After three attempts with no response, the decision was made to exclude these studies from the primary meta-analysis. Nonetheless, a sensitivity analysis on the primary outcome was performed with the inclusion of these data.

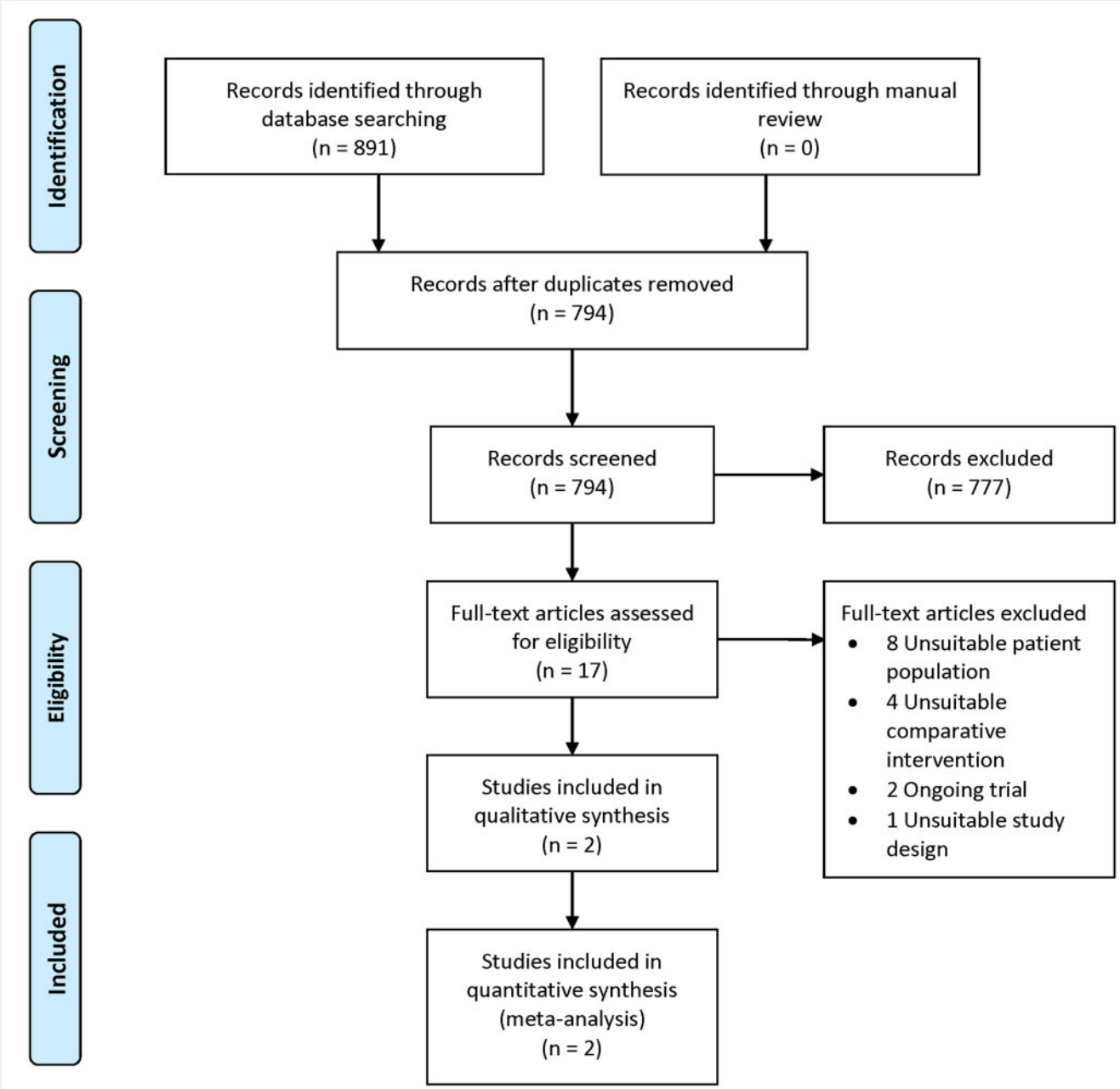

Figure 1 PRISMA flowchart of study selection.

Participants

Participants in all studies were considered haemodynamically stable (van Mello *et al.*, 2013; Silva *et al.*, 2015; Jurkovic *et al.*, 2017). For the studies with exclusively tubal EP, the upper limit of serum β-hCG was set at 1500 IU/l (Jurkovic *et al.*, 2017) and 2000 IU/l (Silva *et al.*, 2015). While participants in one RCT were recruited on the day of diagnosis of EP (Jurkovic *et al.*, 2017), participants in the other were recruited 48 h after the diagnosis of EP and only if there was a spontaneous decline in the β-hCG level (Silva *et al.*, 2015). For the study with EP and PUL diagnoses, recruitment necessitated that participants had either an EP and a plateauing β-hCG level <1500 IU/l or a PUL classification and a plateauing β-hCG level <2000 IU/l) (van Mello *et al.*, 2013, 2015; Wekker *et al.*, 2013). A plateauing serum hCG was defined as a <50% β-hCG increase or decrease between the day of diagnosis and Day 4. Table I summarises study characteristics.

