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SYSTEMATIC REVIEW

Methotrexate versus expectant management for treatment of tubal ectopic pregnancy: An individual participant data meta-analysis

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Abstract

Introduction: Ectopic pregnancy is an important health condition which affects up to 1 in 100 women. Women who present with mild symptoms and low serum human chorionic gonadotrophin (hCG) are often treated with methotrexate (MTX), but expectant management with close monitoring is a feasible alternative. Studies comparing the two treatments have not shown a statistically significant difference in uneventful resolution of ectopic pregnancy, but these studies were too small to define whether certain subgroups could benefit more from either treatment.

Material and methods: We performed a systematic review and individual participant data meta-analysis (IPD-MA) of randomized controlled trials comparing systemic MTX and expectant management in women with tubal ectopic pregnancy and low hCG (<2000 IU/L). A one-stage IPD-MA was performed to assess overall treatment effects of MTX and expectant management to generate a pooled intervention effect. Subgroup analyses and exploratory multivariable analyses were undertaken according to baseline serum hCG and progesterone levels. Primary outcome was treatment success, defined as resolution of clinical symptoms and decline in level of serum hCG to <20 IU/L, or a negative urine pregnancy test by the initial intervention strategy, without any additional treatment. Secondary outcomes were need for blood transfusion, surgical intervention, additional MTX side-effects and hCG resolution times. Trial registration number: PROSPERO: CRD42021214093.

Results: 1547 studies reviewed and 821 remained after duplicates removed. Five studies screened for eligibility and three IPD requested. Two randomized controlled trials supplied IPD, leading to 153 participants for analysis. Treatment success rate was 65/82 (79.3%) after MTX and 48/70 (68.6%) after expectant management (IPD risk ratio [RR] 1.16, 95% confidence interval [CI] 0.95–1.40). Surgical intervention rates were not significantly different: 8/82 (9.8%) vs 13/70 (18.6%) (RR 0.65, 95% CI

Abbreviations: CI, confidence interval; EP, ectopic pregnancy; hCG, human chorionic gonadotrophin; IPD, individual participant data; IPD-MA, individual participant data meta-analysis; MTX, methotrexate; NL, the Netherlands; PUL, pregnancy of unknown location; RCT, randomized controlled trial; RR, risk ratio; UK, United Kingdom.

0.23–1.14). Mean time to success was 19.7 days (95% CI 17.4–22.3) after MTX and 21.2 days (95% CI 17.8–25.2) after expectant management ($P=0.25$). MTX specific side-effects were reported in 33 MTX compared to four in the expectant group.

Conclusions: Our IPD-MA showed no statistically significant difference in treatment efficacy between MTX and expectant management in women with tubal ectopic pregnancy with low hCG. Initial expectant management could be the preferred strategy due to fewer side-effects.

KEYWORDS
expectant management, medical treatment, methotrexate, pregnancy ectopic, pregnancy tubal

1 | INTRODUCTION

Ectopic pregnancies affect 1% of all pregnancies[1] and up to 4.7% of patients presenting to early pregnancy emergency services.[2] Although mortality rates for women with ectopic pregnancies have decreased with advances in the diagnosis and surgical innovations, the cost and burden of the disease including multiple investigations, treatments, follow-up, as well as the psychological impact on women, continue to be high.

The incidence of ectopic pregnancies has been increasing due to increased sensitivity of diagnostic imaging and biochemical algorithms. This enables the detection of small ectopic pregnancies at an early stage which have milder clinical courses. As a result, medical management was introduced into clinical practice 35 years ago.[3,4] Methotrexate (MTX) has been widely used for the treatment of women with ectopic pregnancies presenting with mild clinical symptoms and low human chorionic gonadotrophin (hCG) levels.

Expectant management of ectopic pregnancy (EP) has been shown in observational studies to have a high success rate in women with tubal EP and serum hCG levels <1500 IU/L and avoids the risks of medical and surgical treatment.[5–8] There have been three randomized controlled trials (RCTs), none of which have shown a statistically significant difference between the effectiveness of MTX over expectant management in clinically stable women presenting with low serum hCG levels.[9–11] All studies had relatively small sample sizes and were too small to determine whether certain subgroups of patients could benefit more from either treatment.

An "individual participant data meta-analysis" (IPD-MA) is considered a gold standard of systematic review. It obtains raw individual level data, allowing for a wider scope and range of analyses compared with a meta-analysis, including investigating the impact of participant-level variables on treatment effectiveness. The aims of this study were to undertake an IPD-MA to strengthen evidence that compares systemic MTX with expectant management in the treatment of tubal EP and to identify whether any subgroups benefit more from either treatment.

Key message

Our individual participant data meta-analysis shows no evidence of a difference in treatment efficacy between methotrexate and expectant management of tubal ectopic pregnancies with low hCG. Expectant management with close observation could be the preferred initial strategy in these women. This encourages shared decision-making between the clinician and patient.

2 | MATERIAL AND METHODS

We performed a systematic review and meta-analysis following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Participant Data (PRISMA-IPD) statement.[12]

2.1 | Protocol registration

The finalized protocol was registered with PROSPERO, (http://www.crd.york.ac.uk/PROSPERO), with the ID: CRD42021214093.

2.2 | Inclusion criteria and identification of studies

All studies meeting the following inclusion criteria were proposed for the IPD-MA:

Randomized controlled trial;
Compared systemic MTX with expectant management;
Population was women with tubal EP, defined as either:

- positively identified on ultrasound scan with a baseline serum hCG <1500 IU/L
- or pregnancy of unknown location (PUL) with a plateauing serum hCG concentration <2000 IU/L

Included hemodynamically stable women;

Absence of embryonic cardiac activity;

No evidence of hemoperitoneum;

Approved by the local Institutional Review Board, Ethics Committee, Research Review Board or similar, and participants gave informed consent;

2.3 | Exclusion criteria

Studies were excluded for the following reasons:

Investigator(s) fail to provide data on outcomes of interest;

Inclusion criteria required tubal EP with already declining hCG before randomization;

More than 20% attrition or exclusion of patients after randomization;

Incomplete reporting of reasons for withdrawals and protocol violations if no valid reason upon request;

Imbalance in dropouts across groups;

Incomplete reporting of the study's prespecified outcomes;

Study had not begun enrollment of patients at the time of registration of the IPD-MA protocol

- Quasi-random study designs, to reduce the possibility of bias.

2.4 | Literature search

We searched electronic databases and trial registries for published or registered randomized controlled trials for studies on systemic MTX vs expectant management for the resolution of tubal EP up to August 2020. The Cochrane Gynecology and Fertility Group (CGF) Specialized Register of Controlled Trials, Procite platform and The Cochrane Central Register of Studies Online (CRSO Web platform) were searched from inception. MEDLINE Ovid (from 1946), EMBASE Ovid (from 1974), PsychINFO Ovid (1806), CINAHL Ebsco (1982) were searched. The following trial registers were searched: http://www.clinicaltrials.gov, https://wwww/isrctn.com, BioMed Central ISRCTN registry, WHO International Clinical Trials Registry Platform and Cochrane Central Register of Controlled Trials. The electronic search consisted of terms relating to "tubal pregnancy", "ectopic pregnancy", "methotrexate", "expectant management", "conservative management", "spontaneous resolution", randomized controlled trial", "controlled clinical trial", "random allocation", "double-blind trial", "single-blind", "clinical trial" and "placebos" (Appendix).

All relevant studies were considered for inclusion. Two members of the review team (SAS and MvW) independently performed title and abstract screening using predetermined selection criteria. Full-text review of the eligible studies following title and abstract screening were conducted by two authors (SAS and MvW). Reference lists of relevant articles and reviews were manually searched to identify further papers.

