Systematic Review

Success of Methotrexate for the Management of Recurrent Compared With Primary Ectopic Pregnancy

A Systematic Review and Meta-analysis

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OBJECTIVE: To compare the efficacy of intramuscular (IM) methotrexate in patients with recurrent compared with primary ectopic pregnancy.

DATA SOURCES: Systematic searches of the MEDLINE, EMBASE, and Scopus databases were conducted in February 2025.

METHODS OF STUDY SELECTION: This meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. All English-language, full-text studies in which adult patients (18 years of age or older) were treated with IM methotrexate and stratified by their history of a previous ectopic pregnancy were included. Patients with at least one prior ectopic pregnancy, regardless of which fallopian tube was affected and how it was managed, were defined as having *recurrent ectopic pregnancy*. We excluded studies that did not report patients requiring further treatment, those in which medical management through alternative routes (other than IM) or therapies were studied, and those investigating nontubal ectopic pregnancy or heterotopic pregnancies.

TABULATION, INTEGRATION, AND RESULTS: Two investigators independently identified studies using the eligibility criteria. The primary outcome was treatment success, characterized by the complete resolution of ectopic pregnancy without the need for further treatment. The efficacy of single-dose and multidose (comprising both two doses and fixed multidose, ie, two or more doses) IM methotrexate regimens was evaluated. Outcomes were reported as relative risk (RR) and 95% CI. From 6,349 search results, 15 observational studies comprising 3,944 patients (502 recurrent, 3,442 primary ectopic pregnancy) were included. Administration of a single dose of IM methotrexate was significantly less successful in patients with recurrent compared with those with primary ectopic pregnancy (RR 0.79, 95% CI, 0.63–1.00, P=.050). However, there was no statistical difference in success for patients receiving multidose treatment (RR 1.14, 95% CI, 0.71–1.84, P=.590).

CONCLUSION: Current observational data suggest that patients with recurrent ectopic pregnancy should be considered for multidose IM methotrexate to achieve similar rates of success compared with primary ectopic pregnancy.

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Ectopic pregnancies are characterized by the extrauterine implantation of an embryo and occur in up to 2% of all pregnancies.[1,2] Implantation most frequently occurs in the ampulla region of the fallopian tubes, which are not designed to adapt to a growing pregnancy. This can result in tubal rupture and life-threatening hemorrhage, making ectopic pregnancy

a major cause of maternal morbidity and mortality in the first trimester.[3–6]

Medical management with intramuscular (IM) methotrexate, administered as a single-dose injection of 50 mg/m^2 of body surface area, is an established treatment option for unruptured ectopic pregnancy.[7–9] This allows hemodynamically stable patients to potentially preserve their fertility while avoiding surgery and its associated risks.[10] However, to be eligible for IM methotrexate treatment, patients should broadly satisfy the following eligibility criteria: β-hCG less than 5,000 international units/mL, ectopic mass less than 40 mm, absence of fetal heart rate, no free fluid in the Pouch of Douglas, no intrauterine pregnancy, normal liver and renal function tests, and no clinical signs of hemodynamic instability.[10–12]

The American College of Obstetricians and Gynecologists currently recognizes three published treatment protocols with methotrexate for the medical management of ectopic pregnancy: single dose, two-dose, and fixed multidose regimens.[13,14] For the purposes of this review, a multidose regimen includes both two-dose and fixed multidose treatment, that is, two or more doses. Although a single-dose regimen is commonly used to limit treatment side effects, certain patients with high-risk features (baseline β-hCG between 3,000 and 5,000 international units/L and adnexal mass between 20 and 35 mm) may benefit from a routine second dose because it has been shown to have increased efficacy.[15]

Patients with ectopic pregnancy have a higher prevalence of underlying tubal pathology such as intraluminal adhesions and salpingitis, which may have restricted the progression of the fertilized ovum to the uterus for implantation.[16–18] When these distorted tubes are preserved, patients with a history of at least one previous ectopic pregnancy have a fivefold to 10-fold increased risk of a future ectopic pregnancy event (ie, recurrent ectopic pregnancy).[19] Although IM methotrexate is still offered as a treatment option for patients with recurrent ectopic pregnancy, few studies have directly investigated its effectiveness in treating these individuals,[20,21] and it remains unclear whether IM methotrexate is equally as effective compared with those with their first ectopic pregnancy (ie, primary ectopic pregnancy). In addition, a history of one or more prior ectopic pregnancies is acknowledged as a risk factor for recurrence in subsequent pregnancies; however, it is not considered a factor when patients are counseled on different treatment options.