Interventions

Two studies included a comparison of i.m. injection of single-dose methotrexate (50 mg/m^2; medical management) to an i.m. injection of a placebo (saline injection; EM) (Silva *et al.*, 2015; Jurkovic *et al.*, 2017). The remaining study similarly included i.m. methotrexate (1 mg/kg) though the EM group did not receive any specific treatment (van Mello *et al.*, 2013, 2015; Wekker *et al.*, 2013).

Outcomes

Three studies reported on resolution of EP, the avoidance of surgery and time to resolution (van Mello *et al.*, 2013; Silva *et al.*, 2015; Jurkovic *et al.*, 2017). Only a single adverse outcome was reported in one patient in Jurkovic *et al.* (2017) and none in Silva *et al.* (2015). Adverse events were reported in both the methotrexate and EM groups in van Mello *et al.* (2013). Health-related quality of life (HRQoL) was reported by van Mello *et al.* (2015), and the abstract by Wekker *et al.* (2013) reported on fertility outcomes. There were no identified RCTs that met criteria for the secondary outcome of patient preferences/experience.

Excluded studies

Following removal of duplicates and title and abstract screening, 17 studies remained for full-text review. Three studies were excluded as they were duplicates not previously identified. One study was excluded as only women with PUL were included, and no women with EP were participants. Two studies were excluded as they were not RCTs. Four studies were excluded as the comparison was inappropriate: three of these included prostaglandins as part of the medical management and the other compared placebo to oral methotrexate, which is not considered a viable treatment strategy (Elson *et al.*, 2016; American College of Obstetrics and Gynecology (ACOG), 2018). Two studies were not included as they were unfinished studies. Full details of excluded studies are available in Supplementary Table SI.

Risk of bias of included studies

The risk of bias summary and graph for the included RCTs is depicted in Figs 2 and 3, respectively.

Synthesis of results

The outcomes of the five included studies are summarised in Table I. The study van Mello *et al.* (2013) forms the basis of van Mello *et al.* (2015) and Wekker *et al.* (2013) and therefore was only listed once. The meta-analysis and GRADE assessments, stratified by outcome, are presented in Table II.

For the primary outcome of resolution of tubal EP, there was insufficient evidence of a difference between EM and methotrexate: (RR 1.04, 95% CI 0.88–1.23, $P = 0.67$; $I^2 = 0$, two RCTs, 103 patients, moderate-certainty evidence) (Fig. 4). A sensitivity analysis was performed with the addition of van Mello *et al.* (2013), however, this did not change the outcome magnitude or direction significantly from the main analysis (RR 1.08, 95% CI 0.93–1.26, $P = 0.31$, three RCTs, 175 patients).

Additional outcomes

For the secondary outcome of whether surgery was avoided after the initial management strategy, there was insufficient evidence of a difference between EM and methotrexate (RR 1.10, 95% CI 0.94–1.29, $P = 0.25$; $I^2 = 24\%$, two RCTs, 103 patients, low-certainty evidence) (Fig. 5). Only one adverse event was reported in one patient in the EM group of the Jurkovic *et al.* (2017) study who required a blood transfusion. As such, meta-analysis on adverse events was not possible. The average time to resolution of EP was reported by both studies, finding a mean difference of 3.0 days (Jurkovic *et al.*, 2017) and 1.4 days (Silva *et al.*, 2015) with insufficient evidence of benefit for methotrexate (pooled mean difference = −2.56, 95% CI −7.93–2.80, $P = 0.35$; $I^2 = 0$, two RCTs, 103 patients, low-certainty evidence) (Fig. 6). Certainty of evidence in this case was downgraded two levels for imprecision (recommendation would be altered if the lower versus the upper boundary of the 95% CI represented the true underlying effect).

All HRQoL measures improved over time ($P < 0.05$) and there was no evidence of effect of treatment group on any of the HRQoL measures; Medical Outcome Study 36-Item Short Form Health Survey (SF-36) Physical ($P = 0.49$), SF-36 Mental ($P = 0.71$), Rotterdam Symptom Checklist Physical ($P = 0.14$), Hospital Anxiety and Depression Scale (HADS) Depression ($P = 0.98$) and HADS Anxiety ($P = 0.3$) (van Mello *et al.*, 2015). Similarly, there was no significant difference found in fertility outcomes up to 1 year following treatment, with the methotrexate group having a cumulative ongoing pregnancy rate of 68.8% and the EM group having a rate of 56.5% (RR 1.35, 95% CI 0.87–2.09) (Wekker *et al.*, 2013).

Discussion

Main findings

There is insufficient evidence to conclude there is a difference between EM and intramuscular (IM) methotrexate in stable patients with serum β-hCG <1500 IU/l for the resolution of tubal EP, the avoidance of surgery or time to tubal EP resolution. No studies were identified that compare EM to surgical intervention. The level of certainty of the evidence is moderate for resolution of pregnancy and low for avoidance of surgery, primarily due to small sample sizes resulting in wide CIs, which encompass a wide range of potential benefits and harms.

Table I Summary of study characteristics in a systematic review and meta-analysis of the efficacy and safety of expectant management in the treatment of tubal ectopic pregnancy.

