Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis

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OBJECTIVE: To compare the treatment success and failure rates, as well as side effects and surgery rates, between methotrexate protocols.

DATA SOURCES: PubMed, Embase, and the Cochrane library searched up to July 2018.

STUDY ELIGIBILITY CRITERIA: Randomized controlled trials that compared women with ectopic pregnancies receiving the single-dose, two-dose, or multi-dose methotrexate protocols.

STUDY APPRAISAL AND SYNTHESIS METHODS: Odds of treatment success, treatment failure, side effects, and surgery for tubal rupture, as well as length of follow-up until treatment success, were compared using random and fixed effects meta-analysis. Sensitivity analyses compared treatment success in the groups with high human chorionic gonadatropin (hCG) values and a large adnexal mass, as defined by individual studies. The Cochrane Collaboration tool was used to assess risk of bias.

RESULTS: The 2-dose protocol was associated with higher treatment success compared to the single-dose protocol (odds ratio [OR], 1.84; 95% CI, 1.13, 3.00). The 2-dose protocol was more successful in women with high hCG (OR, 3.23; 95% CI, 1.53, 6.84) and in women with a large adnexal mass (OR, 2.93; 95% CI, 1.23, 6.9). The odds of surgery for tubal rupture were lower in the 2-dose protocol (OR, 0.65; 95% CI, 0.26, 1.63), but this was not statistically significant. The length of follow-up was 7.9 days shorter for the 2-dose protocol (95% CI, −12.2, −3.5). The odds of side effects were higher in the 2-dose protocol (OR, 1.53; 95% CI, 1.01, 2.30). Compared to the single-dose protocol, the multi-dose protocol was associated with a nonsignificant reduction in treatment failure (OR, 0.56; 95% CI, 0.28, 1.13) and a higher chance of side effects (OR, 2.10; 95% CI, 1.24, 3.54). The odds of surgery for tubal rupture (OR, 1.62; 95% CI, 0.41, 6.49) and time to follow-up (OR, −1.3; 95% CI, −5.4, 2.7) were similar.

CONCLUSION: The 2-dose methotrexate protocol is superior to the single-dose protocol for the treatment of ectopic pregnancy in terms of treatment success and time to success. Importantly, these findings hold true in patients thought to be at a lower likelihood of responding to medical management, such as those with higher hCGs and a large adnexal mass.

Key words: doses, ectopic pregnancy, medical management, methotrexate, protocol, tubal pregnancy

Ectopic pregnancies occur in approximately 2% of pregnancies, yet account for 9% of maternal mortality and are the leading cause of pregnancy-related death in the first trimester.[1] Advancements in imaging technology and protocols to screen women at risk have led to earlier detection of ectopic pregnancies.[2–4] As more women with ectopic pregnancies present as clinically stable without concern for rupture, options for treatment have expanded beyond surgical management to medical management. The mainstay of medical management has been methotrexate, a folate antagonist that binds to dihydrofolate reductase, leading to downstream inhibition of DNA synthesis and repair as well as cell replication.[3,5] Multiple publications have demonstrated comparable efficacy of medical management to surgical management in the treatment of stable ectopic pregnancies.[6-9] The most widely used methotrexate protocols include single-dose, 2-dose, and multi-dose protocols.[3] The multi-dose protocol can be beneficial for patients at higher risk for failing medical management and thus requiring additional doses.[5,10] However, because of its frequency of administration, the multi-dose protocol requires the addition of folinic acid rescue, alternating with methotrexate doses, to decrease side effects. The single-dose protocol was introduced to reduce the number of visits, but often requires additional treatment and follow-up. The 2-dose protocol was introduced with the goal of achieving a balance between the benefits of increased treatment success from additional doses of methotrexate, while using the same convenient visit schedule as the single-dose protocol.[11]

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AJOG at a Glance

Why was this study conducted?

This study was conducted to compare the odds of treatment success, side effects, surgery for ruptured ectopic pregnancy, and length of follow-up of commonly used methotrexate protocols for the treatment of ectopic pregnancy.

Key findings

The 2-dose protocol was superior to the single-dose protocol in treatment success, including in women at higher risk for failure, such as those with high human chorionic gonadatropin and large adnexal mass.

What does this add to what is known?

This adds an updated meta-analysis of a 2-dose versus a single-dose protocol and additional analyses of a multi-dose versus a single-dose protocol using only quality randomized controlled trials.

The success rates of medical management of ectopic pregnancies have varied with a range of 70−90% for the single-dose,[12-14] 80−90%[14-16] for the 2-dose, and 89−96% for the multi-dose protocols.[12,13,17] Variation in rates may be influenced by the population being studied, criteria for administering the medication, and definition of treatment success. Treatment failure rates, or chance of failure with a particular protocol, are also important to consider, as they can be clinically useful when counseling patients and can be a driver in deciding which protocol to recommend.

Although several studies have attempted to compare one protocol to another, they are limited by their retrospective nature, nonstandard protocols, and heterogeneous definition of outcomes.[18-21] Randomized controlled trials (RCTs) are considered the gold standard when evaluating such questions, because of their systematic, reproducible approach with minimization of confounding through the process of randomization. Although there have been other meta-analyses on this topic, several do not include more recent studies, thus providing an opportunity to update our understanding.[2,9,12,22] Others are limited by inclusion of retrospective studies and abstracts[12,23] or lack of treatment failure rate reporting.[22,23] Our study sought to compare, via a meta-analysis, quality RCTs evaluating the treatment success, side effect incidence, and surgery rates among the methotrexate protocols.

Materials and Methods

Eligibility criteria

The systematic review and meta-analysis were performed by strictly following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The population being studied was women with an ectopic pregnancy diagnosed by transvaginal ultrasound. Interventions included the single-dose, 2-dose, or multi-dose methotrexate protocol (Table 1). Comparisons included the single-dose to the 2-dose protocol, and the single-dose to the multi-dose protocol. Associations of interest for binary outcomes are presented as odds ratios (OR) with 95% confidence intervals (CI). Only RCTs published as manuscripts with clear randomization protocols were included in this analysis.

Information sources and search strategy

Studies were identified by searching PubMed, Embase, and the Cochrane library in July 2018, with no starting date restrictions. Combinations of the following keywords were used to identify the studies: "methotrexate", "ectopic pregnancy", "tubal pregnancy", "dose", and "protocol". No filters were applied for language or location.

Study selection

Two independent reviewers (S.A.G. and L.C.) used the above-stated eligibility criteria to screen all article titles and abstracts for inclusion. RCTs in human subjects with published manuscripts were considered eligible. A flow diagram of study selection is provided in Figure 1.

Data extraction

Full texts of potentially eligible studies were extracted and examined for the following data: year of study, number of subjects, location of subject recruitment, mean age of subjects, mean body mass index (BMI) of subjects, pretreatment human chorionic gonadatropin (hCG) values, pretreatment adnexal mass diameter, description of methotrexate protocols used, randomization and blinding processes, inclusion and exclusion criteria, and definition of outcomes measured, including treatment success, length of follow-up, side effects, and surgery for tubal rupture, as well as results for these outcomes. Several attempts were made to electronically contact authors of eligible studies that did not explicitly contain the above information (Figure 1).

Assessment of risk of bias

The Cochrane Collaboration tool was used to assess the risk of bias. Two authors (S.A.G. and L.C.) independently reviewed the included studies and assigned values of low, uncertain, or high risk to the 6 domains outlined in the tool (Figure 2).