Therefore, the aim of this meta-analysis was to compare the efficacy of IM methotrexate in patients with recurrent and those with primary ectopic pregnancy. This would allow more accurate counseling about treatment options, their likelihood of success, and the risk of associated side effects.

METHODS

The protocol for this study was prospectively recorded on PROSPERO (CRD42025642895).[22] This review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (Appendix 1A and B, available online at http://links.lww.com/AOG/E229).[23,24]

Sources

Systematic searches of the MEDLINE (OVID), EMBASE (OVID), and Scopus electronic databases were conducted to identify studies published between the inception of the databases and February 2025. ClinicalTrials.gov was also searched but, as expected, no randomized controlled trials were found because the nature of our review; it is not possible to perform randomization based on a patient's medical history.

Boolean operators ("and"/"or") in conjunction with the "explode" function were used, including the following key word and MeSH terms: "ectopic pregnancy," "extra-uterine pregnancy," "tubal pregnancy," "methotrexate," "manage*," "treat*," "recurrent," "repeat*," and "second*." A search string was designed specifically for each database (Appendix 2, available online at http://links.lww.com/AOG/E229). The search was restricted to studies reported in English and performed in human adult (18 years of age or older) populations, although there were no restrictions on publication date, study design, or geographic location.

All studies performed in individuals with a known ectopic pregnancy or pregnancy of unknown location who were deemed to be suitable for medical management with IM methotrexate were eligible for inclusion. For final selection, studies must have stratified patients on the basis of their history of a previous ectopic pregnancy and reported success rates with IM methotrexate. Patients with at least one prior ectopic pregnancy, regardless of which fallopian tube was affected and whether it was treated conservatively, medically or surgically, were defined as having *recurrent ectopic pregnancy*. To minimize the likelihood of sampling bias resulting from the inclusion of duplicate data, only the most recent study was included in cases in which there was potentially an overlapping cohort of patients.

Studies that did not report patients requiring further treatment (ie, failure of IM methotrexate) or medical management through alternative routes (other than IM) or therapies other than methotrexate and those investigating nontubal ectopic pregnancy or heterotopic pregnancies were excluded. Case reports, editorial letters, book chapters, and study protocols were also excluded. Abstracts relating to conference or society presentations or those deemed to be relevant but for which the full text could not be sourced were not included. Although relevant systematic or narrative literature reviews were also excluded, the reference lists were manually reviewed to capture all potentially relevant studies.

Search results from each database were exported into the Rayyan web application.[25] With duplicate records removed, titles, abstracts of texts, or both were independently screened by two study investigators. Potentially relevant full texts were then screened and included after consensus between these two investigators. The corresponding author of one relevant text was contacted[26] to facilitate its inclusion in our review.[27] Any disputes were resolved through discussion and after consultation with a third investigator for consensus.

Extracted data included information on study characteristics (first author, publication year, geographic location, study duration, number of centers, and study design), patient demographic characteristics (selection criterion, total sample size, and stratification based on recurrent compared with primary ectopic pregnancy), methotrexate treatment protocols, and the primary outcome. These data were recorded in a pro forma Microsoft Excel spreadsheet and were verified by a second investigator, although no inconsistencies were detected.

The Joanna Briggs Institute Critical Appraisal Checklist for Cohort Studies was used to appraise the methodologic quality of studies by two authors independently.[28] Studies were assessed according to 11 bias domains, with each graded as yes (ie, low risk of bias), no (ie, high risk of bias), or unclear (ie, some concerns regarding risk of bias).