2.5 | Initial contact with trial authors

Members of the review team were also lead investigators of the relevant trials and agreed to provide individual participant data (IPD) from their respective trial. Other trial investigators were approached for input in the manuscript. There were no studies for which IPD was not available on request.

2.6 | Contribution and collection of data

IPD was requested on contact with trial investigators and provided in an anonymized and non-traceable format. Data was stored on a standard format (spreadsheet on STATA) along with explanations, key codes and a data dictionary regarding the data entries. Data was translated to a common language (English) for analysis at the study site in London, UK. Data were checked for consistency, missing or extreme values, missing items, errors and consistency with published reports, and were re-coded if necessary. Randomization methods and intervention details were cross-checked against published reports, trial protocols and data collection sheets. Individual trial members checked finalized data for each trial before incorporation into the combined database and continuation of any further analysis. Data-sharing contracts and collaboration agreements were secured. Anonymized data was emailed on a secure email account, which was deleted after downloaded onto a secure, centralized and customized database at University College London Hospital, London, UK.

2.7 | Data integrity

All data was checked separately by SAS and MvW. We checked sequence generation, completeness and balance/imbalance and whether results presented in the publication are confirmed by the data.

2.8 | Privacy

Data access, handling, analysis and storage were compliant to the European Union General Data Protection Regulation (GDPR).

2.9 | Scoring of risks of bias

Risks of bias for each participating trial were assessed by using the Cochrane collaboration tool [Higgins & Green, 2011] based on the following characteristics:

- Random sequence generation;
- Allocation concealment;
- Blinding of patient participants and study personnel;

- Incomplete outcome data;
- Selective outcome reporting;
- Blinding of outcome assessment;
- Other sources of bias.

Each item of bias was scored as Low, High or Unclear according to the Cochrane Handbook. We also undertook a GRADE evaluation of the quality of evidence. Risk of bias and GRADE evaluation for each trial were assessed by three collaborators; SAS. who was independent of the trials included, and MvW and BWM. who were independent of the UK trial. Discrepancies in assessment and the final risk scoring were discussed with all authors of this study.

2.10 | Outcomes and subgroups

2.10.1 | Planned analysis – study level

Descriptive comparisons between studies were conducted to assess between-study differences. To avoid bias induced by ignoring missing data, it was assumed to be missing-at-random and multiple imputation techniques were used to replace missing data based on observed individual patient characteristics. To preserve any between-study heterogeneity, any imputation was performed within each original study before the data was pooled and analyzed. We describe the proportion of missing values for each dataset included in the IPD-MA.

2.10.2 | Planned analysis – individual level

Individual participant level information was collected and entered into a database. Outcome variables included age, gravidity, parity, mode of conception, previous miscarriage, previous EP, gestational age, baseline serum hCG and baseline serum progesterone.

Primary outcome:

- Treatment success—resolution of clinical symptoms and decline in level of serum hCG to <20 IU/L or a negative urine pregnancy test by the initial intervention strategy (single injection only), without additional medical treatment

Secondary outcomes:

- severe intra-abdominal bleeding requiring blood transfusion
- need for surgical intervention
- indication for surgical intervention
- side-effects from MTX
- number of additional MTX injections given (excluding the single initial injection)
- hCG resolution times

2.11 | Planned subgroup analyses

We conducted subgroup analyses to compare outcomes according to age, parity, study site, baseline serum hCG and baseline serum progesterone and including only tubal EP visualized on ultrasound scan.

2.12 | Statistical analyses

The statistical analyses of this IPD-MA utilized methods described in the Cochrane Collaboration Handbook. Two people extracted the data independently. We summarized the overall effect of the interventions in relation to each outcome when the data of at least two trials were available. Data were analyzed as intention-to-treat. Time to resolution was handled as a continuous outcome. All other outcomes are binary such that the following analysis accounts for these outcomes. Descriptive comparisons were made to assess between-study differences. Each trial was re-analyzed separately, and the investigators asked to confirm their individual results. A one-stage IPD-MA was then performed to assess overall treatment effects of MTX and expectant management to generate a pooled intervention effect. This included a random intercept (to account for baseline differences between studies) and random slope (to account for differences in treatment effect between studies). A log-binomial model for dichotomous outcomes yielded a risk ratio (RR) with 95% confidence interval (CI). A quantile random effects model was used for continuous non-normally distributed outcomes. All analysis included variables that were used for stratified randomization as covariates.

We performed subgroup analyses and explored treatment–covariate interaction for the following patient-level covariates: female age (cut-off 30 years), gestational age (GA), parity, hCG and progesterone. These analyses were conducted using a two-stage approach and were thus based solely on within-study information as recommended to avoid ecological bias.[13] We performed exploratory multivariable one-stage IPD-MA including the covariates for treatment success with associations presented as odds ratio with 95% CI and for time to resolution with associations presented as hazard rate with 95% CI.

2.13 | Software for analyses

Statistical analyses were performed using STATA 16.1 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC) software and R version 3.6.0.

2.14 | Ethics statement

All involved studies had institutional review board approval and obtained informed consent from all participants. We approached the

Health Research Authority (HRA), who advised that a formal NHS REC (National Health Service Research Ethics Committee) approval was not required, and that a Proportionate Review was sufficient, which we obtained (REC reference: 21/PR/1301). We secured Data Sharing and Collaboration Agreement Contracts with the respective sites (IRAS ID: 293525).

3 | RESULTS

3.1 | Study selection and IPD

We identified 821 non-duplicated studies from our electronic search. Following screening of the title, abstract and full-text