Data synthesis for meta-analysis

The following primary outcome measure was analyzed for included studies: treatment success (as reported in individual studies). Treatment failure (defined as not achieving treatment success with the stated protocol), which is the weighted inverse of treatment success and provides an alternative tool to use when counseling patients, was also described. Secondary outcomes analyzed included side effects, surgery for tubal rupture, and length of follow-up in days (as defined by individual studies). Side effects reported in individual studies

TABLE 1
Methotrexate protocols

	Single-dose	Two-dose	Multi-dose
Day 1	Administer MTX 50 mg/m^2 IM, obtain serum hCG	Administer MTX 50 mg/m^2 IM, obtain serum hCG	Administer MTX 1 mg/kg IM, obtain serum hCG
Day 2	—	—	—
Day 3	—	—	Administer second dose MTX 1 mg/kg IM, obtain serum hCG; if >15% drop, stop MTX and follow hCG levels weekly. If <15% drop, proceed with plan
Day 4	Obtain serum hCG	Administer second dose MTX 50 mg/m^2 IM	Administer leucovorin 0.1 mg/kg IM
Day 5	—	—	Obtain serum hCG. If >15% drop, stop MTX and follow hCG levels weekly. If <15% drop, proceed with plan. Administer third dose MTX 1 mg/kg IM
Day 6	—	—	Administer leucovorin 0.1 mg/kg IM
Day 7	Obtain serum hCG. If >15% drop, follow hCG levels weekly. If <15% drop, administer second dose MTX 50 mg/m^2 IM	Obtain serum hCG. If >15% drop, follow hCG levels weekly. If <15% drop, administer third dose MTX 50 mg/m^2 IM	Obtain serum hCG. If >15% drop, stop MTX and follow hCG levels weekly. If <15% drop, proceed with plan. Administer fourth dose MTX 1 mg/kg IM
Day 8	—	—	Administer leucovorin 0.1 mg/kg IM
Day 11	—	Obtain serum hCG. If >15% drop, follow hCG levels weekly. If <15% drop, administer fourth dose MTX 50 mg/m^2 IM	—
Day 14	Obtain serum hCG, if >15% drop, follow hCG levels weekly. If <15% drop, administer third dose MTX 50 mg/m^2 IM	Obtain serum hCG, if >15% drop, follow hCG levels weekly. If <15% drop, consider surgery	Obtain serum hCG. If >15% drop, stop MTX and follow hCG levels weekly. If <15% drop, proceed with plan. Administer fifth dose MTX 1 mg/kg IM
Day 21	Obtain serum hCG. If >15% drop, follow hCG levels weekly. If <15% drop, consider surgery	—	Obtain serum hCG. If >15% drop, follow hCG levels weekly. If <15% drop, consider surgery

hCG, human chorionic gonadatropin; *IM,* intramuscularly; *MTX,* methotrexate.

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included nausea, diarrhea, mucositis, abdominal pain, and laboratory test abnormalities. Fixed effects meta-analysis was used to report odds ratios (OR) with 95% confidence intervals (CI) for the outcomes with low heterogeneity including treatment success and failure, surgery for tubal rupture, and side effects, whereas random effects meta-analysis was used to report mean days with 95% CI for the outcome of length of follow-up (Figures 3 and 4).

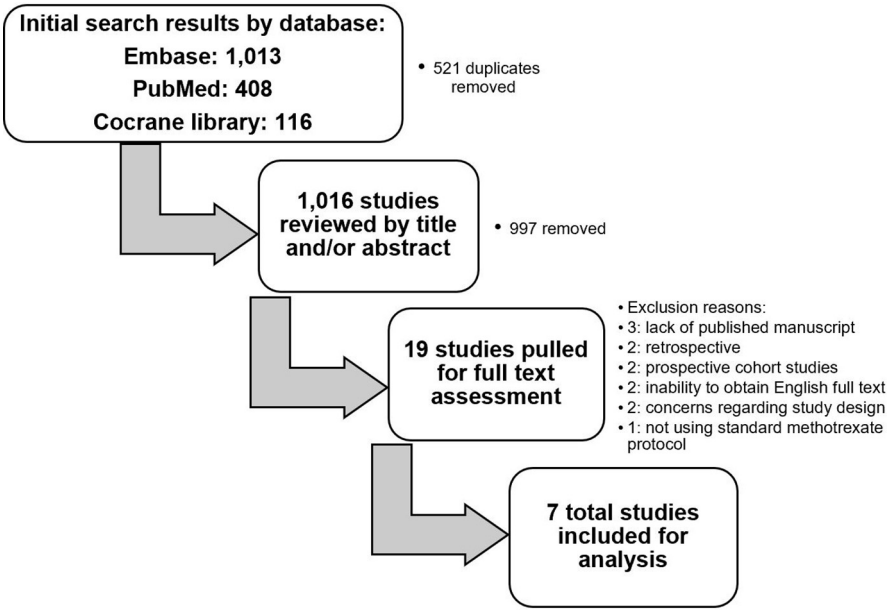
Sensitivity analyses were conducted to assess treatment success rates in high-hCG groups (as reported in individual studies, with a range of >3000−5500 mIU/mL for 2-dose vs single-dose protocols and >800 IU/L for multi-dose vs single-dose protocols) and large adnexal mass groups (as reported in individual studies, with a range of >2−3.5 cm). The heterogeneity among studies was evaluated both via forest plots with 95% CI as well as the I^2 statistic, with $P < .05$ considered as statistically significant. Publication bias was assessed via funnel plots of the log OR (Supplementary Figure 1). Analysis was conducted using STATA v14.2 (StataCorp, College Station, TX).

Results

Study selection

The search strategy yielded 1013 results in Embase, 408 in PubMed, and 116 in the Cochrane Library. The 521 duplicates were removed. The remaining articles' titles and abstracts were screened, along with the bibliography of recently published meta-analyses. A total of 19 potentially eligible articles were identified. Of these articles, 3 were excluded for lack of a published manuscript,[24-26] 2 were excluded for being retrospective studies,[19,20] 2 were excluded for being prospective cohort studies,[21,27] 2 were excluded because of the inability to obtain the full text beyond the abstract in English despite attempts to contact the authors,[28,29], 2 were excluded for concerns regarding whether and how randomization was performed,[30,31] and 1 article was excluded for not using standard methotrexate

FIGURE 1
Flow diagram of study inclusion



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protocols.[18] Therefore, 7 final publications were found to meet our inclusion criteria.

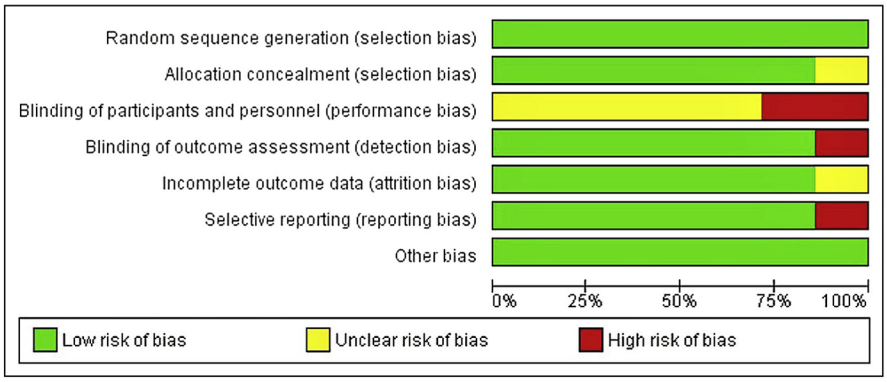
Study characteristics

Study characteristics are presented in Table 2. All studies were RCTs. Study sizes ranged from 70 to 160 total patients. Although all studies reported rates of treatment success, only half reported side effects or length of follow-up. Five reported rates of surgery for tubal rupture: 3 in the single-dose vs 2-dose group, and 2 in the single-dose vs multi-dose group. Although the studies by Saadati et al[14] and Guvendang et al[13] reported data on rates of surgery, indication for surgery as rupture or elective surgery was not specified; therefore these studies were not included for this outcome.