The primary outcome was *treatment success*, characterized by complete resolution of ectopic pregnancy without the need for further treatment. This was broadly defined as either achieving a posttreatment β-hCG level below 15–30 milli–international units/mL and more than 15% decline in β-hCG between days 4 and 7 after the first methotrexate dose or day 11 and 14 after second or further consecutive methotrexate doses or not requiring surgical intervention.[29,30]

Data were quantitatively reported as frequencies and percentages. Continuity corrections of 1 were applied to both the numerator and denominator in studies with zero frequency for outcomes to facilitate meta-analysis.[31] An inverse-variance weighted random-effects meta-analysis was used, with the DerSimonian–Laird estimator used for the between-study variance, because of the anticipated heterogeneity in definitions of treatment success and cohort characteristics between studies.[32,33] Summary effect estimates were reported as the relative risk (RR) with the 95% CI.[34] $P<.05$ was considered to indicate a statistically significant difference in success rates between recurrent and primary ectopic pregnancy. Interstudy heterogeneity were quantified with the I^2 statistic, with 0–29% indicating no significant heterogeneity, 30–49% indicating moderate heterogeneity, 50–74% indicating substantial heterogeneity, and 75–100% indicating considerable heterogeneity heterogeneity.[35] Meta-analysis results were summarized graphically with forest plots.[36] Publication bias was assessed quantitatively with the Egger regression test (where n=10 or more studies) and through visualization of funnel plots for asymmetry.[37,38] All statistical analyses were conducted with R 4.2.2.[39]

In studies in which *failure of treatment* was defined as requiring subsequent doses of IM methotrexate, the efficacy of single-dose and multidose IM methotrexate regimens was evaluated in separate subgroup analyses. For clarity, the term multidose includes both the two-dose and fixed multidose IM methotrexate regimens described by the American College of Obstetricians and Gynecologists.[13,14] In terms of the effectiveness of a single dose of IM methotrexate, administration of a second dose was defined as treatment failure.

To investigate the robustness of our primary analysis, we also performed a sensitivity analysis that included only studies that directly compared outcomes among patients with recurrent and those with primary ectopic pregnancy.[20,21]

RESULTS

Initial electronic database searches yielded 6,349 results, from which 15 studies were included in the quantitative meta-analysis (Fig. 1).[8,20,21,27,30,40–49] Only the most recent publications by two authors were included, with two less contemporary studies potentially including overlapping patient cohorts being excluded to minimize the possibility of sampling bias.[50,51] Three additional studies did not report failure of treatment and hence were unable to be included in the review.[52–54]

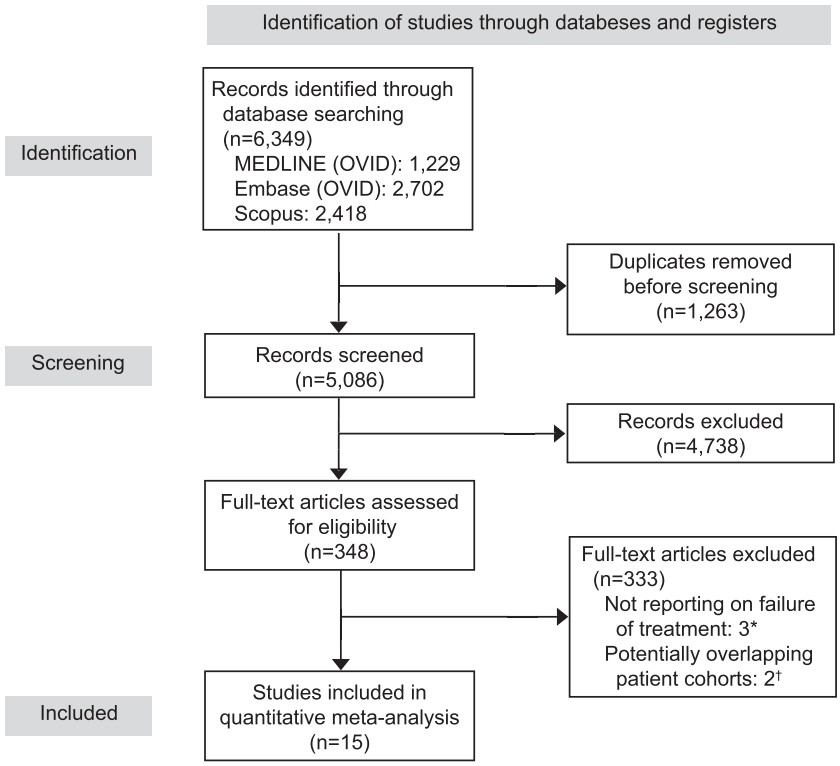

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram demonstrating the selection process for studies included in the meta-analysis. *Akdaş Reis et al,[52] Dai et al,[53] and Yıldırım et al.[54] †Lipscomb et al[50] and Levin et al.[51]

