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REVIEW

Methotrexate versus expectant management in ectopic pregnancy: a meta-analysis

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Abstract

Background Ectopic pregnancy (EP) affects 1–2% of all pregnant females'(Barnhart et al., Expert Opin Pharmacother 2(3):409–417, 2001) that can require emergent surgical intervention.
Noninvasive diagnostic tests like transvaginal ultrasound (TVUS), and serial β-hCG levels have enabled early diagnosis and allowed medical therapy to be tried.
Methotrexate (MTX) versus expectant management, both have been considered safe but superiority of one over the other is lacking.

Methods We searched for RCT that have shown efficacy of MTX versus expectant management in hemodynamically stable patients. Our primary outcome was whether one modality is superior to the other.

Results Four RCT were included in the meta-analysis after review. Our pooled analysis when comparing MTX and expectant management showed us that the difference between the uneventful decline in β-hCG levels (treatment success) was statistically insignificant (RR = 1.06, 95% CI 0.93–1.21) with no significant heterogeneity between trials ($I^2 = 0.0\%$, $P = 0.578$). The difference between need for surgical intervention between methotrexate and expectant management was also statistically insignificant (RR = 0.77, 95% CI 0.43–1.40) with no significant heterogeneity between trials ($I^2 = 0.0\%$, $P = 0.552$).

Conclusion We conclude that expectant management is not inferior to MTX in hemodynamically stable patients with ectopic pregnancy that have declining or low β-hCG levels.

Keywords Tubal pregnancy · Ectopic pregnancy · Methotrexate · Expectant management · β-hCG

Introduction

Ectopic pregnancy (EP), a leading cause of first trimester maternal mortality [1], affects 1–2% of all pregnant women [2]. It is defined as a pregnancy that occurs outside the uterine cavity, with majority (96%) [3] occurring in fallopian tubes, however other sites like cervix and hysterotomy scars have also been reported. Surgical management is considered the gold standard therapy, but advancements in early diagnosis with noninvasive diagnostic tests like β-hCG levels and transvaginal ultrasound (TVUS) [4–6], have enabled clinicians to opt for either expectant management or medical therapy such as methotrexate (MTX) in a select subgroup of patients, avoiding the need for emergent surgical intervention. The overall success rate of medical treatment in appropriately selected patients has been reported to be up to 90% [7, 8].

In 1955, Lund [9] noticed in an observational study that nearly 57% of patients with EP did well without surgical intervention. Further studies [10, 11] also suggested that pregnant patients that are hemodynamically stable with no embryonic cardiac activity on TVUS, declining β-hCG level and minimal risk of tubal rupture can have expectant management. Patients undergoing expectant management must have a complete understanding of the clinical implications and risks of ectopic pregnancy. They should give written consent for close follow-up, as well as be prepared to undergo emergent surgical intervention if required. Alternative option for such patients, traditionally, has been the use of oral methotrexate [12, 13] which is safe and efficacious.

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MTX is a folic acid antagonist that inhibits DNA synthesis and cell reproduction in actively proliferating cells such as trophoblasts and fetal cells. It can be administered in an intermediate dose of 50 gm/m^2 or 1 mg/kg to treat ectopic pregnancy in suitable patients, either as a single dose or a multiple dose regimen. Single dose is preferred as the success rate by both approaches is approximately 90% [14, 15]. If β-hCG levels are high, two or multiple doses of MTX can be considered [16]. Side effects of MTX, although mild, are reported in 30% of cases with single dose and 40% when given two doses [3].

Multiple randomized controlled trials (RCT) have tried to establish the superiority of expectant management over MTX, but the data has been inconclusive. We conducted this meta-analysis on published RCT to see if expectant management is an alternative to MTX in a select group of patients having EP in terms of both safety and efficacy.

Methods

A systematic review of the literature from Scopus, Cochrane Database of Controlled trials (CENTRAL), PubMed and OvidSP was conducted to identify the RCT comparing the effectiveness of Methotrexate versus expectant management for ectopic pregnancy. The keywords used for the literature search included, ''Tubal Pregnancy'', ''Ectopic Pregnancy'', ''Methotrexate'', ''Expectant Management'' and ''β-hCG''. The search was done without any restrictions on language or time.

Our systematic review was conducted in accordance with the PRISMA guidelines. Only RCT were included in our analysis.