	Jurkovic *et al.* (2017)		Silva *et al.* (2015)		van Mello *et al.* (2013)	
	EM	**Methotrexate**	**EM**	**Methotrexate**	**EM**	**Methotrexate**
Sample size	38	42	13	10	32	41
Intervention	i.m. injection; 0.9% NaCl	i.m. injection; 50mg/m^2	i.m. injection; saline	i.m. injection; 50 mg/m^2	No specific treatment	i.m. injection; 1 mg/kg (max 100 mg)
Diagnosis confirmed	Transvaginal ultrasound		Transvaginal ultrasound		Transvaginal ultrasound and serum β-hCG (included women with PUL)	
Mean age (years ± SD)	30 ± 6.7	29 ± 6.9	28 ± 6.8	27.8 ± 4.8	33.1 ± 5.6	32.9 ± 5.7
Parity	0 (IQR 0–1)	0 (IQR 0–1)	0.8 ± 0.8	0.6 ± 0.7	0.5 ± 0.8	0.7 ± 0.9
Previous EP	4 (11%)	3 (7%)	0	1 (10%)	2 (6%)	5 (13%)
Gestational age (weeks)	7.0 ± 2.1	6.9 ± 1.6	8.1 ± 1.6	8.4 ± 1.9	7.7 ± 2.6	6.7 ± 2.0
Diameter of EP (mm)	13.0 ± 7.2	11.4 ± 6.9	25.8 ± 9.7	28.3 ± 8.2	Not stated	
Baseline serum β-hCG (IU/l)	405 (189–784)	465 (238–914)	794 ± 868	883 ± 729	708 ± 376	535 ± 500
Frequency of follow-up	Days 4 and 7; if β-hCG fell by >15% weekly; if β-hCG static, every 2 days		Declining titres of β-hCG >15% between the fourth and seventh days were repeated weekly		Weekly β-hCG	
Successful resolution (intention to treat)	29/38, 76%	34/41, 83%	12/13, 92%	9/10, 90%	19/32, 59%	31/41, 76%
Successful resolution (per protocol)	26/35, 74%	32/36, 89%	12/13, 92%	9/10, 90%	19/32, 59%	29/39, 74%
Surgery required	9/38, 26%	4/41, 11%	1/13, 8%	1/10, 10%	4/32, 13%	1/41, 2%
Time to resolution (days)	14 (IQR 7–29.5)	17.5 (IQR 14–28)	20.6 ± 8.4	22 ± 15.4	38 (range 28–48)	34 (range 27–40)
Adverse events	1[a]	None stated	None stated	None stated	3[b]	Various[c]

Baseline serum β-hCG (IU/l) levels are presented as median (inter-quartile range: IQR) for Jurkovic *et al.* and mean ± SD for Silva *et al.* as presented in original manuscripts. Time to resolution (days) is presented as median (IQR) for Jurkovic *et al.* and mean ± SD for Silva *et al.* as presented in original manuscripts.

[a]Blood transfusion, [b]Nausea, [c]Nausea (n = 9), vomiting (5), diarrhoea (3), bucositis (2), conjunctivitis (4), photosensitivity (2).

EM, expectant management; %, percentage; NaCl, sodium chloride; EP, ectopic pregnancy; PUL, pregnancy of unknown location.