Risk of bias of included studies

Results of bias assessment via the Cochrane Collaboration tool are

FIGURE 2
Risk of bias assessment



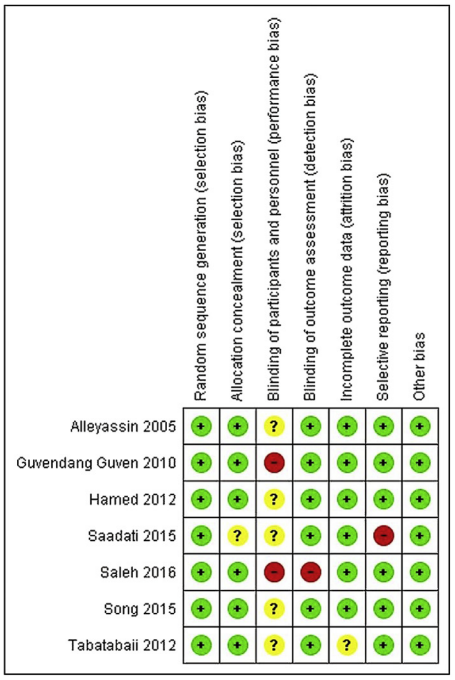


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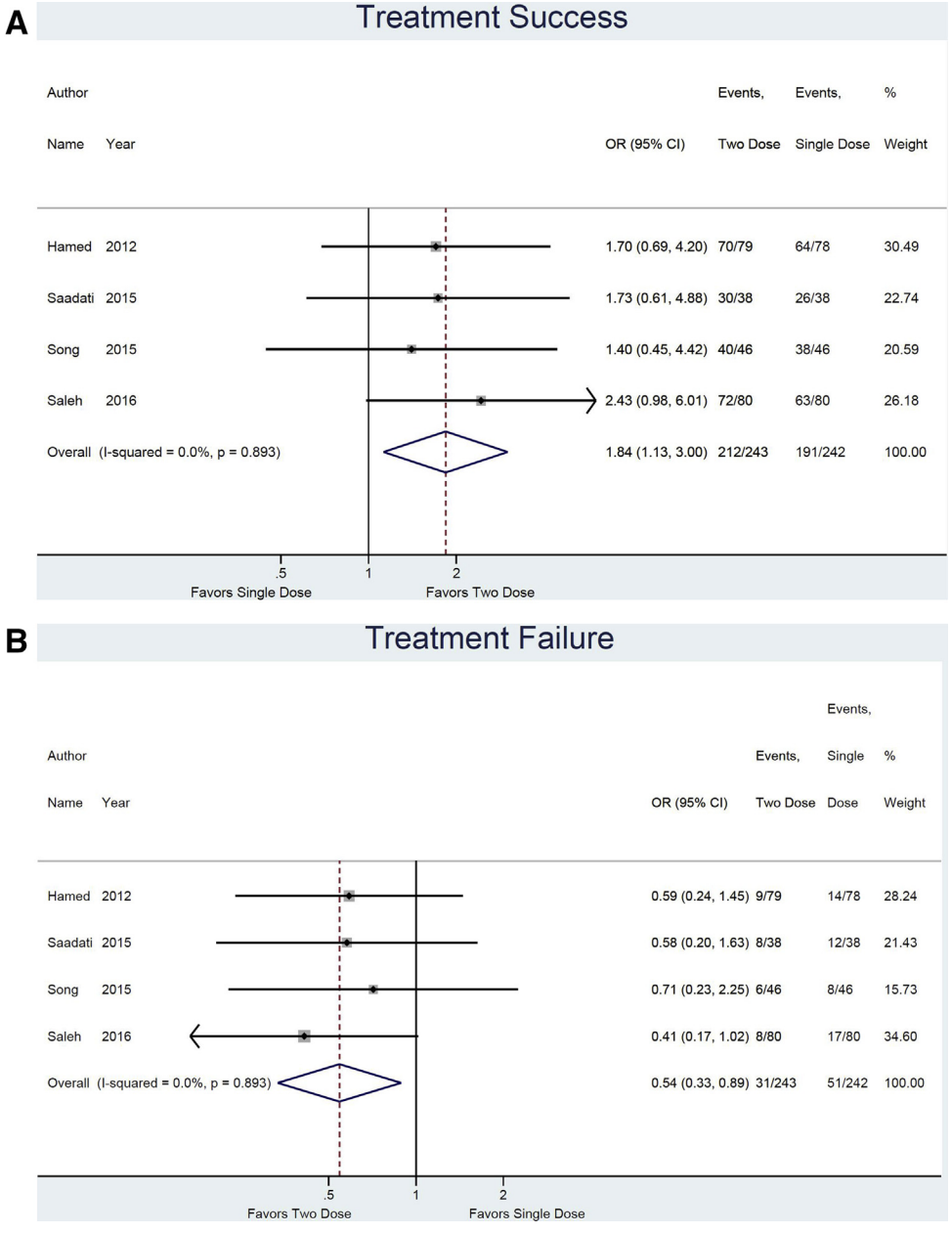
FIGURE 3

A, Forest plot: 2-dose vs single-dose treatment success. B, Forest plot: 2-dose vs single-dose treatment failure. C, Forest plot: 2-dose vs single-dose Treatment success in high-HCG group (defined by individual studies with a range of >3000–5500 mIU/mL). D, Forest plot: 2-dose vs single-dose Treatment success in large group (defined by individual studies with a range of >2–3.5 cm). E, Forest plot: 2-dose vs single-dose side effects. F, forest plot: 2-dose vs single-dose surgery for ruptured ectopic pregnancy. G, Forest plot: 2-dose vs single-dose length of follow-up



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presented in Figure 2. Although all studies discussed random sequence generation clearly, some were not clear as to how allocation concealment was performed. Although several studies were not explicit in reporting blinding to outcomes, reviewers believed that this would be unlikely to significantly skew outcome measures which are mainly objective. The study by Saleh et al,[32] however, was scored as having a high degree of bias in this category because of

FIGURE 3
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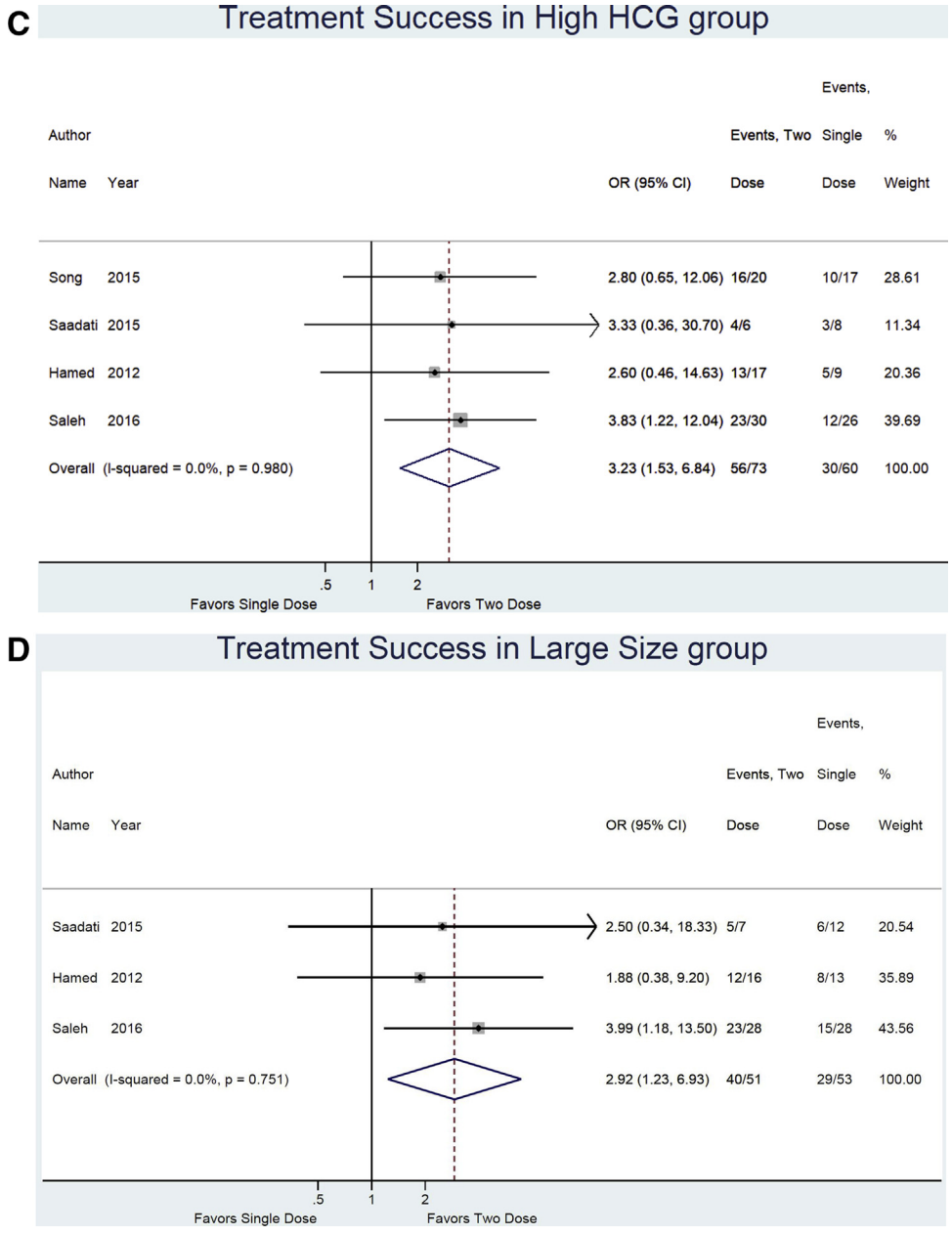