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The characteristics of studies are detailed in Table 1. Relevant studies spanned a period approaching 2 decades (2008–2024) and were most frequently conducted in Israel (n=5, 33.3%), followed by Iran and Turkey (n=2, 13.3%, respectively). All were retrospective cohort studies involving a single center, with the exception of one study.[46] Mackenzie et al[46] performed a secondary prospective analysis based on a multicenter, double-blinded, placebo-controlled randomized controlled trial.[55]

A total of 3,944 patients were diagnosed with an ectopic pregnancy and met prespecified criteria for medical management with IM methotrexate, of whom 502 (12.7%) had recurrent ectopic pregnancy and 3,442 (87.3%) had primary ectopic pregnancy. Diagnostic criteria for included ectopic pregnancy cases are provided in Appendix 3, and respective methotrexate treatment protocols are outlined in Appendix 4 (Appendices 3 and 4 are available online at http://links.lww.com/AOG/E229).

Studies were most frequently judged as at high risk of bias because of the inability to identify confounding factors (9/15, 60.0%) or to account for their effect in the study design or statistical analysis (8/15, 53.3%). There were some concerns with regard to recruitment bias in a majority of the studies (13/15, 86.7%) because only two studies directly compared baseline characteristics between patients with recurrent and those with primary ectopic pregnancy.[20,21] Domain-specific quality assessment in each study is reported in Appendix 5 (available online at http://links.lww.com/AOG/E229). It is likely that these methodologic drawbacks influenced the strength of our meta-analysis results and subsequent conclusions.

Nine studies including 2,662 patients with ectopic pregnancy (375 with recurrent and 2,287 with primary ectopic pregnancy) reported rates of *treatment success*, defined as those who did not require surgical intervention.[20,21,27,30,41,43,45,47,48] There was no significant difference in success of medical management with IM methotrexate between patients with recurrent and those with primary ectopic pregnancy (RR 0.95, 95% CI, .90–1.00, P=.054; Fig. 2A). There was no significant heterogeneity between the analyzed studies (I^2=12.7%). No evidence of funnel plot asymmetry, indicating publication bias, was detected (Egger regression test P=.852; Fig. 2B).

Ten studies including 2,106 patients with ectopic pregnancy (237 with recurrent vs 1,869 with primary ectopic pregnancy) analyzed success of treatment with a single dose of IM methotrexate.[8,20,28,31,41,43–45,47,49]

Table 1. Characteristics of Included Studies

First Author	Publication Year	Study Design	No. of Centers	Country	Sample Size (n)		
					Total	Recurrent EP	Primary EP
Aiob et al[40]	2023	Observational cohort study (R)	1	Israel	257	13	244
Aybatli et al[30]	2011	Observational cohort study (R)	1	Turkey	32	3	29
Bonin et al[41]	2016	Observational cohort study (R)	1	France	400	44	356
Chegini et al[26]	2024	Observational cohort study (R)	1	Iran	396	62	334
Cirik et al[21]	2015	Observational cohort study (R)	1	Turkey	399	55	344
Goh et al[42]	2020	Observational cohort study (R)	1	Australia	108	6	102
Krissi et al[43]	2013	Observational cohort study (R)	1	Israel	102	13	89
Lavie et al[44]	2021	Observational cohort study (R)	1	Israel	119	7	112
Levin et al[20]	2020	Observational cohort study (R)	1	Israel	294	32	262
Lipscomb et al[45]	2008	Observational cohort study (R)	1	United States	559	131	428
Mackenzie et al[46]	2023	Observational cohort study (P)*	50	United Kingdom	321	54	267
Mirbolouk et al[47]	2015	Observational cohort study (R)	1	Iran	370	27	343
Sindiani et al[48]	2020	Observational cohort study (R)	1	Jordan	110	8	102
Wong et al[8]	2017	Observational cohort study (R)	1	Hong Kong	105	22	83
Zeevi et al[49]	2024	Observational cohort study (R)	1	Israel	372	25	347

EP, ectopic pregnancy; R, retrospective; P, prospective.
* Secondary analysis of data derived from a multicenter, double-blinded, placebo-controlled randomized controlled trial.