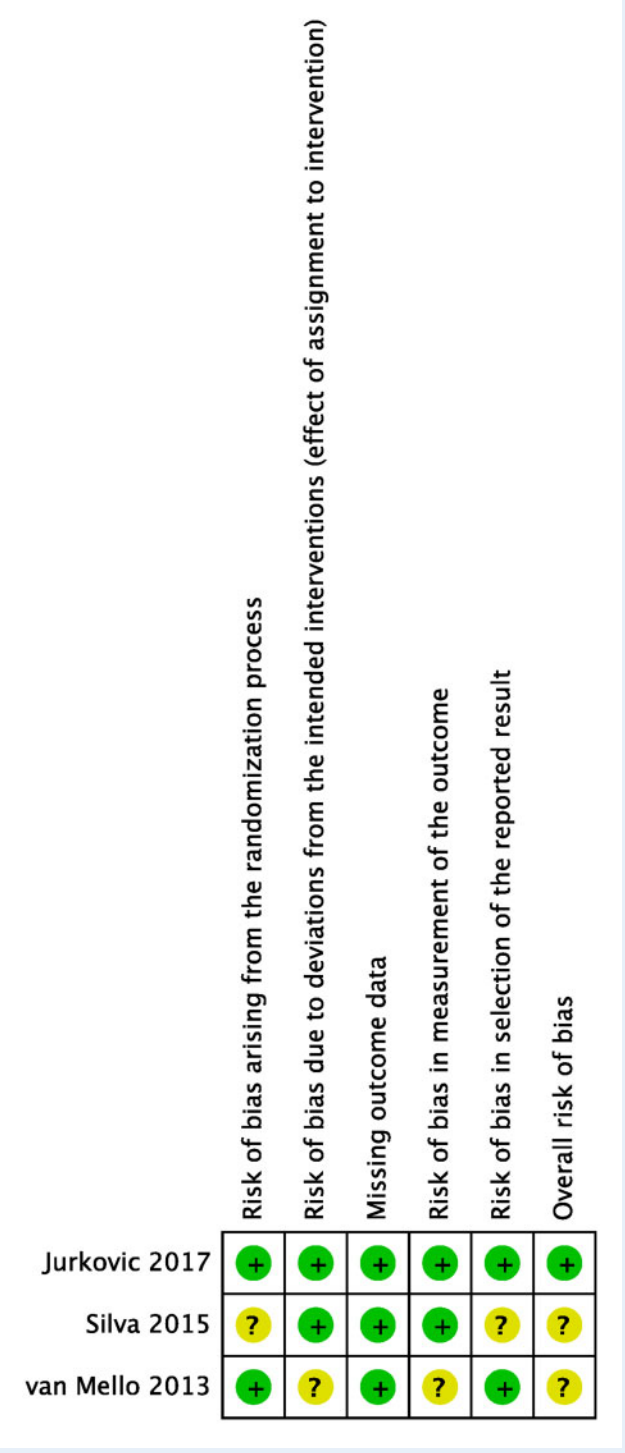

Figure 2 Risk of bias summary table. The Cochrane Risk of Bias 2 tool was used to guide and generate this table.

Three RCTs were not included in the primary meta-analysis due to the inclusion of patients with both PUL and EP (van Mello *et al.*, 2013, 2015; Wekker *et al.*, 2013), based on the data from a single trial. The data showed no significant difference between treatment with methotrexate or EM for the outcomes of resolution of EP, avoidance of surgery or time to resolution. To determine the effect of our decision to exclude these data owing to the inclusion of PUL, we performed a sensitivity analysis including these data in the primary outcome, which showed a similar result to the main meta-analysis. Nine women in the methotrexate group reported side effects, including nausea, vomiting, diarrhoea, bucositis, conjunctivitis and photosensitivity, in comparison to three women in the EM group, who experienced nausea (van Mello *et al.*, 2013). HRQoL of the two groups was compared before, during and after their treatment by van Mello *et al.* (2015), and no significant difference between methotrexate and EM was found. The abstract presented by Wekker *et al.* stated that no significant difference was found in fertility outcomes between the two groups up to 1 year following treatment. However, the design for this part of the RCT was unblinded, leading to some concern regarding risk of bias. Due to the open design of this study, participants in the EM group of this trial may have been more likely to receive surgery, due to concerns regarding tubal rupture. One participant in the methotrexate group received surgery as opposed to four participants in the EM group (van Mello *et al.*, 2013).

Given the insufficient evidence of a difference between EM and methotrexate and the low-moderate certainty of evidence for all outcomes in this meta-analysis, caution should be exercised when deciding between EM and methotrexate at this time. The EM strategy does still offer the potential benefit of avoiding the side effects of IM methotrexate or surgery. We were unable to perform a meta-analysis on side effects or other adverse events as only one adverse event was reported in the papers included in this meta-analysis. Though these side effects may be rare, they can be significant (Gaies and Jebabli, 2012), and include elevated transaminase aspartate level, thrombocytopaenia and neutropaenia (Saleh *et al.*, 2016).

A further potential advantage of EM is that there is the possibility to attempt to conceive again more quickly than patients treated with methotrexate, who are advised to wait 3 months (Elson *et al.*, 2016). However, a recent prospective observational cohort study found that in 5% of patients with tubal EP managed expectantly, it took longer than 3 months for the physical resolution on transvaginal ultrasonography after the β-hCG had normalised (Dooley *et al.*, 2020). This suggests that further research may be required to determine when patients can attempt to conceive again following EM of tubal EP. Currently, there are no official guidelines stating when conception can be attempted following EM (American College of Obstetrics and Gynecology (ACOG), 2018; National Institute for Health and Care Excellence (NICE), 2019).

It is important to note that all the participants in the studies included in this systematic review and meta-analysis were low-risk EPs. The selection criteria for all three studies (van Mello *et al.*, 2013; Silva *et al.*, 2015; Jurkovic *et al.*, 2017) specified a relatively low maximum β-hCG level, required participants to be haemodynamically stable and excluded any patients with signs of potential tubal rupture on ultrasound. van Mello *et al.* (2013) also required women to have a plateauing serum β-hCG level, defined as <50% increase between Day 0 and Day 4. Similarly, Silva *et al.* (2015) required declining titres of β-hCG 48 h prior to treatment. As such, generalisability of these studies' results and the results of this meta-analysis may be limited beyond patients that meet these particular criteria.