The total number of studies identified after the initial search was 210, however, only four RCT [17–20] remained after exclusion and these were included in the meta-analysis. The detailed search is illustrated in the PRISMA flow chart (Fig. 1). The total number of patients randomized in all four trials was 235.

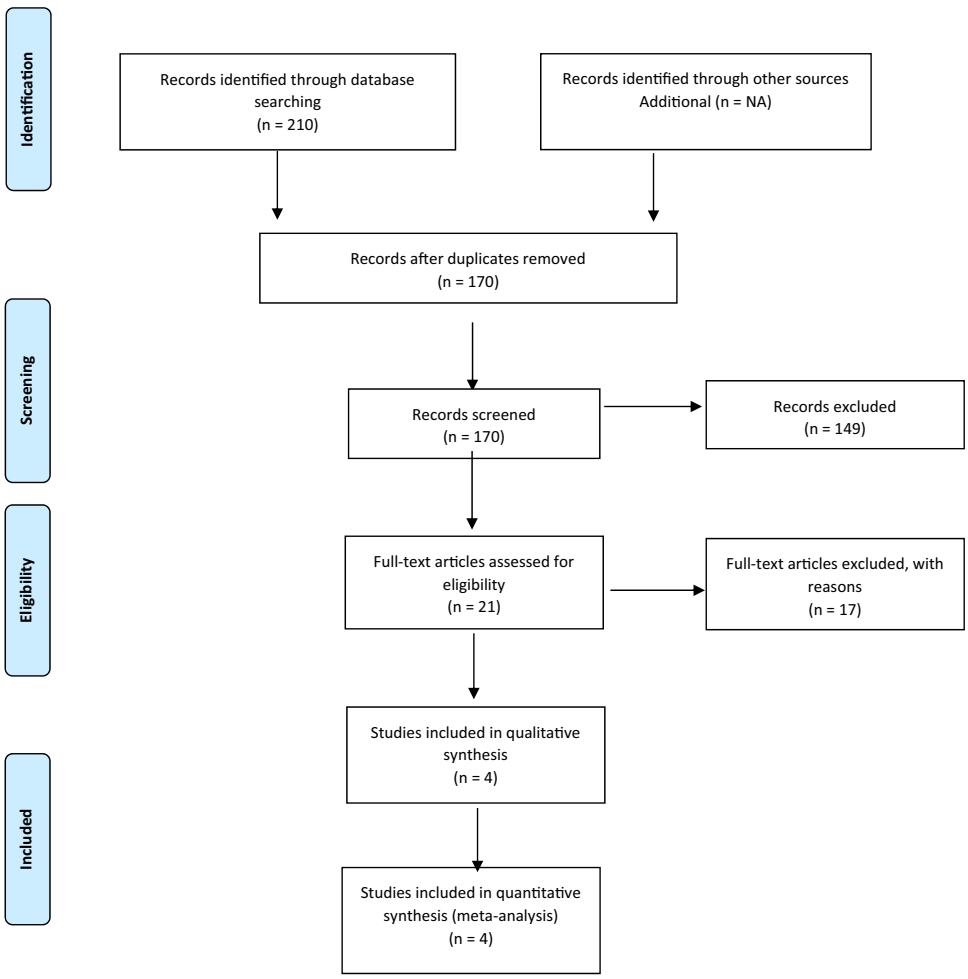

Fig. 1 PRISMA flow chart

The inclusion criteria for this meta-analysis were: (a) study type: RCT; (b) β-hCG levels < 2000 IU/L for ectopic pregnancy (c) hemodynamically stable patients.

Only data that met these criteria was extracted from the respective RCT and data failing to meet these criteria was excluded.

Two independent investigators (MUA) and (AKN) reviewed the remaining studies and consulted a third reviewer (SNM) in case of any discrepancy. The screening of the articles was done from their titles and abstracts followed by their eligibility assessment from the complete text.

Our primary efficacy outcome was to determine whether Methotrexate administration had a statistically significant impact in declining β-hCG levels of ectopic pregnancy versus expectant management. Our secondary outcome was to assess statistical significance in requirement for surgical intervention between the two groups.

The quality of the RCT was assessed using Cochrane Collaboration's risk of bias tool (Table 1). Trials were pooled using a random effects model and presented as risk ratios (RR) and 95% confidence intervals (CI). RR < 1 favored use of Methotrexate. Statistical heterogeneity across studies was quantified using I^2 statistics. All data was analyzed using STATA-11. Publication bias could not be assessed due to a few number of RCT.