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the description of differential counseling regarding elective surgery based upon group.[32] Blinding of personnel was similarly not explicitly stated in multiple studies. Although blinding of personnel may not have been as practically feasible because of the requirement for intramuscular injections, it is possible that this could have affected patient reporting of side effects, which was 1 of the subjective outcomes measured. The study by Saleh et al[32] was scored high in this category, as envelopes were opened in front of patients, whereas the study by Guvendang et al[13] was also scored high, as they discussed that the study team was not blinded. The study by Saadati et al[14] hospitalized patients during treatment and discharged them when hCG was less than 200 mIU/mL; therefore, reporting of outcomes may have been biased away

FIGURE 3
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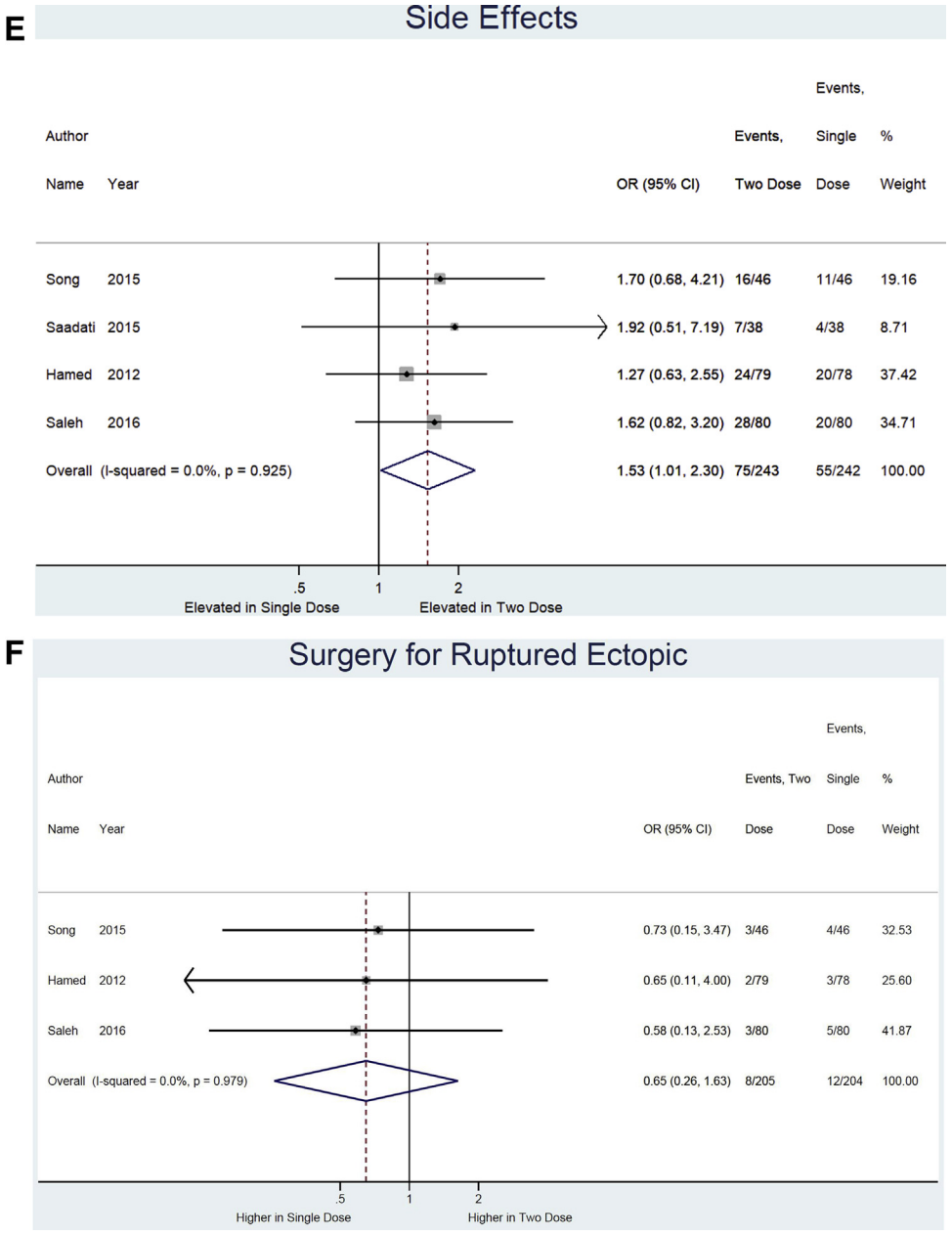

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from the null because of a nonstandard follow-up protocol as well as definition of treatment success. Publication bias was not noted to be significant when looking at studies that compared either the 2-dose to the single-dose protocol or studies that compared the multi-dose to the single-dose protocol (Supplementary Figure 1).

Meta-analysis results

Single-dose vs 2-dose protocols. Meta-analysis results are shown as forest plots in Figure 3. For the primary outcome of treatment success, 4 studies were identified comparing the single-dose to the 2-dose protocol, with the 2-dose protocol associated with 1.84 times the odds of achieving treatment success (95% CI, 1.13, 3.00) compared to the single-dose protocol[14,15,32,33] (Figure 3a). Odds of treatment failure were 0.54 times lower in the 2-dose protocol (95% CI, 0.33, 0.89) (Figure 3b). For the secondary outcome of side effects, 4 studies were identified with a combined odds of side effects that were 1.53 times higher in the 2-dose protocol compared to the single-

FIGURE 3
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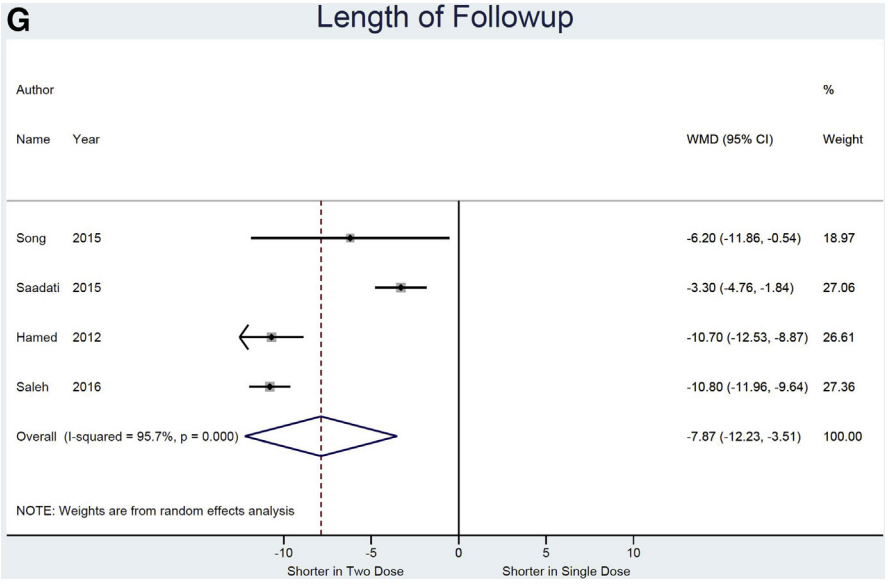

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dose protocol (95% CI, 1.01, 2.30).[14,15,32,33] (Figure 3e). Odds of surgery for tubal rupture were lower when comparing the 2-dose to the single-dose protocol (OR, 0.65; 95% CI, 0.26, 1.63), but the difference was not statistically significant (Figure 3f). The length of follow up was 7.9 days shorter for the 2-dose protocol compared to the single-dose protocol (95% CI: −12.2, −3.5) (Figure 3g).