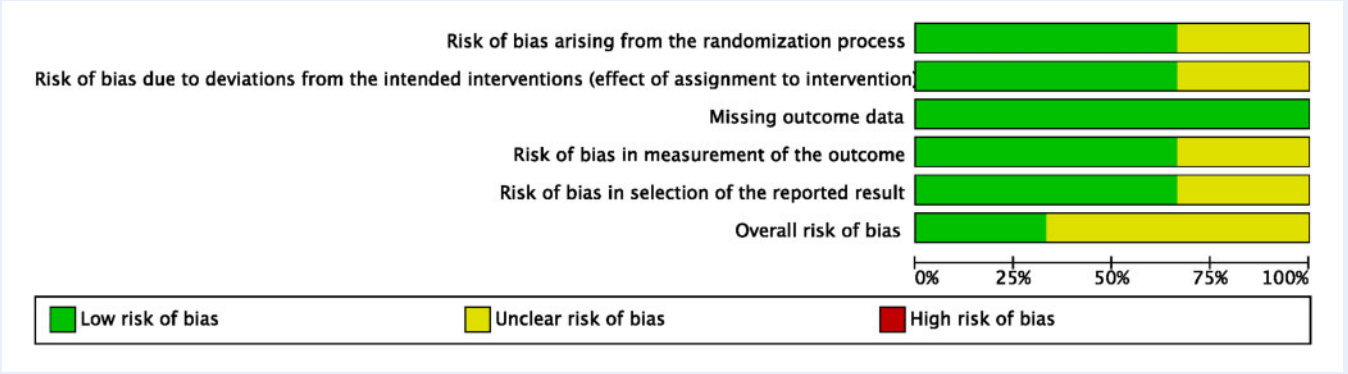

Figure 3 Risk of bias graph. The Cochrane Risk of Bias 2 tool was used to guide and generate this graph.

Table II Meta-analysis and GRADE assessments, stratified by outcome: summary of findings.

Outcomes	n studies	Number of patients		Effect		Certainty (GRADE)	Importance
		Methotrexate	Placebo	Relative risk (95% CI)	Absolute per 1000 (95% CI)		
Resolution of EP	2 RCTs	43/52 (82.7%)	41/51 (80.4%)	1.04 (0.88–1.23)	34 more per 1000 (from 103 fewer to 196 more)	⊕⊕⊕ MODERATE[1]	There is insufficient evidence that methotrexate yields a difference in resolution of EP compared to EM.
Avoidance of surgery	2 RCTs	44/52 (84.6%)	41/51 (80.4%)	1.09 (0.91–1.32)	76 more per 1000 (from 76 fewer to 271 more)	⊕⊕ LOW[2]	There is insufficient evidence that methotrexate yields a difference in the avoidance of surgery compared to EM.
		Time to resolution (days)		**95% CI**	***P*-value**		
Time to resolution of EP	2 RCTs	−2.56 days, favouring EM		−7.93–2.80	0.35	⊕⊕ LOW[2]	There is insufficient evidence that methotrexate yields a difference in time to resolution compared to EM.

GRADE Working Group grades of evidence:
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
[1]Downgraded one level for imprecision: small sample size, 95% CI crosses both benefit and harm.
[2]Downgraded two levels for imprecision: small sample size, very wide 95% confidence interval.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; EM, expectant management.

Strengths and limitations

The systematic review and meta-analysis were conducted with rigorous methodology. An extensive search strategy was created for this study, with strict inclusion and exclusion criteria. Valid data synthesis methods were applied, and no language restrictions were imposed. Validated tools were utilised for quality assessment, including the most up-to-date Cochrane Risk of Bias 2 tool (Sterne *et al.*, 2019) and the GRADE guidelines (Guyatt *et al.*, 2009), as well as the GRADEpro and Cochrane methods tool (GRADEpro GDT, 2015). The rigid inclusion criteria were necessary so that only RCTs with a clearly described methodology were included, diminishing the risk of bias due to poor study design and execution. This meta-analysis was limited by the lack of RCTs on this topic. Following full-text screening, five studies were eligible for this systematic review, but only two were eligible for primary meta-analysis, reducing its potential impact. Though there is some clinical heterogeneity between the two RCTs regarding the trend in β-hCG at the time of recruitment, there is overall much less clinical heterogeneity than present in the most recent NICE guidelines (National Institute for Health and Care Excellence (NICE), 2019).

Comparison with existing literature

The studies included in our analysis are the only RCTs comparing EM to i.m. methotrexate in women with a tubal EP. The UK's NICE guidelines suggest offering EM to women that are asymptomatic, with the gestational sac measuring <35 mm, no foetal heartbeat on ultrasound

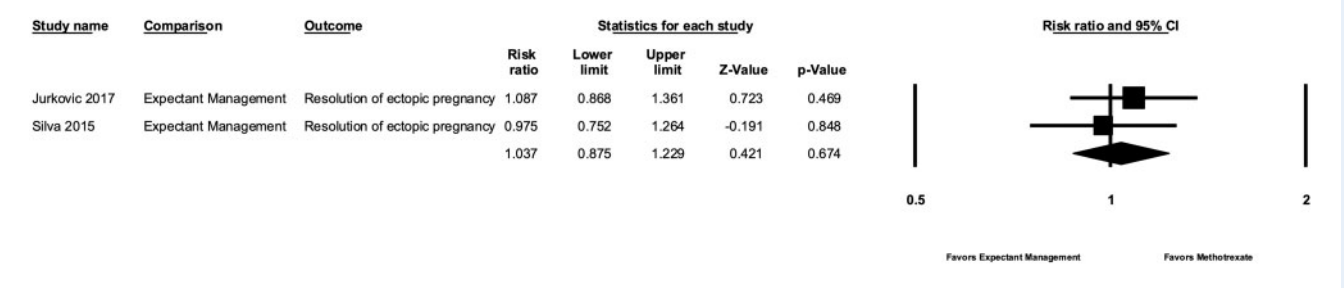

Figure 4 **Forest plot for successful resolution of tubal ectopic pregnancy after initial treatment with methotrexate or expectant management**.