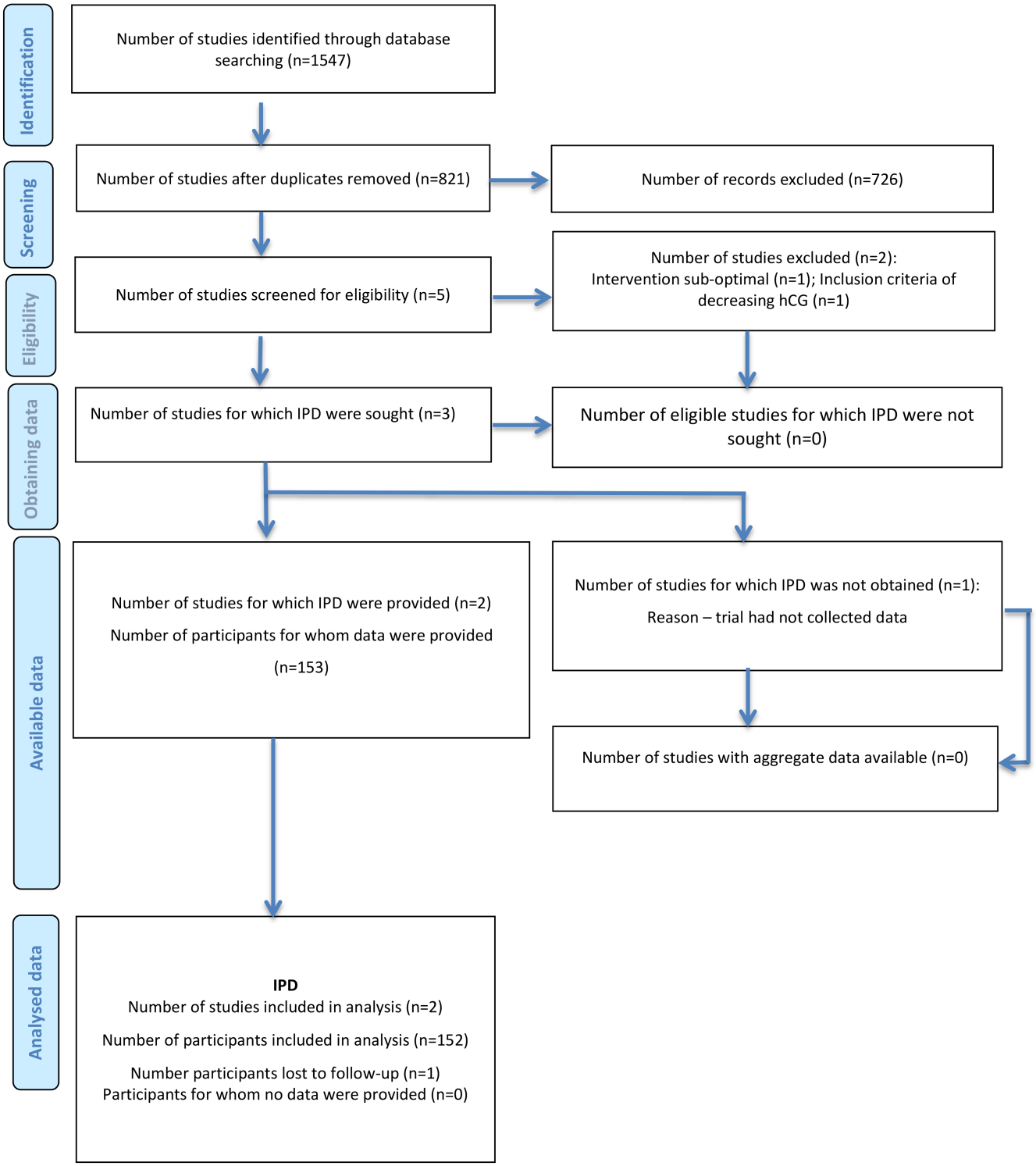

FIGURE 1 PRISMA IPD flow diagram. IPD, individual participant data.

screening, five RCTs were assessed for eligibility: Korhonen et al.,[14] Van Mello et al.,[9] Silva et al.,[10] Jurkovic et al.,[11] Casikar et al..[15] The study by Korhonen et al. was excluded because of the use of a very low dosage of MTX (2.5 mg/day for 5 days), which is unlikely to be effective and could be classified as placebo.[16] The study by Silva et al. was also excluded from the systematic review as one of the key inclusion criteria for this study was decreasing hCG levels before randomization, thereby including only women with already failing pregnancies. A third RCT on MTX vs placebo was registered but the authors informed us that they had not recruited any participants and the study had been stopped.[15] Two studies were included for systematic review, Van Mello et al.[9] (NL study) and Jurkovic et al.[11] (UK study), providing IPD for 153 women (Figure 1).

We assessed the ACT or NOT trial[17] and concluded that it was not eligible for inclusion, as their study focused on "persisting pregnancy of unknown location" rather than tubal EP. On review of the cases that failed treatment and had unscheduled surgery, the majority had dilation and curettage and less than 2% were eventually diagnosed with an EP. In addition, the reported attrition rate was 39%.

3.2 | Study characteristics

The NL study ran between April 2007 and January 2012 and included 73 women with conclusive ultrasound diagnosis of tubal EP with hCG <1500 IU/L or suspected tubal EP (PUL with plateauing serum hCG) <2000 IU/L.[9] This was funded by a grant of the Netherlands Organization for Health Research and Development (ZonMw Clinical fellow grant 90700154). The UK study ran between August 2005 and June 2014 and included 80 women with conclusive ultrasound diagnosis of tubal EP and a serum hCG <1500 IU/L.[11] This did not receive external funding. Baseline characteristics of intervention and comparison groups were similar and all prespecified outcomes were reported in both studies. Further characteristics of both studies are outlined in Table 1.

TABLE 1 Characteristics of included studies of medical vs expectant management of tubal ectopic pregnancy.

Study	Van Mello (2012)	Jurkovic (2017)
Setting	The Netherlands (NL)	United Kingdom (UK)
Study design	Multi-center, open-label RCT • 11 centers	Multi-center, placebo controlled RCT • 2 centers
Sample size	73 • 41 to MTX • 32 to expectant	79 • 42 to MTX • 38 to expectant
Inclusion criteria	Hemodynamically stable women with tubal EP visible on US and plateauing serum hCG <1500 IU/L or a PUL and a plateauing serum hCG <2000 (persisting PUL)	Clinically stable women with conclusive US diagnosis of tubal EP, baseline serum hCG <1500 IU/L
Exclusion criteria	Live ectopic pregnancy, signs of tubal rupture and/or active intra-abdominal bleeding, contraindication for MTX (e.g., abnormalities in liver or renal function or at the time of a full blood count) or <18 years of age	Ectopic pregnancy with embryonic heart rate, hemoperitoneum, contraindication to MTX (abnormal full blood count, liver and renal function tests, history of hepatic, renal or pulmonary disease).
Diagnostic criteria for TEP	Ectopic ring or ectopic mass and/or pouch of Douglas fluid	NR
Intervention	IM MTX 1 mg/kg, (max. 100 mg) ± second MTX if <15% decrease serum hCG in weekly follow-up, max. 3 injections	Single IM MTX 50 mg/m^2
Comparison	Expectant management ± IM MTX if serum hCG increase >15%, max. 3 injections	Single IM 0.9% NaCl IM
Treatment success definition	Uneventful decline serum hCG <2 IU/L by initial intervention	Resolution clinical symptoms and decline hCG <20 IU/L or negative UPT without additional intervention
Outcomes	*Primary*—Treatment success *Secondary*—additional MTX injections, surgical procedures, treatment complications (i.e. hemorrhage, severe allergic reaction to MTX), mild-to-moderate side-effects of MTX treatment (i.e. nausea, diarrhea, vomiting, buccositis and conjunctivitis), clinical symptoms and serum hCG clearance time	*Primary*—Treatment success *Secondary*—intra-abdominal bleeding requiring blood transfusion, number of emergency laparotomies performed, proportion of women experiencing significant pelvic pain or gastrointestinal side-effects and serum hCG resolution times
hCG monitoring	Weekly until hCG undetectable	Day 4 and 7 after treatment then every 2 days if static hCG (within 15% of previous reading) or weekly if levels fell >15%
Loss to follow-up	0	1

Abbreviations: EP, tubal ectopic pregnancy; FBC, full blood count; IM, intramuscular; MTX, methotrexate; NR, not recorded; POD, pouch of Douglas; PUL, pregnancy of unknown location; SD, standard deviation; UPT, urine pregnancy test; US, ultrasound.

3.3 | IPD integrity

There were no issues identified in checking IPD.

3.4 | Risk of bias within studies

The details of risks of bias assessments within individual studies are presented in Figures 2 and 3. The UK study had a low risk of bias in randomization method. The NL study had a high number of participating centers and was stratified by center. They used a "block size of four" for randomization and therefore had unequal allocation. The randomization was organized by an independent party and use of "block size of four" was only revealed after the study was finished. We therefore assessed this to have a low risk of bias in randomization. Performance and detection bias in the UK study were assessed as low risk due to blinding of participants, personnel and outcome assessors. Performance and detection bias in the NL study were assessed as high risk. This study was unable to blind participants and personnel as they did not have a licence for placebo production at the time and outcome assessors were also not blinded. Although some outcomes were objective (hCG resolution times and need for blood transfusion) and unlikely to be affected by non-blinding, other outcomes could have been influenced by knowledge of intervention (need for surgical procedure, side-effects and additional MTX given). Attrition and reporting bias were low in both studies.