Sensitivity analyses of 4 studies in the high hCG groups revealed a 3.23 times higher odds of treatment success with the 2-dose protocol as compared to the single-dose protocol (95% CI, 1.53, 6.84)[14,15,32,33] (Figure 3c). Evaluation of treatment success in the large adnexal mass groups from 3 studies showed a 2.92 times higher odds of treatment success with use of the 2-dose protocol as compared to the single-dose protocol (95% CI, 1.23, 6.93)[14,15,32] (Figure 3d).

Single-dose vs multi-dose protocols. We also identified 3 studies comparing treatment success rates for single-dose vs multi-dose protocol. The multi-dose protocol is associated with a higher, albeit nonsignificant, odds of treatment success compared to the single-dose (OR, 1.79; 95% CI, 0.89, 3.62) 13,17,22,34 (not shown). Similarly, the multi-dose was associated with a nonsignificant 0.56 times lower odds of treatment failure (95% CI, 0.28, 1.13) (Figure 4a). The odds of side effects were significantly higher in the multi-dose protocol compared to the single-dose protocol (OR, 2.10; 95% CI, 1.24, 3.54)[13,17,34] (not shown). The odds of surgery for tubal rupture and length of follow-up were comparable between the multi-dose and single-dose protocols (OR, 1.62; 95% CI, 0.41, 6.49) (Figure 4d) and −1.3 days (95% CI, −5.4, 2.7), respectively (Figure 4e).

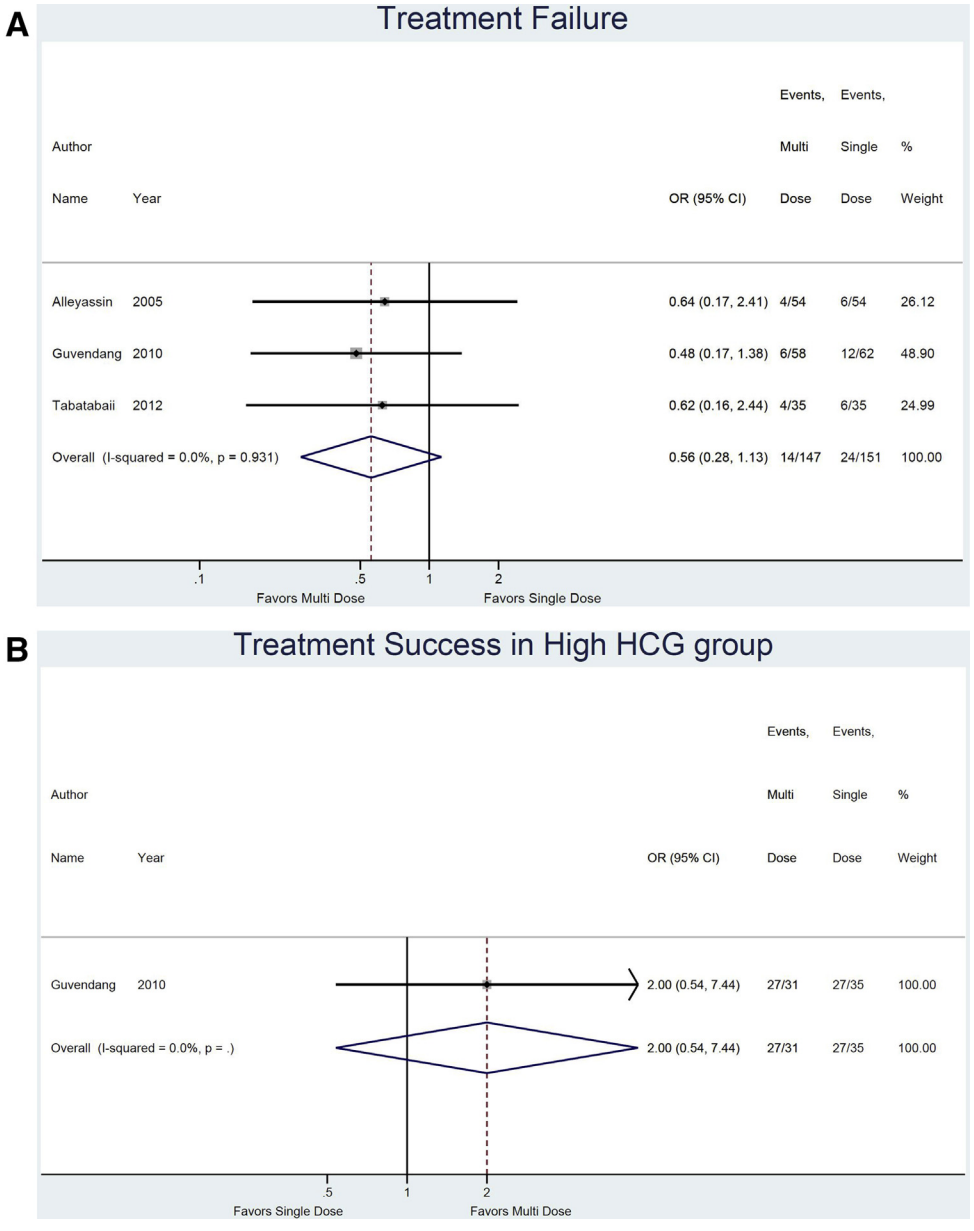
Only 1 study was identified assessing treatment success when initial hCG was high, when comparing the multi-dose to the single-dose protocol, and found a nonsignificant 2.00 times higher odds of treatment success (95% CI, 0.54, 7.44)[13] (Figure 4b). Only 1 study was also identified assessing treatment success with larger adnexal mass when comparing the multi-dose to the single-dose protocol, and found a nonsignificant 1.63 times higher odds of treatment success (95% CI, 0.38, 6.96)[13] (Figure 4c).

Comment

Overall, the 2-dose protocol was found to result in a significantly higher odds of treatment success, and thus a significantly lower odds of treatment failure, when compared to the single-dose protocol. These findings held true in patients with higher hCGs as well as in patients with large adnexal mass as defined by the individual studies. In addition, the length of follow-up for women receiving the 2-dose protocol was more than 1 week shorter than for women receiving the single-dose protocol. There was also a non−statistically significant reduction in the odds of surgery for tubal rupture with the use of the 2-dose protocol. The 2-dose protocol did have a higher rate of side effects, but it should be noted that most side effects described in the included studies were mild and transient. No patients required hospitalization or long-term management, nor did side effects preclude continuation of treatment. Taken

FIGURE 4

A, Forest plot: multi-dose vs single-dose treatment failure. B, Forest plot: multi-dose vs single-dose treatment success in high-hCG group (defined by study as >800 IU/L). C, Forest plot: multi-dose vs single-dose treatment success in large size group (defined by study as >2 cm). D, Forest plot: multi-dose vs single-dose surgery for ruptured ectopic pregnancy. E, Forest plot: multi-dose vs single-dose length of follow-up



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together, the 2-dose protocol is superior to the single-dose protocol and should be considered first-line therapy.

A meta-analysis has recently compared treatment success and side effects rates between multi-dose and single-dose protocols.[22] Given there have been no additional RCTs evaluating this comparison since this analysis was performed, we validated these findings and focused the analysis on odds of failure, odds of surgery for tubal rupture, length of follow-up, and sensitivity analyses, which were not performed in the prior meta-analysis. Overall there is a non–statistically significant trend toward lower treatment failure and higher treatment success, with use of the multidose protocol. In addition, we found that the length of follow-up was only roughly 1 day shorter in the multi-dose