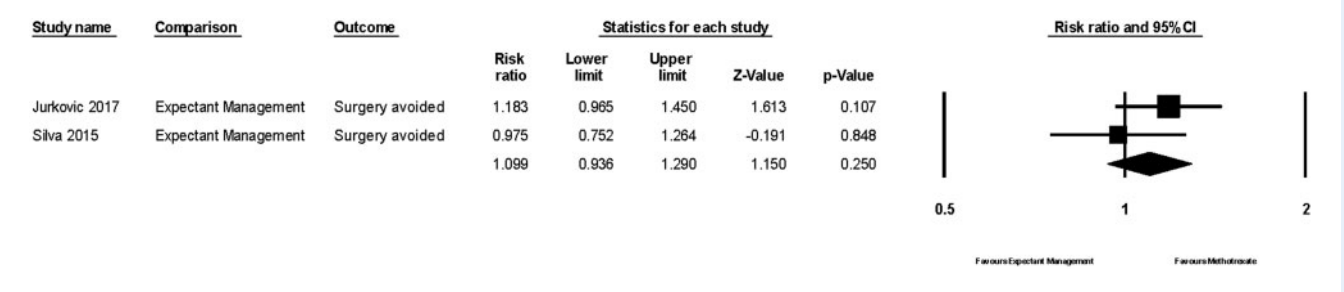

Figure 5 **Forest plot for avoidance of surgery after initial treatment with methotrexate or expectant management**.

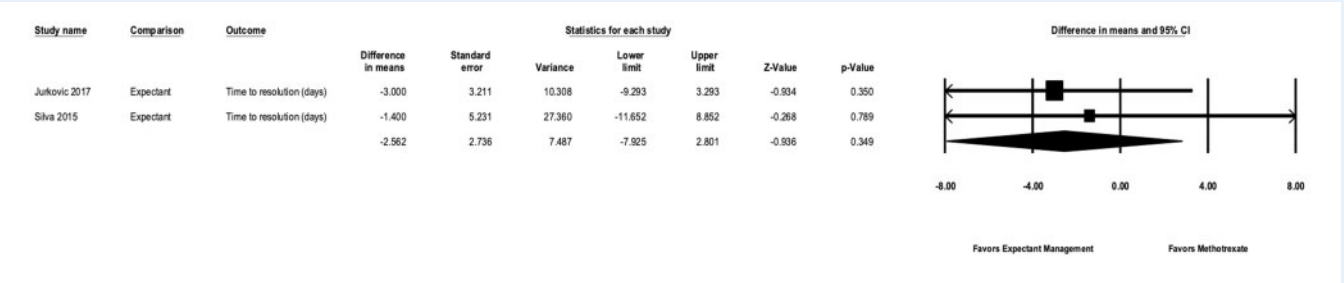

Figure 6 **Forest plot for time to resolution (days) of tubal ectopic pregnancy after initial treatment with methotrexate or expectant management**.

and a serum β-hCG level of <1000 IU/l; and considering EM for patients with the same criteria but serum β-hCG level of 1000–1500 IU/l (National Institute for Health and Care Excellence (NICE), 2019). The NICE recommendations are based on an 'evidence review' including the following: the two RCTs comparing EM to i.m. methotrexate that we included in our meta-analysis (Silva *et al.*, 2015; Jurkovic *et al.*, 2017); the RCT conducted on women both with EP and PUL, including a second publication investigating the outcome of HRQoL (van Mello *et al.*, 2013, 2015) which were included in our systematic review; and an RCT comparing EM to oral methotrexate (Korhonen *et al.*, 1996). The NICE recommendations study inclusion criteria may be considered questionable, as current standard of care includes use of i.m. methotrexate but not oral methotrexate (American College of Obstetrics and Gynecology (ACOG), 2018; National Institute for Health and Care Excellence (NICE), 2019) and not treating patients with PUL classification with methotrexate (Fridman *et al.*, 2019). Our sensitivity analysis included the van Mello (2013, 2015) studies that recruited patients with PULs and this did not change the result of our primary analysis, but we did not include the study with oral methotrexate, which may explain the difference in results from the NICE recommendations. While there may be appropriate indications for EM, we do not believe the current guidance provided by large governing bodies (American College of Obstetrics and Gynecology (ACOG), 2018; National Institute for Health and

Care Excellence (NICE), 2019) encompasses the most relevant literature and/or up-to-date evidence.

Although the trials included in our systematic review are the only RCTs comparing EM to i.m. methotrexate, larger non-randomised studies have been conducted. A prospective observational study with 146 participants found that in 71.2% of patients, the tubal EP resolved spontaneously without the need for any further intervention (Mavrelos et al., 2013). Similarly, a retrospective cohort study with 266 participants had a 61% success rate of EM (Helmy et al., 2015). Another prospective observational study found a success rate of 70%, with 107 patients (Elson et al., 2004). Despite these studies not being conducted with the rigorous methodology of an RCT, these results are important to consider in the evidence base for EM and show that some centres are implementing this management strategy relatively successfully.