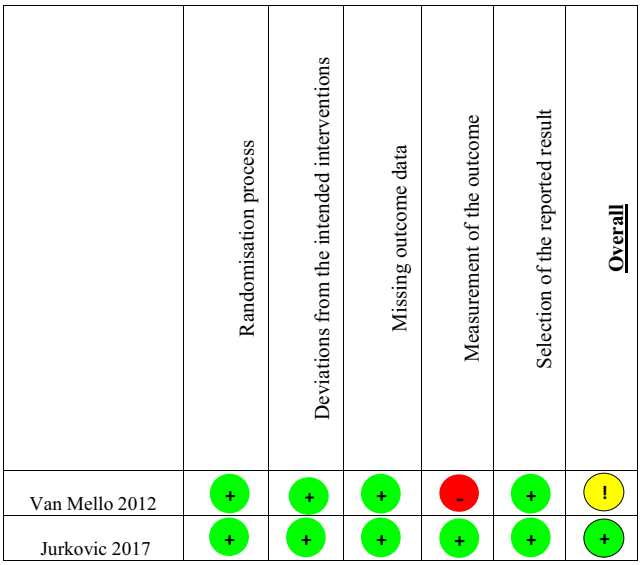

FIGURE 2 Risk of bias grading of randomized controlled trials.

3.5 | GRADE evaluation of studies

A GRADE evaluation of the quality of evidence of the two randomized controlled trials is presented in a Summary of Findings (SoF) in Table 2. Quality of evidence for treatment success was downgraded to low certainty due to serious risk of bias in one study and imprecision due to inadequate confidence in the estimate of effect. Quality of evidence for severe intra-abdominal bleeding requiring blood transfusion was downgraded to moderate certainty due to imprecision. It was felt that the risk of bias due to lack of blinding in one study did not influence need for blood transfusion. Quality of evidence for surgical intervention, side-effects and additional MTX given were downgraded to very low certainty. This was due to a serious risk of bias in one study and high imprecision due to inadequate confidence in the estimate of effect and wide CI. Quality of evidence for hCG resolution time was downgraded to moderate certainty due to imprecision. It was felt that the risk of bias due to lack of blinding in one study did not influence the hCG resolution times.

3.6 | Results of individual studies

The results of each study are shown in Table 3. Surgical intervention was 20% in the UK study and 7% in the NL study.

3.7 | Aggregate meta-analysis

An aggregate meta-analysis did not identify any statistically significant differences in treatment success, need for surgical intervention,

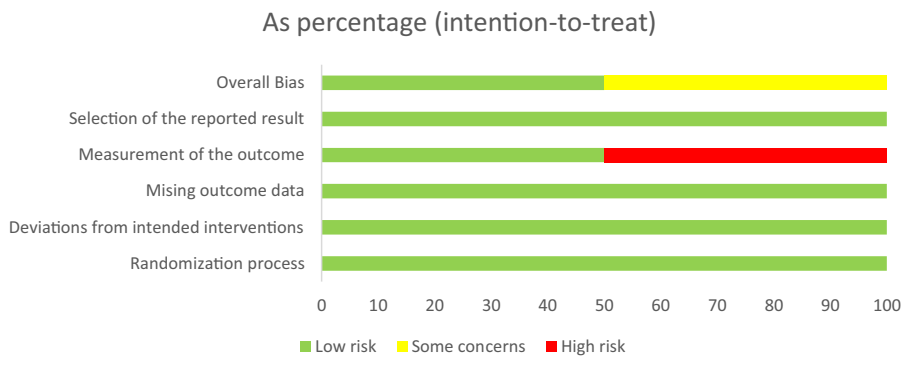

FIGURE 3 Risk of bias graph. The Cochrane Risk of Bias 2 tool was used to guide and generate this graph.

TABLE 2 Summary of findings: GRADE evaluation of critical outcomes of randomized trials of methotrexate vs expectant management for tubal ectopic pregnancy in clinically stable women with hCG <2000 IU/L.

Certainty assessment						No. of patients			Effect	
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Expectant management	Relative (95% CI)	Absolute (95% CI)	Certainty
Treatment success (assessed with: uneventful resolution of clinical symptoms and decline of hCG to <20 IU/L)										
2	Serious[a]	Not serious	Not serious	Serious[b]	None	65/82 (79.3%)	48/70 (68.6%)	RR 1.16 (0.95– 1.40)	**110 more per 1000** (from 34 fewer to 274 more)	⨁⨁◯◯ Low
Severe intra-abdominal blood loss (assessed with: need for blood transfusion)										
2	Not serious	Not serious	Not serious	Serious[b]	None	0/82 (0.0%)	1/70 (1.4%)	Not estimable		⨁⨁⨁◯ Moderate
Surgical intervention (assessed with: need for surgical procedure)										
2	Serious[a]	Not serious	Not serious	Very serious[c]	None	8/82 (9.8%)	13/70 (18.6%)	RR 0.53 (0.23– 1.14)	**87 fewer per 1000** (from 143 fewer to 26 more)	⨁◯◯◯ Very low
Side effects (assessed with: number of side-effects)										
2	Serious[a]	Not serious	Not serious	Very serious[c]	None	37/82 (45.1%)	28/70 (40.0%)	RR 1.11 (0.77– 1.62)	**44 more per 1000** (from 92 fewer to 248 more)	⨁◯◯◯ Very low

TABLE 2 (Continued)

Certainty assessment						No. of patients			Effect	
No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methotrexate	Expectant management	Relative (95% CI)	Absolute (95% CI)	Certainty
Additional methotrexate injections given (assessed with: number of additional MTX injections)										
1	Serious	Not serious	Not serious	Very serious[c]	None	9/41 (22.0%)	9/32 (28.1%)	RR 0.78 (0.35– 1.74)	**62 fewer per 1000** (from 183 fewer to 208 more)	⨁◯◯◯ Very low
hCG resolution times (follow-up: range 4 days to 50 days; assessed with: days)										
2	Not serious	Not serious	Not serious	Serious[b]	None	19.7	21.2	-	MD **1.53 days lower** (6.06 lower to 3.01 higher)	⨁⨁⨁◯ Moderate

Abbreviations: CI, confidence interval; MD, mean difference; RR, risk ratio.

[a]Downgraded one level due to non-blinding in one study.

[b]Downgraded one level due to inadequate confidence in the estimate of effect.

[c]Downgraded two levels due to inadequate confidence and wide confidence interval in the estimate of effect.

additional MTX or side-effects overall between MTX and expectant management of tubal EP (Figure 4).

3.8 | IPD meta-analysis

3.8.1 | Results of syntheses

We obtained data from two trials reporting on 153 women with tubal EP and suspected tubal EP who were randomized to MTX or expectant management. Maternal demographic characteristics were similar in both groups and are shown in Table 4. One woman was lost to follow-up, leaving 152 for analysis.

The IPD RR are presented in Table 5 and Figure 5. These are similar to the aggregate RR. The primary outcome, treatment success or uneventful decline in hCG was not significantly different between MTX and expectant management (IPD RR 1.16, 95% CI 0.95–1.40, $I^2=0\%$, low certainty of evidence). This implies that if the success rate following expectant management is 69%, the success rate following MTX is expected to be between 66% and 94%. The mean time to hCG resolution was 19.7 days (95% CI 17.4–22.3) after MTX and 21.2 days (95% CI 17.8–25.2) after expectant management ($P=0.25$).