Administration of a single dose of IM methotrexate was less successful in patients with recurrent than in those with primary ectopic pregnancy (RR 0.79, 95% CI, 0.63–1.00, P=.050; Fig. 3A). Substantial heterogeneity among the analyzed studies was identified (I^2=73.0%). Again, there was no evidence of publication bias (Egger regression test P=.413; Fig. 3B).

Success of treatment with multiple doses (two or more) of IM methotrexate was reported in four studies totaling 259 patients with ectopic pregnancy (72 with recurrent and 187 with primary ectopic pregnancy).[20,28,31,44] The efficacy of multidose IM methotrexate was not significantly different between patients with recurrent and those with primary ectopic pregnancy (RR 1.14, 95% CI, 0.71–1.84, P=.59; Fig. 4A). Substantial heterogeneity among the studies (I^2=64.0%) was observed. Quantitative evaluation of publication bias could not be performed as a result of an insufficient number of studies for comparison; however, the funnel plot suggested asymmetry (Fig. 4B).

The high heterogeneity observed between studies included within our single-dose and multidose subgroup analyses likely resulted from differences in demographic characteristic profiles between patients with recurrent and patients with primary ectopic pregnancy, as well as variability in definitions of treatment failure. Potential confounding demographic variables may consist of differences in baseline β-hCG levels, adnexal mass or size, timing of diagnosis, or delays in treatment.

Two studies primarily reported the success of IM methotrexate in patients with recurrent compared with patients with primary ectopic pregnancy.[20,21] The potential for confounding bias to influence results was minimized because baseline characteristics between the two cohorts were shown to be similar in both studies. Results of the sensitivity analysis were congruent with that of our primary analysis, with no difference seen in rates of treatment success among patients with recurrent compared with primary ectopic pregnancy managed medically with IM methotrexate (RR 0.92, 95% CI, 0.84–1.01, P=.071).[20,21] However, stratification of outcomes by single-dose and multidose IM methotrexate was reported only by Levin et al,[20] who similarly demonstrated less success in recurrent ectopic pregnancy managed with a single IM methotrexate dose (RR 0.40, 95% CI, 0.40–0.94, P=.024) and no difference between the two cohorts when multiple doses of IM methotrexate were administered (RR 0.57, 95% CI, 0.57–1.30, P=.481).