FIGURE 4
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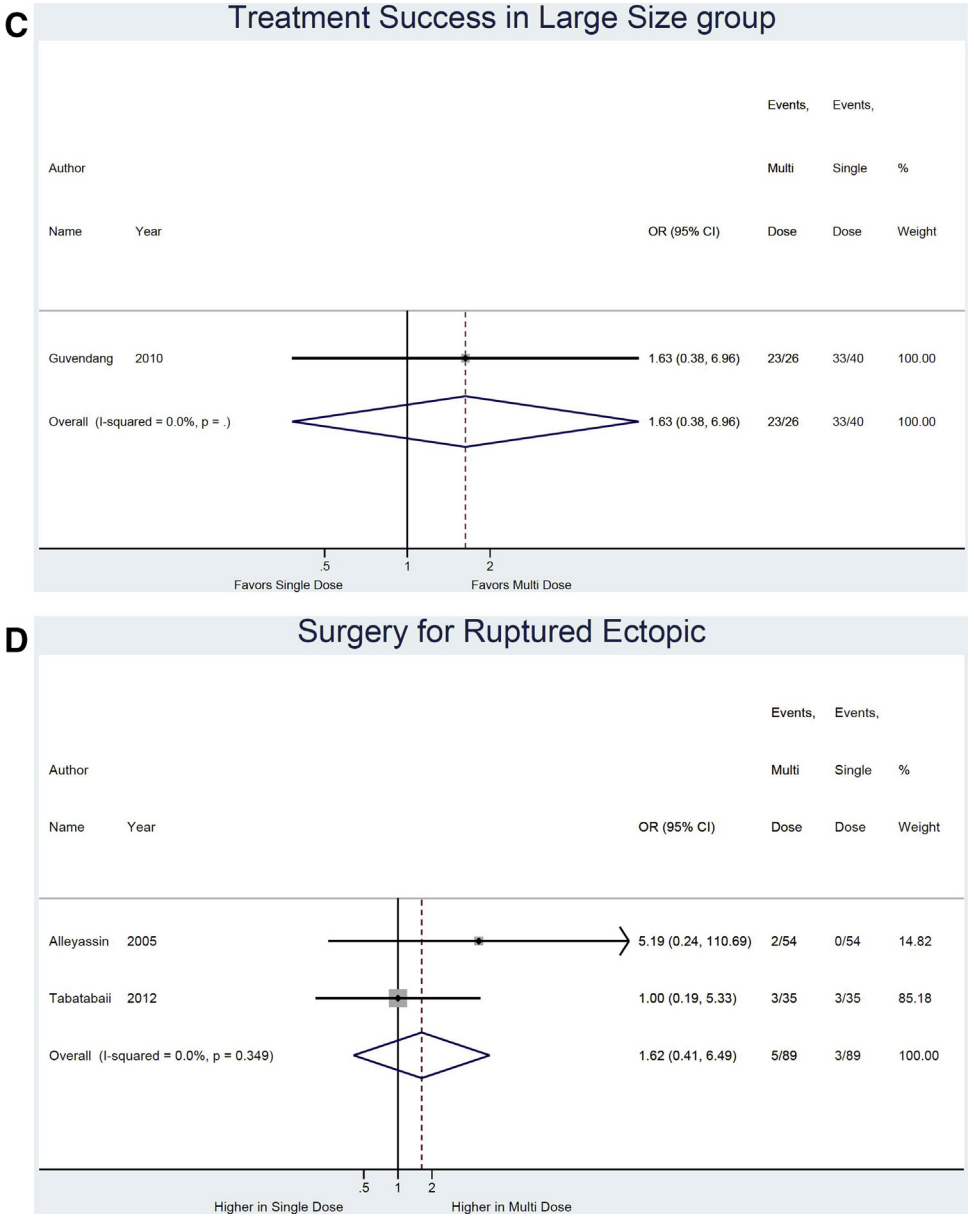

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protocol and odds of surgery for tubal rupture were not significantly different.

The quality of a meta-analysis is directly dependent on the quality of the studies included in the analysis. Previous meta-analyses have been limited by including retrospective or observational studies.[12] Moreover, additional randomized trials have been conducted since the publication of recent analyses. For example, the meta-analysis by Yang et al[22] did not include the study by Saleh et al[32] performed in 2016, and therefore did not find statistically significant differences when comparing the 2-dose to the single-dose protocol. The meta-analysis by Yuk et al.[23] included poor-quality data, including a meeting abstract without a full published manuscript[26] as well as RCTs that did not specify how randomization was performed or how many patients were in each arm[30] and that described their randomization process as "patients were alternatively selected"[31] (and yet had different numbers of patients in each arm). Attempts were made to

FIGURE 4
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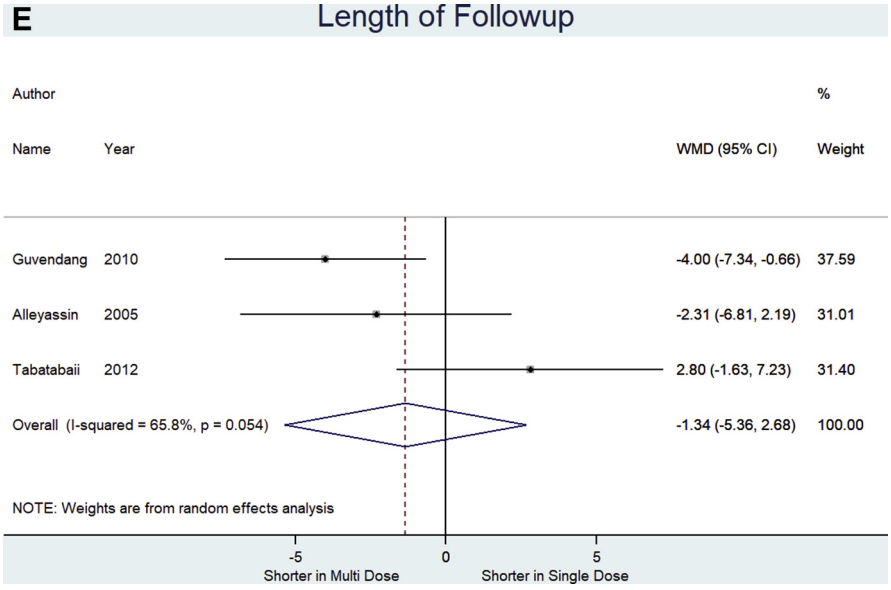

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electronically contact both authors regarding these study details prior to exclusion from our meta-analysis.

This meta-analysis has several strengths, most importantly its rigid inclusion criteria. Only RCTs with clearly stated methodology were included, limiting the chances that results would be biased by flaws in study design or execution. In addition to treatment success reporting, odds of failure were also calculated, which can provide an additional useful tool and way to conceptualize data when counseling patients.

The meta-analysis was limited by the relatively few RCTs conducted on this topic, particularly for the single versus multi-dose protocols. In this category, 3 total quality RCTs were identified assessing the main outcomes of treatment success. It is possible that the reason that our data cannot confirm a higher success rate (and lower failure rate) for the multi-dose protocol is lack of power or inherent bias in the few studies comparing multi-dose to single-dose therapy. Only 1 of these studies contained data for subgroup sensitivity analyses. Based on the odds of treatment success found with this meta-analysis, we calculated that an additional study with 70 patients per arm would be needed for the odds of treatment success to be significantly higher in the multi-dose group as compared to the single-dose group (assuming that the same differences were to be found in 1 additional study). In addition, the meta-analysis is limited in the ability to evaluate effectiveness in multiple subgroups. For example, it is possible that there are clinical situations when a single dose of methotrexate is sufficient for the treatment of an ectopic pregnancy, such as in women with a low hCG value. However, the limited data from the included randomized clinical trials does not allow such a conclusion from this meta-analysis, and could be the focus of future study.