In the NL study, 15 were tubal EP visualized on ultrasound, and 58 were PUL. A sensitivity analysis including tubal EP visualized on scan only and excluding PULs suggested a similar result (IPD RR 1.14, 95% CI 0.92–1.42).

Only the NL study used additional MTX in their treatment protocol, of which 9/41 (22%) had additional treatment in the MTX group vs 9/32 (28%) in the expectant management group (RR 0.78, 95% CI 0.35–1.74).

Surgical intervention was required in 8/82 (9.8%) in the MTX group and 13/70 (18.6%) in the expectant group (RR 0.53, 95% CI 0.23–1.14). Of those who had surgical intervention, 9/13 (69%) were tubal EP visualized on ultrasound scan, and 4/13 (31%) were PUL. All women requiring surgery had confirmed tubal EP at laparoscopy. The commonest indication for surgery in the MTX group was abdominal pain with evidence of intra-abdominal bleeding on ultrasound scan (6/8, 75%). The commonest indications for surgery in the expectant management group were abdominal pain with evidence of intra-abdominal bleeding on ultrasound scan (4/13, 31%), rising hCG (4/13, 31%) and abdominal pain only (3/13, 23%).

One woman (1.4%) in the expectant group required a blood transfusion of two units with no women needing it in the MTX group. We could therefore not analyze this difference between the groups.

There was no difference in reported side-effects between MTX and expectant management, although the commonest side-effects in both groups were abdominal pain and vaginal bleeding, which could be due to the natural presentation of EP. Those given MTX reported more side-effects specific to MTX,, including nausea, vomiting, diarrhea, mucositis conjunctivitis and photosensitivity. These side-effects were reported 33 times compared with four times (nausea only) in the expectant management group.

The main IPD results were also calculated as risk differences (Figure S1).

3.8.2 | Treatment–covariate interaction (subgroup analyses)

There was no significant difference in the treatment effect on uneventful decline of hCG according to maternal age, gestational age, parity, baseline serum hCG or progesterone (Figure 6). The heterogeneity measure I^2 was 0% for all subgroups, except for hCG: hCG <1000, $I^2=26$ and ≥1000, $I^2=48\%$.

There was no significant difference in the treatment effect on surgical intervention according to maternal age, gestational age, parity, baseline serum hCG or progesterone (Figure 7). The heterogeneity measure I^2 was 0% for all subgroups, except for hCG: hCG <1000, $I^2=51\%$ and ≥1000, $I^2=74\%$.

There were center differences in reported MTX specific side-effects, with most seen in the NL study and only one side-effect in the UK study (diarrhea in the MTX group). Therefore, we could not evaluate treatment–covariate interaction.

3.8.3 | Exploratory multivariable analysis

In exploratory multivariable IPD analysis we found nulliparity, serum hCG >1000 IU/L and progesterone >15 nmol/L to be negatively associated with treatment success (Table 6). Serum hCG >1000 IU/L

TABLE 3 Individual study data.

	NL ($n=73$)	UK ($n=79$)
Uneventful decline in hCG (%)		
Methotrexate	31/41 (76)	34/41 (83)
Expectant	19/32 (59)	29/38 (76)
Blood transfusion		
Methotrexate	0	0
Expectant	0	1
Surgical intervention (%)	5/73 (7)	16/79 (20)
Methotrexate	1/41 (2)	7/41 (17)
Expectant	4/32 (13)	9/38 (24)
Additional MTX (%)		
Methotrexate	9/41 (22)	0
Expectant	9/32 (28)	0
Resolution time[a], mean (95% CI)		
Methotrexate	22.9 (17.6–28.2)	20.0 (14.3–25.6)
Expectant	20.3 (16.8–23.7)	19.2 (15.3–23.1)

[a]Days

was the only variable found to be negatively associated with resolution time.

Those who had surgical intervention were too small a group for an exploratory multivariable analysis.

4 | DISCUSSION

Our IPD-MA findings did not show a significant difference in treatment success between MTX and expectant management of tubal EP in clinically stable women with hCG <2000 IU/L. There was no covariate interaction or a difference in treatment success according to maternal age, gestational age, parity, baseline serum hCG or progesterone. In an exploratory multivariable analysis, a serum hCG ≤1000 IU/L and progesterone ≤15 nmol/L were associated with a higher success rate in both groups. Given no significant difference between MTX and expectant management in these women, this encourages shared decision-making between the clinician and patient, factoring in the latter's voice, values and preferences.

Our study is the first to provide an IPD-MA of MTX vs expectant management of tubal EP, obtaining all IPD from eligible RCTs. We observed robust and recommended methodology, assessed the risk of bias of included trials, graded quality of evidence and strengthened clinical data of interest to inform future practice.

Our main limitation is that there were only two trials of limited sample size. However, these are the only eligible trials available, highlighting the paucity of data. One trial did not have a placebo comparison, introducing performance, bias as surgical intervention could be more readily applied to women with mild clinical symptoms in the expectant group and participants were more likely to report side-effects in the MTX group. There were also selection criteria differences in that the NL study had a higher proportion of PUL, presumed to be tubal EP due to plateauing serum hCG levels, and the UK study had positively identified all tubal EP on ultrasound. When analyzing only tubal EP seen on ultrasound scan we