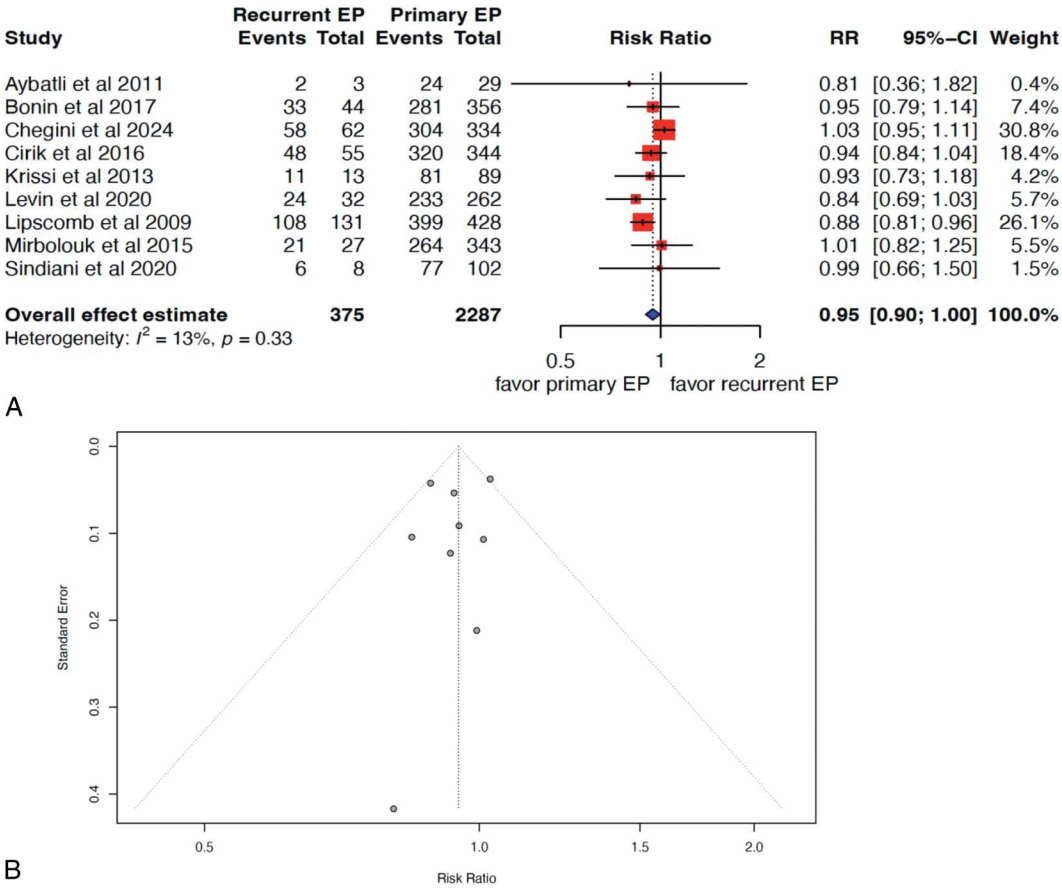

Fig. 2. A. Forest plot comparing success of medical management with intramuscular methotrexate in patients with recurrent and those with primary ectopic pregnancy (EP). **B.** Funnel plot of the SE according to the effect estimate (relative risk [RR]) for each analyzed study.

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DISCUSSION

The present meta-analysis analyzed 15 studies with a total of 3,944 patients with ectopic pregnancy and found that medical management with IM methotrexate was equally effective in patients with recurrent compared with those with primary ectopic pregnancy. When treatment failure was defined by the need for further doses of IM methotrexate, single-dose treatment was found to be significantly less effective in patients with recurrent ectopic pregnancy, whereas no difference in efficacy was observed among patients with recurrent compared with patients with primary ectopic pregnancy receiving multidose treatment. The consistency of these results was also demonstrated in sensitivity analysis after controlling for potentially confounding demographic variables.

Patients with ectopic pregnancy are more likely to have pathologic fallopian tubes ,including salpingitis, endometriosis, or a history of tubal or pelvic surgery.[16–18] Scarring of the tubes or impaired motility prevents normal progression of the pregnancy into the uterine cavity, resulting in extrauterine implantation and ultimately in higher risk of ectopic pregnancy recurrence.[17,56] Although surgical removal of these tubes may prevent future ectopic pregnancy events, bilateral salpingectomies result in sterilization, thus impairing future fertility.[57] Medical management with IM methotrexate in patients with recurrent ectopic pregnancy allows preservation of the fallopian tubes, which is important for patients whose family remains incomplete, while also potentially avoiding the need for surgery and its associated risks.[10] We have demonstrated similar rates of successful treatment with IM methotrexate among patients with recurrent and those with primary ectopic pregnancy, indicating that it may be reasonable to consider medical management with IM methotrexate as a tubal-sparing option in patients with recurrent ectopic pregnancy.

Typically, management algorithms with IM methotrexate for ectopic pregnancy involve a single-dose