Based on the pharmacokinetics of methotrexate, it is logical that a second dose would improve success rates compared to a single dose, because a second dose will affect a greater percentage of trophoblast cells in the S phase (DNA synthesis). It is not clear why an even greater number of doses, as part of the multi-dose protocol, does not result in greater efficacy. This may be related to low power, as stated earlier, or to the possibility that the use of alternating doses of leucovorin, in an attempt to decrease side effects, may also limit efficacy of the treatment. Multi-dose treatment is not currently considered first-line therapy and may be best reserved for women with advanced ectopic pregnancy or those in unusual locations such as cervical, intestinal, or ovarian ectopic pregnancy.[35,36]

In conclusion, the 2-dose protocol is significantly superior to the single-dose protocol in terms of odds of treatment success and treatment failure. These findings hold true in patients thought to be at a lower likelihood of responding to medical management, such as those with higher hCGs and large adnexal mass. Although the multi-dose protocol showed similar trends when compared to the single-dose protocol, none of these parameters reached statistical significance. Therefore, we would recommend the 2-dose protocol as the first-line protocol in patients being medically managed for ectopic pregnancies. ■

TABLE 2
Included study characteristics

Author /study location /year	Ectopic pregnancy diagnostic criteria	Total patients per arm	Inclusion criteria	Exclusion criteria	Method of randomization	Definition of treatment success	Other outcomes studied
Single versus Two dose							
Song South Korea 2015	bHCG, TVUS, physical exam, Medical history	46 46	1. bHCG <15,000 mIU/mL 2. GS <4 cm 3. Hemodynamically stable	1. Heterotopic pregnancy or persistent tubal pregnancy 2. +FHR 3. Suspected tubal rupture 4. Laboratory test results contraindicating MTX use	Randomly permuted blocks with allocation concealment (1:1 ratio)	bHCG <5 mIU/mL	1. Side effects 2. Length of follow-up 3. Rate of operation 4. Need for repeat doses 3. Cost of care received 4. Days of work/school missed 5. Treatment satisfaction
Saadati Iran 2015	bHCG, TVUS	38 38	1. bHCG <15,000 mIU/mL 2. Hemodynamically stable	1. Women with history of liver, kidney disease, or blood dyscrasia 2. Breastfeeding	Block randomization with enclosed envelopes (1:1 ratio)	bHCG ≤200 mIU/mL	1. Side effects 2. Length of follow-up 3. Rate of operation 4. Need for repeat doses
Hamed Saudi Arabia 2012	bHCG, TVUS, progesterone and D&C when abortion suspected	78 79	1. bHCG of <15,000 mIU/mL 2. GS ≤4 cm 3. Hemodynamically stable 4. Absence of FHR	1. Women suspected of having nonadnexal ectopic pregnancy 2. Suspected tubal rupture 3. Free fluid extending beyond Douglas pouch on TVUS 4. Laboratory test results contraindicating MTX use	Computer-generated random numbers table with opaque envelopes	bHCG <15 mIU/mL within 6 weeks without surgery or repeat dose	1. Side effects 2. Length of follow-up 3. Rate of operation 4. Need for repeat doses
Saleh Egypt 2016	bHCG, TVUS	80 80	1. bHCG ≤6000 mIU/mL 2. GS ≤4 cm 3. Hemodynamically stable 4. Absence of FHR 5. <300 mL hemoperitoneum on TVUS	1. Hemodynamically unstable 2. Suspected tubal rupture 2. Uncertain diagnosis 3. Falling bHCGs 4. Nonadnexal ectopic pregnancy 5. Laboratory test results contraindicating MTX use 6. Breastfeeding 7. Immunodeficiency or use of corticosteroids	Computer-generated randomization with sealed, opaque envelopes	bHCG <15 mIU/mL within 6 weeks without surgery or repeated dose	1. Side effects 2. Length of follow-up 3. Rate of operation 4. Need for repeat doses

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(continued)

TABLE 2
Included study characteristics *(continued)*

Author /study location /year	Ectopic pregnancy diagnostic criteria	Total patients per arm	Inclusion criteria	Exclusion criteria	Method of randomization	Definition of treatment success	Other outcomes studied
Single-dose vs multi-dose							
Guvendang Guven Turkey 2010	bHCG, TVUS, progesterone	62 58	1. bHCG reaching plateau or increased by ≤50% in 48 hours 2. Adnexal mass ≤3.5cm 3. Hemodynamically stable	1. Prior tubal surgery 2. Hemodynamically unstable 3. Hepatic or renal disease	Computer-assisted randomization with sealed envelopes	bHCG <5 mIU/mL	1. Side effects 2. Length of follow-up 3. Need for repeat doses
Alleyassin Iran 2005	bHCG, TVUS	54 54	1. bHCG <15,000 mIU/mL 2. Adnexal mass <3.5 cm 3. Hemodynamically stable 4. Absence of FHR	None listed	Computer-generated block randomization with sealed envelopes	bHCG <15mIU/mL within 6 weeks	1. Side-effects 2. Length of follow-up 3. Rate of operation 4. Need for repeat doses
Tabatabaii Iran 2012	TVUS, Laparoscopic surgery	35 35	1. bHCG <15,000 mIU/mL 2. Adnexal mass ≤4cm 3. Hemodynamically stable 4. Absence of FHR 5. Absence of bleeding in laparoscopic surgery or TVUS	None listed	Computer-generated block randomization with sealed envelopes	bHCG <15 mIU/mL within 6 weeks	1. Side effects 2. Length of follow-up 3. Rate of operation 4. Need for repeat doses 5. Outcomes of subsequent pregnancies

bHCG, beta human chorionic gonadotropin; *D&C*, dilation and curettage; *FHR*, fetal heart rate; *GS*, gestational sac; *MTX*, methotrexate; *TVUS*, transvaginal ultrasound.

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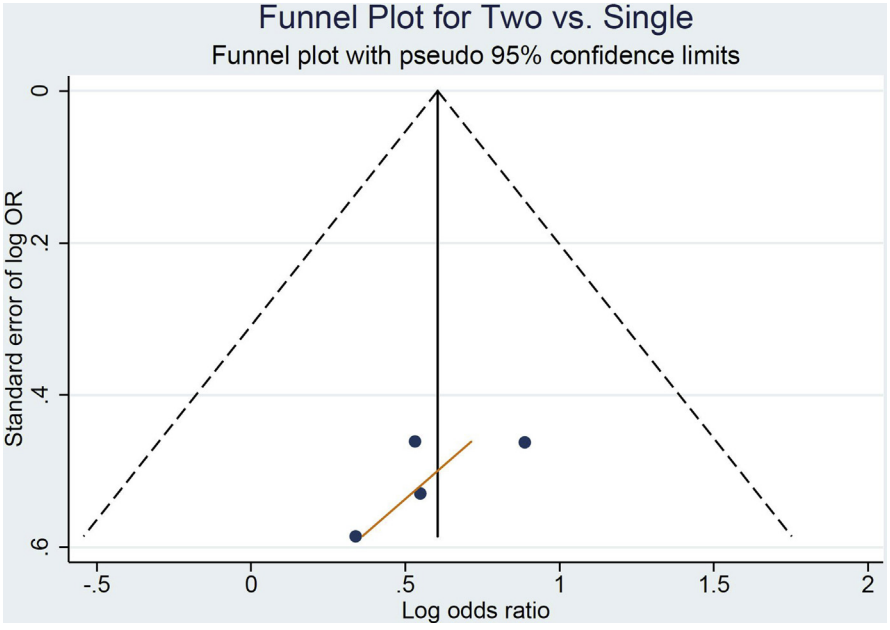
REFERENCES

1. Marion LL, Meeks GR. Ectopic pregnancy: History, incidence, epidemiology, and risk factors. Clin Obstet Gynecol 2012;55:376–86.
2. Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. Cochrane Database Syst Rev 2007:CD00324.
3. ACOG. ACOG practice bulletin no. 193: tubal ectopic pregnancy. Obstet Gynecol 2018;131:e91–103.
4. Barnhart KT. Clinical practice. Ectopic pregnancy. N Engl J Med 2009;361:379–87.
5. Barnhart K, Coutifaris C, Esposito M. The pharmacology of methotrexate. Expert Opin Pharmacother 2001;2:409–17.
6. Hajenius PJ, Engelsbel S, Mol BW, et al. Randomised trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy. Lancet 1997;350:774–9.
7. Kazandi M, Turan V. Ectopic pregnancy; risk factors and comparison of intervention success rates in tubal ectopic pregnancy. Clin Exp Obstet Gynecol 2011;38:67–70.
8. Krag Moeller LB, Moeller C, Thomsen SG, et al. Success and spontaneous pregnancy rates following systemic methotrexate versus laparoscopic surgery for tubal pregnancies: a randomized trial. Acta Obstet Gynecol Scand 2009;88:1331–7.
9. Mol F, Mol BW, Ankum WM, van der Veen F, Hajenius PJ. Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis. Hum Reprod Update 2008;14:309–19.
10. Lipscomb GH, McCord ML, Stovall TG, Huff G, Portera SG, Ling FW. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. N Engl J Med 1999;341:1974–8.
11. Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Chakhtoura N. Use of "2-dose" regimen of methotrexate to treat ectopic pregnancy. Fertil Steril 2007;87:250–6.
12. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. Obstet Gynecol 2003;101:778–84.
13. Guvendag Guven ES, Dilbaz S, Dilbaz B, Aykan Yildirim B, Akdag D, Haberal A. Comparison of single and multiple dose methotrexate therapy for unruptured tubal ectopic pregnancy: a prospective randomized study. Acta Obstet Gynecol Scand 2010;89:889–95.
14. Saadati N, Najafian M, Masihi S, Safiary S, Abedi P. Comparison of two different protocols of methotrexate therapy in medical management of ectopic pregnancy. Iranian Red Crescent Med J 2015;17:e20147.
15. Hamed HO, Ahmed SR, Alghasham AA. Comparison of double- and single-dose methotrexate protocols for treatment of ectopic pregnancy. Int J Gynaecol Obstet 2012;116:67–71.