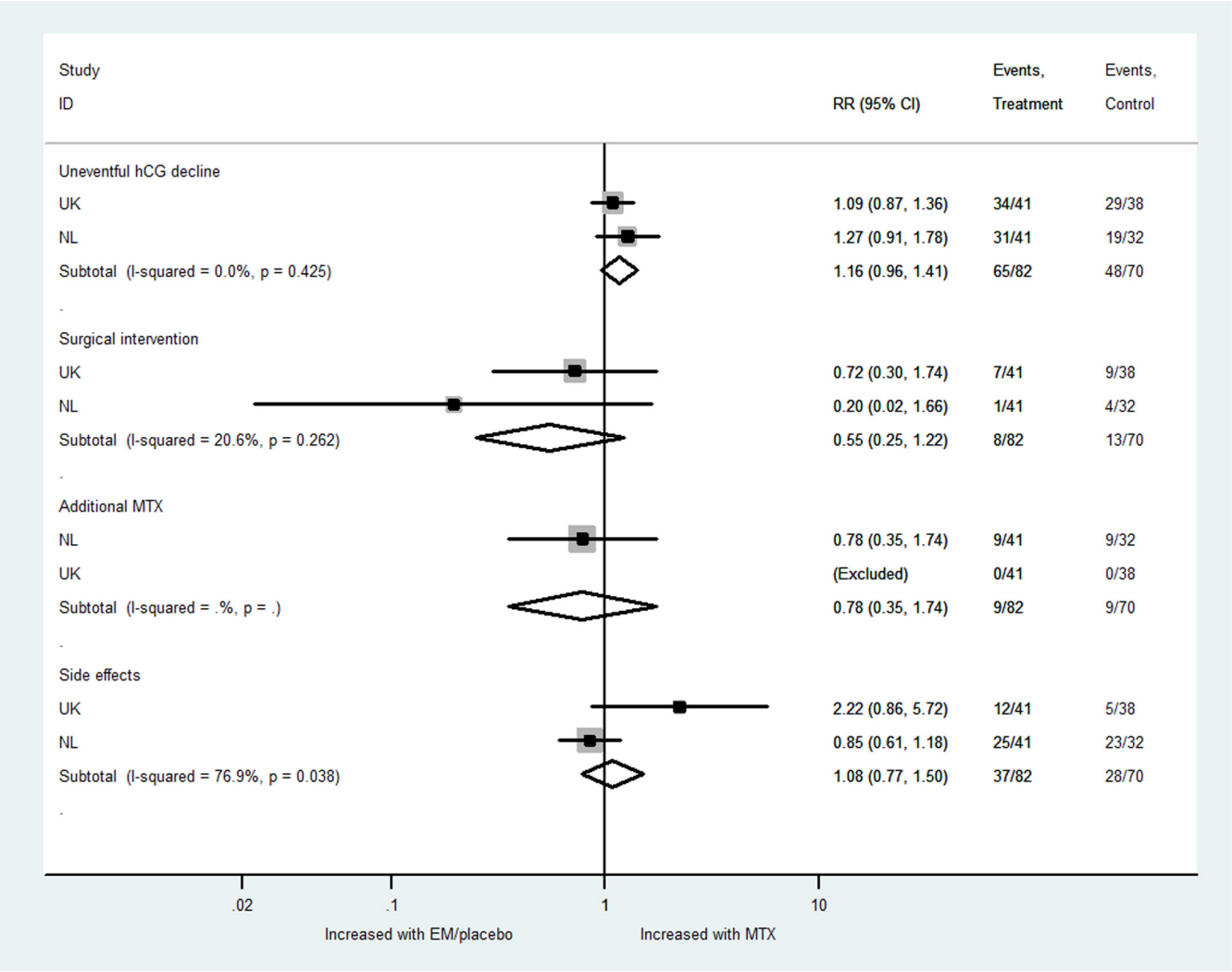

FIGURE 4 Aggregate meta-analysis. EM, expectant management; MTX, methotrexate; NL, the Netherlands; RR, risk ratio; UK, United Kingdom.

TABLE 4 Demographic characteristics of studies combined at baseline.

	MTX ($n=83$)	Placebo/expectant ($n=70$)	*P*-value
Maternal age[a], mean (95% CI)	30.9 (29.4–32.3)	31.52 (29.9–32.5)	0.590
Gestational age[b], mean (95% CI in days)[e]	7^{+2} (47.1–55.7)	7^{+6} (44.2–49.9)	0.057
Parity, *n* (%)			0.673
0	43/81 (53.1)	42/70 (60.0)	
1	23/81 (28.4)	15/70 (21.4)	
2+	15/81 (18.5)	13/70 (18.6)	
Previous miscarriage, *n* (%)			0.696
0	61/81 (75.3)	51/70 (72.9)	
1	14/81 (17.3)	12/70 (17.1)	
>2	6/81 (7.4)	7/70 (10.0)	
Previous EP, *n* (%)	8/81 (9.9)	6/70 (8.6)	0.783
hCG[c], median (Q1–Q3)	504 (231–960)	468 (238–906)	0.929
Progesterone[d], median (Q1– Q3)	9.8 (5.0–24.9)	12.8 (7.0–19.0)	0.728

Abbreviations: EP, ectopic pregnancy; IQR, interquartile range.

[a]Years.

[b]Weeks and days.

[c]Missing data = 8 MTX, 10 placebo/expectant.

[d]IU/L.

[e]nmol/L.

TABLE 5 Combined outcomes.

Outcome	MTX ($n=82$)	Placebo/expectant ($n=70$)	IPD RR (95% CI)
Including all data			
Uneventful decline in hCG, *n* (%)	65/82 (79.3)	48/70 (68.6)	1.16 (0.95–1.40)
Including only tubal EP seen on scan			
Uneventful decline in hCG, *n* (%)	41/49 (83.7)	33/45 (73.3)	1.14 (0.92–1.42)
Additional MTX (one study)	9/41 (22.0)	9/32 (28.1)	0.78 (0.35–1.74)
Surgical intervention	8/82 (9.8)	13/70 (18.6)	0.53 (0.23–1.14)
Any side-effects	37/82 (45.1)	28/70 (40.0)	1.11 (0.77–1.62)

Abbreviations: ACI, confidence interval; hCG, human chorionic gonadotrophin; IPD, individual participant data; MTX, methotrexate; RR, relative risk.

still did not find a significant difference between the two groups, although this was a smaller sample. The selection criteria difference could explain why the surgical intervention rate was higher in the UK study than the NL study, as studies have shown that the majority of PULs resolve spontaneously without intervention.[18] Another explanation for surgical intervention difference between the studies could be the use of additional MTX in the NL study only. This could have increased the pharmacological effectiveness of MTX or allowed more time for the EP to resolve. As there was no option to administer additional doses of MTX in the UK study, clinicians were compelled to offer surgical intervention to women with rising hCG.

Our findings corroborate an aggregate meta-analysis that did not find evidence in differences in resolution, need for surgery or time to resolution between expectant and medical management of EP.[19] An RCT of 23 participants also found no difference between single dose MTX and placebo (saline solution), with a treatment success of 90% vs 92.3%, respectively.[10] The higher treatment success rates in this study could be due to inclusion of participants who already had declining hCG levels introducing bias into treatment effectiveness.

The success rate of expectant management in our study was similar to retrospective studies which where success rates ranged between 63% and 75%.[6,8,20–23]

Our study showed that an hCG level <1000 mIU/mL was associated with higher success rates and shorter resolution time in both groups. Several studies on MTX noted a higher treatment success with lower hCG levels.[20,24–27] Similarly, studies on expectant management favor a lower hCG for successful resolution,[6,14,22,23,28] with the subgroup of women with initial hCG <1500 IU/L having a 77% success rate.[8] Our mean time to resolution of 19.7 days with MTX and 21.2 days with expectant management was similar to that of other studies.[10,23,29]

Our study showed that women with progesterone ≤15 nmol/L were more likely to have treatment success than those with progesterone >15 nmol/L. Several papers have attempted to determine the influence of progesterone levels on the resolution of EP. One study found that all women with a progesterone <32 nmol/L were successfully treated with a single dose of MTX compared with 45% when progesterone >32 nmol/L.[30] Another found a 97% positive predictive value for successful resolution with single dose MTX if progesterone <22 nmol/L.[31] Elson et al. identified a 90% success rate for expectant management if progesterone <10 nmol/L with hCG <1500 IU/L.[8]

MTX has long been used for treatment for EP in different regimens and administration routes.[16] However, it has a strong dose-related potential for toxicity and adverse effects include stomatitis, conjunctivitis, photosensitivity, bone marrow suppression, pulmonary fibrosis, liver cirrhosis, renal failure and gastric ulceration. Women are also advised to avoid conceiving 3 months after administration.[32] Its effectiveness ranges between 65% and 95%,[33–37] with studies comparing different MTX regimens to each other rather than to a control. The variation in effectiveness is also due to differences in selection criteria, diagnosis of tubal EP and definitions of treatment success. In studies where tubal EP is not visualized on ultrasound scan, one must be cautious caution not to use MTX to treat miscarriages or normally sited live pregnancies.[38,39] There could be scope for use in ectopic pregnancies with higher hCG.[27,40–42] A recent multi-center RCT compared MTX and Gefitinib with MTX and placebo to treat tubal EP with hCG 1000–5000 IU/L. Although there was no difference in need for surgical intervention between the two treatments, resolution of tubal EP was 70% vs 71%, respectively.[39]

Our IPD-MA highlights the need to standardize outcome definitions and reporting to compare studies more effectively. The recent development of a core outcome set for treatment of ectopic pregnancies for future investigators will enable this.[43] All future studies should state clear diagnostic criteria for an EP to eliminate uncertainty as to what condition is being treated, whether a true tubal EP or a PUL, the latter of which could be a miscarriage or live normally