Results

We included a total of four randomized controlled trials [17–20], accounting for 235 patients.

Overall, the studies were deemed to be of low-risk as per the Cochrane Collaboration's tool for risk of bias (Table 1). Tables 2 and 3 summarize the demographic and clinical characteristics of the included studies.

Study characteristics

All the studies included had a parallel design [17–20]. The least number of participants included in a study were 23 [17], while the most were 80 [19]. The mean maternal age in the MTX group ranged from 27.8 to 32.9 years, whereas in the group undergoing expectant management the mean maternal age was 28 to 33.1 years. Two studies were multi center [18, 19] while the other two were single center trials [17, 20].

Outcomes

Pooled analysis of RCT comparing Methotrexate and Expectant Management showed that the difference between the uneventful decline in β-hCG levels (treatment success) was statistically insignificant (RR = 1.06, 95% CI 0.93–1.21) with no significant heterogeneity between trials ($I^2 = 0.0\%$, $P = 0.578$) (Fig. 2).

The difference between need for surgical intervention between methotrexate and expectant management was also statistically insignificant (RR = 0.77, 95% CI 0.43–1.40) with no significant heterogeneity between trials ($I^2 = 0.0\%$, $P = 0.552$) (Fig. 3).

Table 1 Quality assessment

	Van Mello 2012	Silva 2014	Jurkovic 2016	Korhonen 1996
Random sequence generation	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Allocation concealment	High risk of bias	Unclear	Low risk of bias	Low risk of bias
Selective reporting	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Incomplete outcome data	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Other bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of participants/personnel	High risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
Blinding of outcome assessment	High risk of bias	Low risk of bias	Low risk of bias	High risk of bias

Table 2 Demographics and design

Author-year	Maternal age/mean years		Study design	Methotrexate dose
	MTX	Placebo		
Van Mello 2012 [18]	32.9 ± 5.7	33.1 ± 5.6	Multi center	1 mg/kg body weight (single IM dose)
Silva 2014 [17]	27.8 ± 4.8	28 ± 6.8	Single center	50 mg/m^2 (single IM dose)
Jurkovic 2016 [19]	29 ± 6.9	30 ± 6.7	Multi center	50 mg/m^2 (single IM dose)
Korhonen 1996 [24]	31.8 ± 5.2	31.7 ± 4.4	Single center	2.5 mg/day for 5 days (oral)

Table 3 Criteria

Author/year	Ectopic pregnancy diagnostic criteria	Total patients per arm		Inclusion criteria	Exclusion criteria	Definition of treatment success
		MTX	Placebo			
Van Mello 2012 [18]	β-hCG, TVUS	41	32	1) β-hCG < 1500 IU/I or PUL and β-hCG < 2500 IU/I 2) Hemodynamically stable	1) Viable ectopic pregnancy 2) Tubal rupture 3) Active intraabdominal bleeding 4) < 18 years	Decline In β-hCG < 2 IU/I
Silva 2014 [17]	β-hCG, TVUS	10	13	1) β-hCG < 2000 IU/I 2) Visible tubal pregnancy 3) Tubal mass < 5 cm 4) Fertility desire 5) Hemodynamically stable	1) Embryonic cardiac activity 2) Signs of tubal rupture 3) Contraindication for MTX	Declining titers of β-hCG 15% between the 4th and 7th days were repeated weekly until they became undetectable (5 IU/L)
Jurkovic 2016 [19]	β-hCG	42	38	1) β-hCG < 1500 IU/I 2) Normal Full blood count, Liver and Renal function tests 3) Clinically stable	1) Embryonic heart rate 2) Hemoperitoneum 3) History of hepatic, renal or pulmonary disease	1)Decline in β-hCG < 20 IU/I 2)Negative urine pregnancy test without the need of any additional medical intervention
Korhonen 1996 [24]	β-hCG TVUS	30	30	1) < 50% increase in β-hCG within 2 days 2) Diameter of Ectopic mass < 40 mm	1) Signs of intrabdominal bleeding on TVUS 2) Secondary reasons for laparoscopy	Recovering without the need for laparoscopy

TVUS transvaginal ultrasound, *PUL* pregnancy of unknown location, *MTX* methotrexate