16. Gungorduk K, Asicioglu O, Yildirim G, Gungorduk OC, Besimoglu B, Ark C. Comparison of single-dose and two-dose methotrexate protocols for the treatment of unruptured ectopic pregnancy. J Obstet Gynaecol 2011;31:330–4.
17. Tabatabaii Bafghi A, Zaretezerjani F, Sekhavat L, Dehghani Firouzabadi R, Ramazankhani Z. Fertility outcome after treatment of unruptured ectopic pregnancy with two different methotrexate protocols. Int J Fertil Steril 2012;6:189–94.
18. Chen YX, Mao YY, Xie X. Efficacy and side effects of methotrexate in the treatment of ectopic pregnancy. Zhonghua Fu Chan Ke Za Zhi 2003;38:749–51.
19. Lipscomb GH, Givens VM, Meyer NL, Bran D. Comparison of multidose and single-dose methotrexate protocols for the treatment of ectopic pregnancy. Am J Obstet Gynecol 2005;192:1844–7; discussion 47-8.
20. Kim J, Jung YM, Lee DY, Jee BC. Pretreatment serum human chorionic gonadotropin cutoff value for medical treatment success with single-dose and multi-dose regimen of methotrexate in tubal ectopic pregnancy. Obstet Gynecol Science 2017;60:79–86.
21. Mergenthal MC, Senapati S, Zee J, et al. Medical management of ectopic pregnancy with single-dose and 2-dose methotrexate protocols: human chorionic gonadotropin trends and patient outcomes. Am J Obstet Gynecol 2016;215:590.
22. Yang C, Cai J, Geng Y, Gao Y. Multiple-dose and double-dose versus single-dose administration of methotrexate for the treatment of ectopic pregnancy: a systematic review and meta-analysis. Reprod Biomed Online 2017;34:383–91.
23. Yuk JS, Lee JH, Park WI, Ahn HS, Kim HJ. Systematic review and meta-analysis of single-dose and non-single-dose methotrexate protocols in the treatment of ectopic pregnancy. Int J Gynaecol Obstet 2018;141:295–303.
24. Cardamakis E, Kourounis G, Tzeferakos A, Korantzis A, Ginopoulos P. Three different regimens of methotrexate for the treatment of ectopic pregnancy. XV FIGO World Congress of Obstetrics & Gynecology 1997:92.
25. Shahrzad M. Comparison of single and multiple-dose methotrexate therapy for ectopic pregnancy: a clinical trial. Clinicaltrials.gov. Study ID: NCT01662167. Available at: https://clinicaltrials.gov/show/nct01662167. Accessed July 16, 2018.
26. Klauser CK, May WL, Johnson VK, Cowan BD, Hines RS. Methotrexate for ectopic pregnancy: a randomized "single dose" compared with "multidose" trial. Obstet Gynecol 2005;105:64S.
27. Olofsson JI, Poromaa IS, Ottander U, Kjellberg L, Damber MG. Clinical and pregnancy outcome following ectopic pregnancy; a prospective study comparing expectancy, surgery and systemic methotrexate treatment. Acta Obstet Gynecol Scand 2001;80:744–9.
28. Golmohammadlou S, Hajishafiha M, Hasankhani Z. Comparison of single and two dose of methotrexate in treatment of ectopic pregnancy. Iran J Reprod Med 2012;10:74.
29. Fakheri T, Nankali A, Shahlazadeh H, Ataee M, Shahri MN. Comparison of single-dose and multiple-dose systemic methotrexate regimen for ectopic pregnancy. J Isfahan Med Sch 2014;32:1054–60.
30. Zargar M, Razi T, Barati M. Comparision of single and multidose of methotrexate in medical treatment of ectopic pregnancy. Pakistan J Med Sci 2008;24:586–9.
31. Amirian M, Rajaee M, Moayedi U, Mohammadi F, Hosseini S. Comparison of single and multiple-dose methotrexate therapy for ectopic pregnancy: a clinical trial. Life Sci J 2013;10:564–7.
32. Saleh H. Double versus single dose methotrexate regimens in management of undisturbed ectopic pregnancy. Crit Care Obstet Gynecol 2016;2:6.
33. Song T, Kim MK, Kim ML, Jung YW, Yun BS, Seong SJ. Single-dose versus two-dose administration of methotrexate for the treatment of ectopic pregnancy: a randomized controlled trial. Hum Reprod 2016;31:332–8.
34. Alleyassin A, Khademi A, Aghahosseini M, Safdarian L, Badenoosh B, Hamed EA. Comparison of success rates in the medical management of ectopic pregnancy with single-dose and multiple-dose administration of methotrexate: a prospective, randomized clinical trial. Fertil Steril 2006;85:1661–6.
35. Ramkrishna J, Kan GR, Reidy KL, Ang WC, Palma-Dias R. Comparison of management regimens following ultrasound diagnosis of nontubal ectopic pregnancies: a retrospective cohort study. Br J Obstet Gynecol 2018;125:567–75.
36. Hunt SP, Talmor A, Vollenhoven B. Management of non-tubal ectopic pregnancies at a large tertiary hospital. Reprod Biomed Online 2016;33:79–84.

SUPPLEMENTARY FIGURE 1A

Funnel plot of publication bias: Two dose versus single dose protocols. Points refer to individual study results. Dotted lines refer to 95% confidence interval. The symmetric nature of the dots about the solid vertical line (representing the average association measure) indicates lack of publication bias



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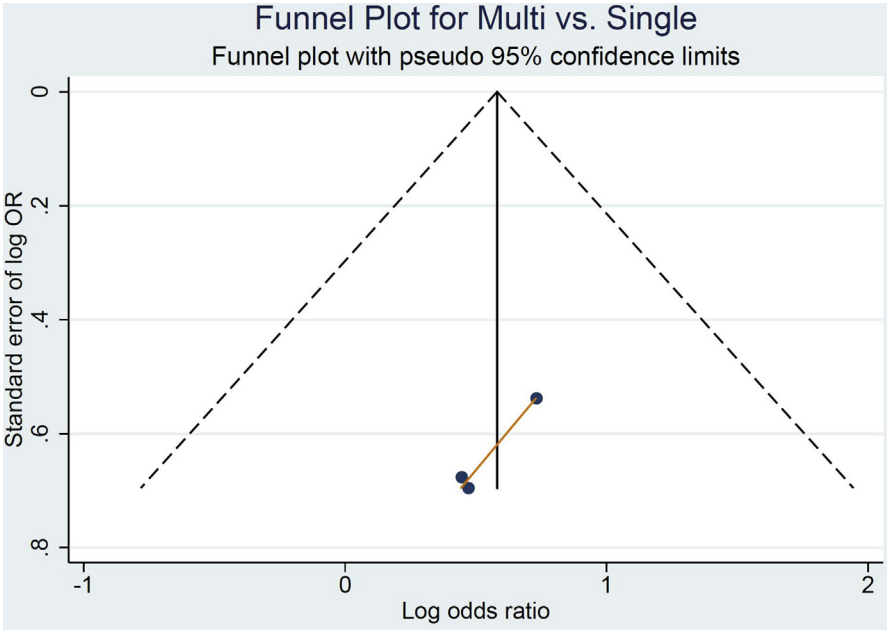
SUPPLEMENTARY FIGURE 1B

Funnel plot of publication bias: Multi-dose versus single dose protocols. Points refer to individual study results. Dotted lines refer to 95% confidence interval. The symmetric nature of the dots about the solid vertical line (representing the average association measure) indicates lack of publication bias



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