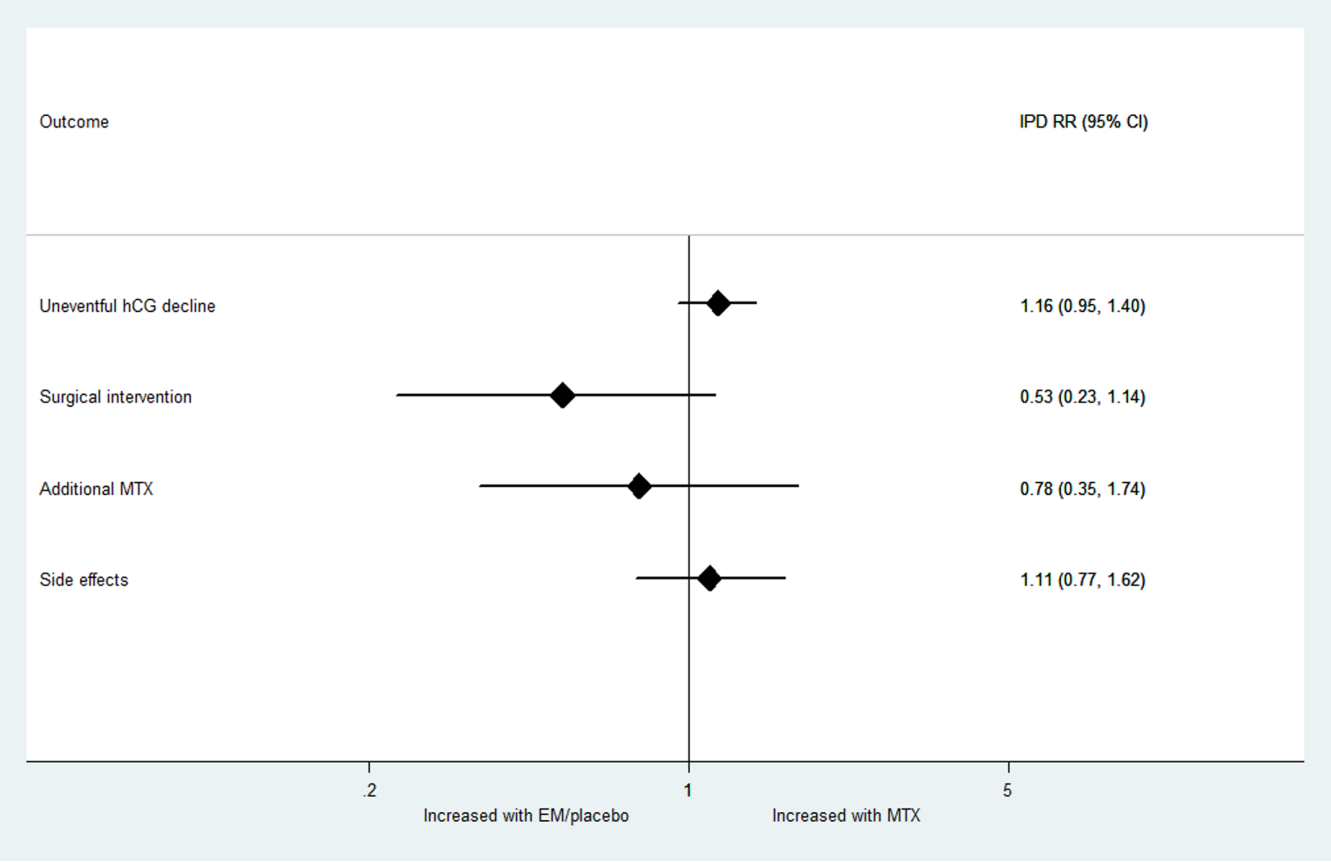

FIGURE 5 Individual Participant Data (IPD) risk ratio. EM, expectant management; MTX, methotrexate.

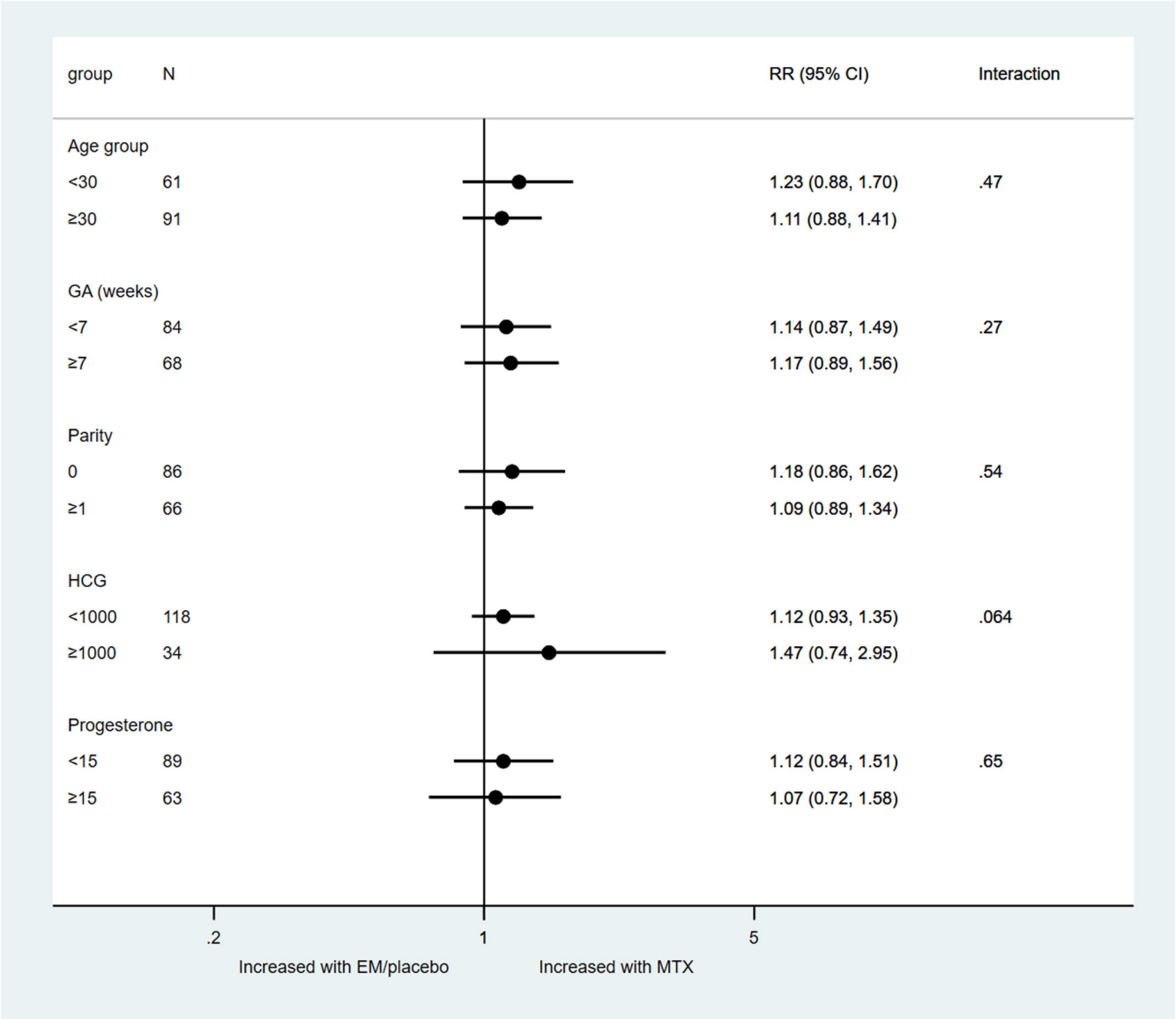

FIGURE 6 Treatment-covariate interaction for uneventful decline of human chorionic gonadotrophin. EM, expectant management; GA, gestational age; MTX, methotrexate; RR, risk ratio.

sited pregnancy too small to visualize on ultrasound scan. Advances in ultrasound have enabled accurate detection of tubal EP with studies demonstrating high sensitivity, specificity and positive predictive values,[2,44–46] and we should therefore define tubal EP as a scan diagnosis. Further high-quality RCTs are needed, in particular to determine whether MTX reduces surgical intervention and need for blood transfusion. We should also assess the effectiveness of MTX in hCG between 1000 and 5000 IU/L to identify subgroups that may benefit.