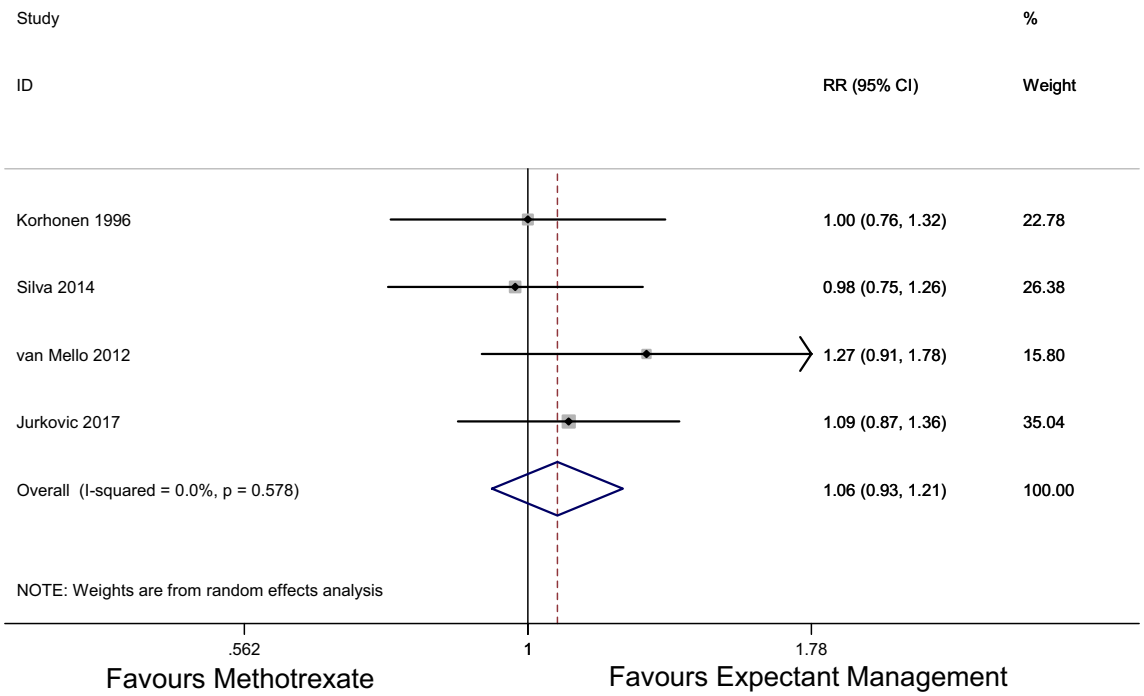

Fig. 2 Treatment success

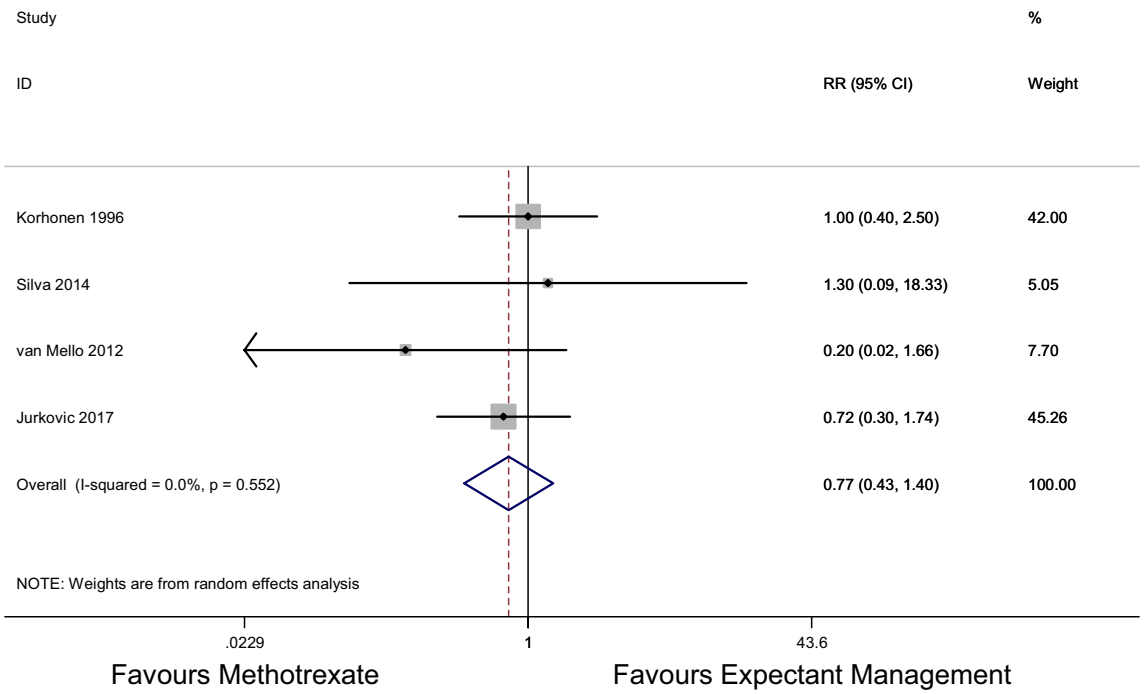

Fig. 3 Surgical intervention

Discussion

Ectopic pregnancy is a condition that requires an accurate and prompt diagnosis. A delay in diagnosis can result in a life-threatening hemorrhage due to rupture of fallopian tube or other adjacent structures.

Hence, surgical intervention has remained the gold standard. Medical advances in the field of radiology aided early diagnosis due to better visualization and therefore facilitated the use of medical therapy with MTX in the 1980s era. The reported rates of tubal rupture with MTX treatment range from 7 to 14% [21]. Later on, the success of expectant management in a small subgroup of patients allowed avoidance of both medical and surgical therapy. A study conducted in France reported an 18% rate of tubal rupture in 843 patients who underwent only expectant management [22].

Various studies published on different aspects of the illness have shown that patients with EP and low β-hCG levels can be managed successfully with medical therapy, without undergoing surgical intervention. The medical treatment options for such patients who are otherwise hemodynamically stable and have unruptured tubal EP include MTX and expectant management. Our meta-analysis showed no statistically significant difference in the results of four RCT comparing the two treatment regimens.

MTX is given in patients with tubal EP or pregnancy of unknown location (PUL) and shortens the duration of follow-up. Different doses and routes of MTX have been tried including high doses, intramuscular administration, and recently low doses to minimize the side effects and improve future fertility.

Data on threshold levels to allow expectant management is sparse due to paucity of studies available. Studies published have used a β-hCG threshold of 1000–2000 mIU/mL [18, 20, 23], with levels of < 1800 mIU/mL for ectopic pregnancy or < 2000 mIU/mL for pregnancy of unknown location and have found high success rates of about 59% and 76% with medical management [18, 19]. Studies by Korhonen et al. [24] and Ylostalo et al. [10] used β-hCG levels up to 5000 IU/L to show resolution