Beyond the trend to consider EM as a viable option in the treatment of EP, predictors of success of the EM strategy have begun to be explored, which has resulted in improved criteria for patient selection (Kirk et al., 2011). A cohort study found that the serum β-hCG ratio (the trend in serum β-hCG from diagnosis to 48 h following diagnosis) was the most important predictor of successful medical management and EM, with lower ratios being predictive of success of non-surgical management (Kirk et al., 2011). A history of EP was another important variable in the participants treated expectantly. In this group, patients with a history of EP had a 38% rate of successful EM in comparison to 88% in those with no history of EP (Kirk et al., 2011). Additionally, EM was more likely to be successful in participants presenting with bleeding and pain, which may have been indicative of active resolution of tubal EP (Kirk et al., 2011). The results of this study provide an important insight into predictors of successful EM that should be considered when deciding on a treatment strategy.

The findings from Kirk et al. (2011) are in line with the multivariate logistic regression conducted by Jurkovic et al. (2017), which found that for each unit increase in β-hCG, there was a 0.15% increase in the odds of treatment failure (odds ratio 1.00, 95% CI 1.00–1.00, $P = 0.02$). Additionally, participants with a baseline serum β-hCG of 1000–1500 IU/l had a significantly higher failure rate (RR 3.6, 95% CI 1.60–8.00, $P = 0.00$) in both methotrexate and EM groups. Silva et al. (2015) and van Mello et al. (2013) did not conduct any analysis with regards to predictors of success, and we are therefore unable to draw any conclusions from these studies.

A recent meta-analysis demonstrated that the two-dose methotrexate protocol is more effective than single-dose methotrexate for resolution of tubal EP (Alur-Gupta et al., 2019). At present, single-dose methotrexate is still recommended by ACOG (American College of Obstetrics and Gynecology (ACOG), 2018) though there is no comment by NICE on dosing regimens in their latest guideline (National Institute for Health and Care Excellence (NICE), 2019). The patients in the methotrexate group of van Mello et al. (2013) were given further doses of methotrexate if the β-hCG level did not decrease by 15% at the weekly follow-up appointment, up to a maximum of four doses. The patients in the EM group of van Mello et al. (2013) were not given any specific treatment initially, but were given i.m. methotrexate if the β-hCG had increased at the weekly follow-up appointments, up to a maximum of four doses. Participants in Jurkovic et al. (2017) and Silva et al. (2015) were not given any further doses of methotrexate. This brings into question whether the medical treatment of tubal EP would have been demonstrated to be more successful than EM if a two-dose protocol had been implemented in all studies included in this meta-analysis. While a two-dose protocol would increase the active intervention rate and increase resource utilisation at the time of initial intervention, if it decreases the need for subsequent intervention, particularly surgery, which is costly and has greater morbidity, this could be preferable. What is missing in these studies and in the literature broadly is guidance on patient preference and this should ideally be described through formal efforts on patient-reported outcome measures.

Conclusions and implications

We found insufficient evidence of differences in terms of resolution, avoidance of surgery and time to resolution between EM and medical (i.m. methotrexate) management. Given the low-moderate certainty of evidence for all outcomes in this meta-analysis, large RCTs comparing interventions for tubal EP are needed, including surgical management. At this time, caution should be exercised when deciding between EM and methotrexate, always contextualising the patient characteristics and patient preferences.

Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Authors' roles

M.L., F.D.S.C., L.W. and G.C. conceived the idea. G.E.C., M.L., M.A., T.D., H.D., F.D.S.C., L.W., S.A. and G.C. wrote the protocol. G.E.C., T.D. and M.L. conducted the systematic search. G.E.C., H.D. and M.L. performed data extraction. M.A. and S.A. performed meta-analysis and provided expertise on statistical analysis. All authors took part in interpretation of the data and contributed to the manuscript preparation and approval.

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Conflict of interest

M.L. reports grants from Australian Women and Children's Research Foundation, outside the submitted work. M.A.: As a medical research institute, NICM Health Research Institute receives research grants and donations from foundations, universities, government agencies and industry. Sponsors and donors provide untied and tied funding for work to advance the vision and mission of the Institute. This systematic

review was not specifically supported by donor or sponsor funding to NICM. M.A. reports a partnership grant with Metagenetics outside the submitted work. G.C. reports grants from Australian Women and Children's Research Foundation, personal fees from Roche and GE Healthcare, outside the submitted work. The remaining authors report no conflicts of interest.

References

Alur-Gupta S, Cooney LG, Senapati S, Sammel MD, Barnhart KT. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. *Am J Obstet Gynecol* 2019;**221**:95–108.e2.

American College of Obstetrics and Gynecology (ACOG). ACOG practice bulletin no. 193: tubal ectopic pregnancy. *Obstet Gynecol* 2018;**131**:e91–e103.