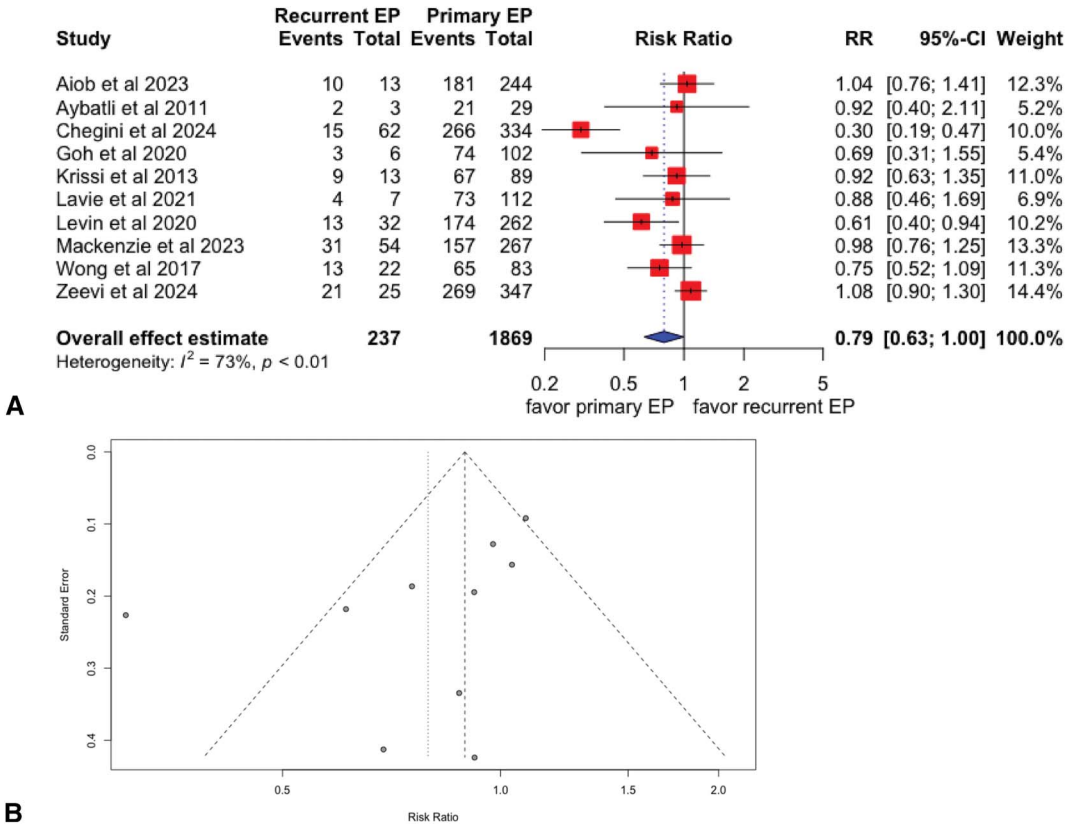

Fig. 3. A. Forest plot comparing success of a single dose of intramuscular methotrexate in patients with recurrent and those with primary ectopic pregnancy (EP). **B.** Funnel plot of the SE according to the effect estimate (relative risk [RR]) for each analyzed study.

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regimen.[30] In this protocol, first introduced by Stovall et al,[29] after receiving a first dose of IM methotrexate, patients undergo serial serum β-hCG measurements on days 4 and 7. A decline in serum β-hCG of more than 15% between days 4 and 7 is considered an accurate predictor of treatment success in up to 93% of patients.[9,58] Patients who fail to achieve a 15% drop during this time period are offered a second dose of IM methotrexate.[59,60] As a result of the findings of Alur-Gupta et al,[15] in Australia and Aotearoa New Zealand, routine administration of a second dose of IM methotrexate dose is increasingly observed in patients with elevated baseline β-hCG levels (of 3,000 to 5,000 international units/L) or large adnexal mass (20–35 mm) because of the increased efficacy demonstrated in these patients. Other confounding factors likely to influence methotrexate dosing include the timing of diagnosis and possible delays to treatment, which likely influence our meta-analysis results. Although multidose treatment is associated with higher rates of success, there is also a greater risk of adverse events; hence, multidose treatment is not routinely given unless serial serum β-hCG thresholds are not met.[59,60] Although these side effects are usually transient, they can consist of debilitating symptoms such as nausea, diarrhea, abdominal pain, mucositis, and mild derangement in laboratory results. The exact reasons why select patients with ectopic pregnancy require further doses of IM methotrexate remain unknown. We postulate that for patients with recurrent ectopic pregnancy, the presence of abnormal scarred fallopian tubes may predispose to poor blood supply and thus reduced delivery of medication. Our meta-analysis showed that administration of a single dose of IM methotrexate was less efficacious in those with recurrent than in those with primary ectopic pregnancy. However, no such difference in treatment success was observed between patients receiving multidose treatment. Therefore, these data support the consideration of routinely counseling patients with recurrent ectopic pregnancy on the option of multidose treatment with IM methotrexate to achieve