5 | CONCLUSION

Our study did not identify a significant difference in treatment success, need for surgical intervention or tubal EP resolution time between expectant and medical management of clinically stable tubal EP with low hCG. Serum hCG <1000 IU/L and progesterone <15 nmol/L were associated with a higher success rate in both groups. However, only two trials were eligible for inclusion, and we therefore propose the need for more well-designed RCTs to better determine who would benefit from either treatment. Our result of no significant difference encourages shared decision-making between the clinician and patient. At present, expectant management should be offered as the preferred initial strategy for clinically stable women with tubal EP presenting with low hCG levels, particularly if <1000 IU/L. This can have positive implications for policy makers, service providers and service users in reducing cost, reducing adverse effects and offering patients a wider choice of treatment options. The American College of Obstetricians and Gynecologists,

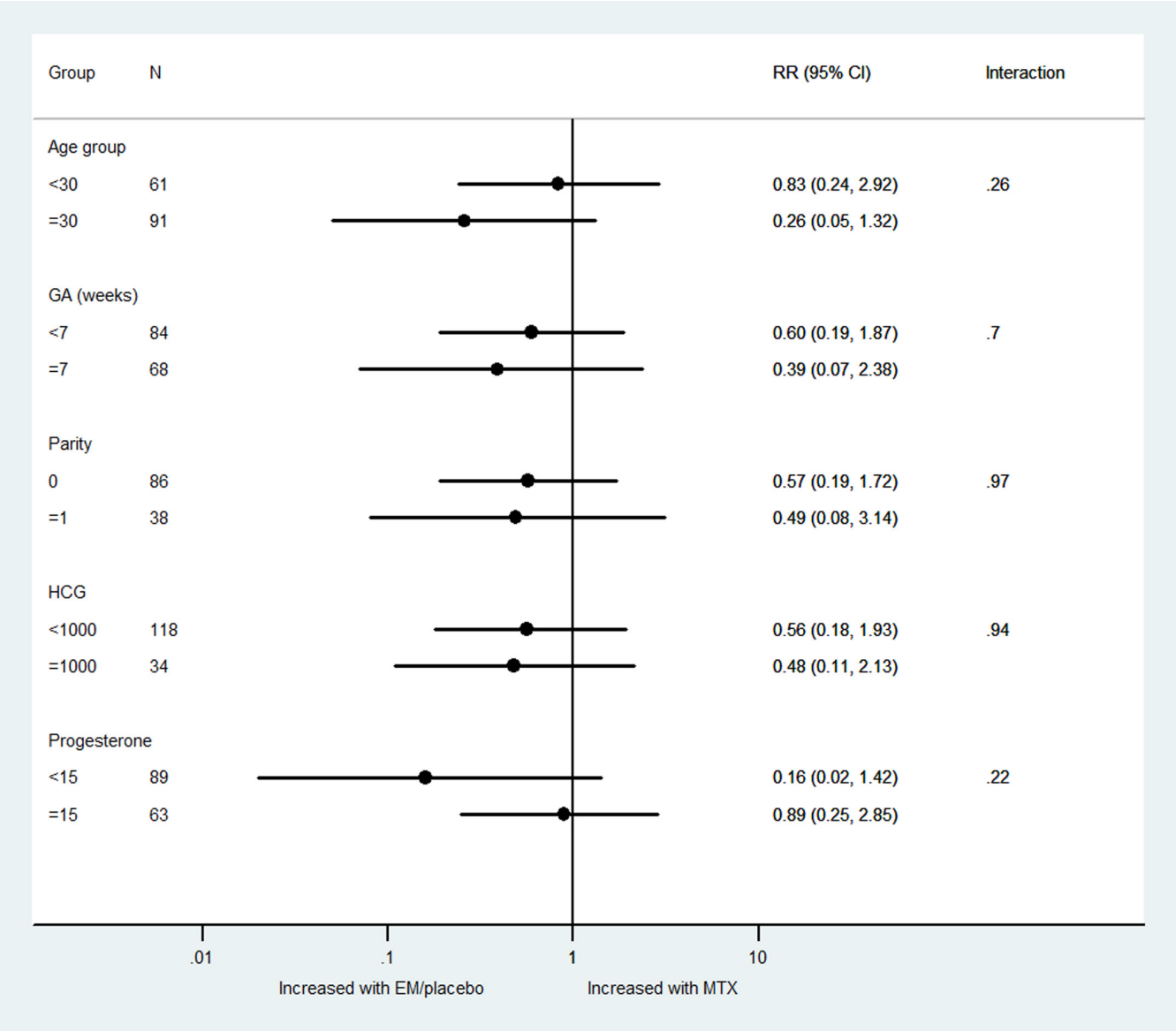

FIGURE 7 Treatment-covariate interaction for surgical intervention. EM, expectant management; GA, gestational age; MTX, methotrexate; RR, risk ratio.

Royal College of Obstetricians and Gynaecologists and National Institute for Health and Care Excellence guidelines on EP have already endorsed the use expectant management of EP when clinically safe.[47–49]

AUTHOR CONTRIBUTIONS

SAS conducted the systematic review, risk of bias assessment, obtained Data Sharing contracts, collated the data, interpreted the data and drafted the article. MVW was responsible for the methodology of the study, conducted the systematic review, risk of bias assessment, analysis and interpretation of data and revised the article. NVM provided IPD for the NL study, supervised the study and revised the article. BWM was responsible for the conception of the study, conducted risk of bias of assessment, supervised the study and revised the article. JAR was a researcher in the UK study and secured a data-sharing agreement with King's College Hospital. DJ was overall supervisor of the study, provided IPD for the UK study, contributed to interpretation of data and revised the article critically for intellectual content. All authors approved the final version.

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CONFLICT OF INTEREST STATEMENT

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TABLE 6 Multivariable analysis of factors associated with treatment success.

Variable	OR (95% CI)	HR (95% CI)
MTX vs expectant	1.93 (0.87–4.29)	1.38 (0.93–2.06)
Study: NL vs UK	0.51 (0.21–1.21)	0.87 (0.57–1.31)
Age per year	1.03 (0.97–1.11)	1.01 (0.98–1.04)
GA per week	1.02 (0.96–1.10)	1.00 (0.94–1.07)
Parity	1.75 (1.04–2.93)	1.10 (0.91–1.33)
hCG		
>1000 vs ≤1000	0.28 (0.12–0.66)	0.50 (0.29–0.84)
Progesterone		
>15 vs ≤15	0.44 (0.20–0.99)	0.68 (0.46–1.02)

Abbreviations: GA, gestational age; hCG, human chorionic gonadotrophin; HR, hazard ratio; MTX, methotrexate; NL, the Netherlands; OR, odds ratio; UK, United Kingdom.

from Merck. The other authors do not have any conflict of interests to declare.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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