Barnhart K, Mello NV, Bourne T, Kirk E, Calster BV, Bottomley C, Chung K, Condous G, Goldstein S, Hajenius PJ *et al.* Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. *Fertil Steril* 2011;**95**:857–866.

Creanga AA, Syverson C, Seed K, Callaghan WM. Pregnancy-related mortality in the United States, 2011–2013. 2017;**130**:366–373.

Dooley W, Braud LD, Memtsa M, Thanatsis N, Jauniaux E, Jurkovic D. Physical resolution of tubal ectopic pregnancy on ultrasound imaging following successful expectant management. *Reprod Biomed Online* 2020;40:880-886.

Elson CJ, Salim R, Potdar N, Chetty M, Ross JA, Kirk EJ. Diagnosis and management of ectopic pregnancy. *BJOG Int J Obstet Gynaecol* 2016;**123**:e15–e55.

Elson J, Tailor A, Banerjee S, Salim R, Hillaby K, Jurkovic D. Expectant management of tubal ectopic pregnancy: prediction of successful outcome using decision tree analysis. *Ultrasound Obstet Gynecol* 2004;**23**:552–556.

Fridman D, Hawkins E, Dar P, Chudnoff S, Rotenberg O, Chong W, Xie X, Mehta S, Levie M. Methotrexate administration to patients with presumed ectopic pregnancy leads to methotrexate exposure of intrauterine pregnancies. *J Ultrasound Med* 2019;**38**:675–684.

Gaies E, Methotrexate J N. side effects: review article. J Drug Metab Toxicol 2012;3:4. DOI: 10.4172/2157-7609.1000125.

GRADEpro GDT. GRADEpro Guideline Development Tool *[Software]*. 2015. https://gradepro.org/ (date last accessed, 15 April 2020).

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Chin J Evidence-Based Med* 2009;**9**:8–11.

Helmy S, Mavrelos D, Sawyer E, Ben-Nagi J, Koch M, Day A, Jurkovic D. Serum human chorionic gonadotropin (β-hCG) clearance curves in women with successfully expectantly managed tubal ectopic pregnancies: a retrospective cohort study. *PLoS One* 2015;**10**:e0130598.

Jurkovic D, Memtsa M, Sawyer E, Donaldson ANA, Jamil A, Schramm K, Sana Y, Otify M, Farahani L, Nunes N *et al.* Single-dose systemic methotrexate vs expectant management for treatment of tubal ectopic pregnancy: a placebo-controlled randomized trial. *Ultrasound Obstet Gynecol* 2017;**49**:171–176.

Kirk E, Calster BV, Condous G, Papageorghiou AT, Gevaert O, Huffel SV, Moor BD, Timmerman D, Bourne T. Ectopic pregnancy: using the hCG ratio to select women for expectant or medical management. *Acta Obstet Gynecol Scand* 2011;**90**:264–272.

Korhonen J, Stenman UH, Ylöstalo P. Low-dose oral methotrexate with expectant management of ectopic pregnancy. *Obstet Gynecol* 1996;**88**:775–778.

Lee R, Dupuis C, Chen B, Smith A, Kim YH. Diagnosing ectopic pregnancy in the emergency setting. *Ultrasonography* 2018;**37**:78–87.

Mavrelos D, Nicks H, Jamil A, Hoo W, Jauniaux E, Jurkovic D. Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy. *Ultrasound Obstet Gynecol* 2013;**42**:102–107.

Moher D, Liberati A, Tetzlaff J, Altman DG; for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.

National Institute for Health and Crare Excellence (NICE). *Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management*. 2019. https://www.nice.org.uk/guidance/ng126 (date last accessed, 15 April 2020).

Saleh HS, Mowafy HE, abd El Hameid AA, Abdelsalam WA, Sherif HE. Double versus single dose methotrexate regimens in management of undisturbed ectopic pregnancy. *Crit Care Obstet Gynecol* 2016;**2**:1–5.

Silva PM, Araujo Junior E, Cecchino GN, Elito Junior J, Camano L. Effectiveness of expectant management versus methotrexate in tubal ectopic pregnancy: a double-blind randomized trial. *Arch Gynecol Obstet* 2015;**291**:939–943.

Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;**366**:l4898.

van den Berg MMJ, Hajenius PJ, Mol F, Hermens RPMG, van der Veen F, Goddijn M, van den Boogaard E. Guideline-based quality indicators for early pregnancy assessment units. *Reprod Biomed Online* 2020;**40**:453–459.

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. *Eur J Obstet Gynecol Reprod Biol* 2015;**192**:1–5.

van Mello NM, Mol F, Verhoeve HR, van Wely M, Adriaanse AH, Boss EA, Dijkman AB, Bayram N, Emanuel MH, Friederich J *et al.* Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? A randomized comparison. *Hum Reprod* 2013;**28**:60–67.

Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;**14**:135.

Wekker MZ, Mol F, van Wely M, Ankum WM, Mol BW, van der Veen F, Hajenius PJ, van Mello NM. P-059 Randomised comparison of fertility outcome in women with ectopic pregnancy or pregnancy of unknown location treated with systemic methotrexate or expectant management. *Hum Reprod* 2013;**28(Suppl. 1)**:i139–i149.