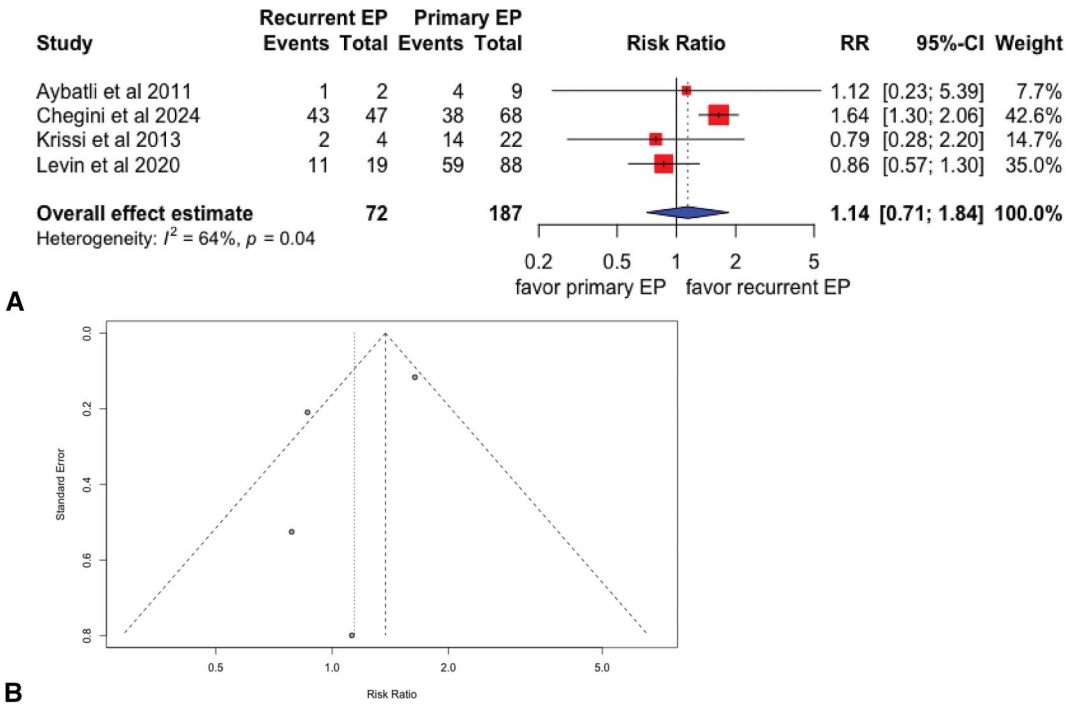

Fig. 4. A. Forest plot comparing success of multidose (two or more) intramuscular methotrexate in patients with recurrent and those with primary ectopic pregnancy (EP). **B.** Funnel plot of the SE according to the effect estimate (relative risk [RR]) for each analyzed study.

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similar rates of success compared with those with primary ectopic pregnancy, as well as the associated increased risk of side effects.

There are some limitations to the present meta-analysis. Substantial heterogeneity in the outcome of treatment success was observed between the analyzed studies. This likely reflects variability in outcome definitions and differences in baseline cohort characteristics among those with recurrent and those with primary ectopic pregnancy.[30] To mitigate the effect of this heterogeneity, a random-effects meta-analysis model was used, as well as subgroup analyses evaluating the efficacy of single-dose and multidose (two or more) IM methotrexate treatments separately. With the exception of one study,[47] all were retrospective cohort studies in design. This inherently presents risk of selection bias and confounding. Most studies (more than 50%) did not identify relevant confounding factors, which likely explains the large observed 95% CIs for effect estimates. However, these confounding variables did not have a significant influence on our overall results, as demonstrated by the concordant results of our sensitivity analysis, which suggest robustness of our meta-analysis results.[20,21] Furthermore, it is not logistically feasible to perform a randomized controlled trial according to a patient's history of ectopic pregnancy, so this design limitation is expected for a research question of this nature. Acknowledging these limitations, we performed a comprehensive synthesis of 15 studies with more than 3,900 patients and used nearly 2 decades worth of published data to demonstrate efficacy of medical management with IM methotrexate in patients with recurrent compared with those with primary ectopic pregnancy.

In conclusion, it is reasonable to continue offering medical management with IM methotrexate as a treatment option for patients with recurrent ectopic pregnancy. However, single-dose treatment is associated with lower rates of success relative to those with primary ectopic pregnancy. Therefore, patients with recurrent ectopic pregnancy should be considered for multidose (two or more) IM methotrexate to achieve similar rates of treatment success.

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