times in expectant management patients. However, patients with high baseline β-hCG concentration > 5000 mIU/mL are more likely to require multiple courses of MTX. They have an increased chance to undergo treatment failure as the risk of failure increases by 0.12% for each unit increase in β-hCG. Hence, we excluded studies that used higher levels of β-hCG due to the significant risk of tubal rupture associated with expectant management in such patients. Large sized Ectopic Pregnancy (> 3.5 cm) is an exclusion criterion for MTX therapy but the studies using this criterion are sparse with inconsistent protocols, hence we excluded these studies from our meta-analysis.

These studies require long periods of follow-up and the participants need to be meticulously selected. Another drawback to these studies is that not all patients consent to have expectant management because of fear of emergency surgical procedures. Therefore, these studies usually involve a limited number of patients. Despite all these limitations, RCT have shown expectant management to have a similar efficacy as MTX therapy.

Our meta-analysis will help in better counseling of such patients and avoid unnecessary drug intervention.

Limitations

Our meta-analysis includes a very limited number of RCT and this study can only be applied to hemodynamically stable patients with EP.

Conclusion

We conclude that expectant management is as safe and efficacious as MTX in patients with EP who are clinically stable with declining serum β-hCG levels.

Author contributions AKN project development, data collection, manuscript writing (Discussion) and editing. MUA data analysis, data collection, manuscript writing (Results) and editing. AH forming tables, manuscript writing (Introduction) and referencing. SNM forming tables and manuscript writing (Methods).

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Data availability N/A.

Code availability N/A.

Declarations

Conflict of interest The authors declare no competing interests.

IRB ethical approval N/A.

Informed consent All the RCT selected for this meta-analysis had taken consent form their respective patient population.

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