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CLINICAL ARTICLE

Comparison of double- and single-dose methotrexate protocols for treatment of ectopic pregnancy

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ABSTRACT

Objective: To compare efficacy between double-dose methotrexate and single-dose methotrexate for treatment of tubal ectopic pregnancy (EP). *Methods:* Between March 2008 and February 2011,157 patients who had tubal EP diagnosed by a non-laparoscopic approach and were hemodynamically stable were enrolled in a prospective study in Qassim, Saudi Arabia. The participants were randomized to receive either double-dose (50 mg/m^2 intramuscularly on days 0 and 4; group 1) or single-dose (50 mg/m^2 intramuscularly on day 0; group 2) methotrexate. Serum human chorionic gonadotropin (β-hCG) levels were followed until negative. *Results:* The overall success rate was comparable between groups 1 and 2 (88.6% versus 82.0%, $P=0.1$). The duration of follow up until negative β-hCG was shorter in group 1 ($P=0.001$). Receiver operative characteristics showed that higher cut-off levels of β-hCG and gestational mass diameter were associated with successful outcome in group 1. Among participants with initial β-hCG of 3600–5500 mIU/mL, the success rate was higher in group 1 ($P=0.03$). There was no significant difference between groups in adverse effects. *Conclusion:* For treatment of EP, double-dose methotrexate had efficacy and safety comparable to that of single-dose methotrexate; it had better success among patients with moderately high β-hCG and led to a shorter follow up.

1. Introduction

It is notable that treatment of EP by methotrexate has been developed and accepted as a first-line therapy [1,2] or a cost-effective alternative to laparoscopy for selected patients [3]. Among various protocols for treating EP, the multi-dose regimen includes the administration of 4 methotrexate doses alternating with folinic acid, similar to the rescue regimen used for gestational trophoblastic diseases [4,5], whereas the single-dose protocol comprises a single dose of methotrexate, which can be repeated weekly in non-responders [1,6]. Although both regimens have been studied extensively, there is no consensus on the optimum protocol [7–11].

The potential advantages of the single-dose protocol include elimination of a rescue regimen, lower incidence of adverse effects, and better compliance [7]. In a large meta-analysis of 1327 women, however, the single-dose protocol was found to be associated with a considerably lower success rate as compared with the multi-dose regimen (88% versus 93%) [10]. Those findings are inconsistent with subsequent reports, which demonstrated comparable success rates of 88%–90% for single- and 86%–-95% for multi-dose regimens [7,8]. In other studies, the outcome of the single-dose regimen has been shown to vary widely depending on initial human chorionic gonadotropin (β-hCG) levels, gestational mass size, and number of repeated dosages [12–14]. Success rates as low as 35% with a β-hCG level of more than 4000 IU/L [12], and as high as 98% with a level of less than 1000 IU/L [13], have been reported.

The challenge to develop an optimum regimen that balances efficacy and safety on the one hand and convenience on the other hand was attempted by Barnhart et al. [11], who first described what is called the "double-dose protocol". In a study that included 101 patients, 2 doses of methotrexate were administered on days 0 and 4 without measuring β-hCG between doses. The authors reported a success rate of 76% after 2 doses and 87% after a further 2 doses [11]. Although these rates are comparable to those of the single-dose regimen, there are no clinical trials comparing both regimens. We considered that the efficacy of the double-dose regimen could surpass that of the non-repeated single-dose regimen, especially among women with high baseline levels of β-hCG and large gestational mass.

The aim of the present study was therefore to assess the efficacy and safety of a double-dose regimen, in which methotrexate was given alone and only on days 0 and 4, to that of a non-repeated single dosage on day 0 for the treatment of adnexal EP.

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2. Materials and methods

In a prospective randomized trial conducted at the Obstetrics and Pharmacology Departments of Qassim University, and a tertiary Maternity Hospital in Qassim Region, Saudi Arabia, women diagnosed to have tubal EP were enrolled between March 1, 2008, and February 28, 2011. The study was approved by the institutional research committees, and the women provided informed consent.

Diagnosis of tubal EP was done by a non-laparoscopic approach using clinical and vaginal ultrasound examination, discriminatory zones of β-hCG, serum progesterone, and uterine curettage for presence of chorionic villi when abortion was suspected [15]. Women suspected to have cervical or cornual pregnancy during ultrasound evaluation were excluded. The inclusion and exclusion criteria for the current trial were extracted from Stovall and Ling [16], and the American College of Obstetricians and Gynecologists recommendations for methotrexate treatment [17].

The inclusion criteria were: (1) a gestational mass in the adnexa with a maximum diameter of 4 cm of less; (2) a baseline β-hCG level of less than 15 000 mIU/mL; (3) hemodynamic stability (no hypotension, blood pressure >90/60 mm Hg; no tachycardia, pulse <100 beats/min); (4) absence of gestational cardiac activity; (5) agreement to methotrexate therapy and follow up. The exclusion criteria were: (1) non-adnexal EP; (2) clinically suspected tubal rupture; (3) free fluid extending beyond the Douglas pouch on transvaginal sonography (TVS); (4) laboratory tests showing possible deleterious effects of methotrexate treatment on organ functions (platelet count <120 000/μL, serum creatinine >1.2 mg/dL, or aspartate aminotransferase more than double the normal level).

The study sample size was calculated on the basis of the biggest difference reported between the success rates of the non-repeated double- and single-dose protocols. The lowest success rate of the single-dose regimen and the highest success rate for the double-dose protocol in an unselected population with tubal EP were 65% and 76%, respectively [7,9,11]. Thus, 152 patients were required to find a statistically significant difference of 11% in success rate with a α value of 0.05 and a β value of 0.2.

After baseline β-hCG, blood count, liver, and kidney function tests, the participants underwent TVS after they had been counseled and had consented to the detailed treatment protocol. Enrolled patients were randomized to either group 1, which received the non-repeated double-dose methotrexate regimen (50 mg/m^2 intramuscularly on days 0 and 4) [11], or group 2, which received a single dose (50 mg/m^2 intramuscularly on day 0) [16]. Randomization was performed via a computer-generated random numbers table. Allocation concealment was done via serially numbered opaque envelopes. The patient's allocation was not changed after the envelope was opened. For both groups, β-hCG was measured on day 4 and day 7, and then weekly until a negative value was obtained (<15 mIU/mL) or for 6 weeks, whichever came first. Other baseline investigations were reevaluated on day 7. All participants were admitted to the hospital during the first week of treatment and then followed as outpatients, when appropriate.

The measured outcomes were success rate, treatment duration, and adverse effects of methotrexate. For both groups, success was defined as confirmation of a 15% or higher drop in serum β-hCG level between day 4 and day 7, with a continued drop to less than 15 mIU/mL within 6 weeks without surgical intervention or a repeat dosage [8,11]. For both groups, patients whose β-hCG level had risen or dropped by less than 15% at day 7, or persisted at high levels for more than 6 weeks, and those who needed elective or emergency surgery during follow up were considered to have failed treatment. Further management of patients with failed treatment was arranged but not included in the present results. Women with failed treatment in group 1 were managed by elective surgical intervention, where those in group 2 had a repeat methotrexate dosage or underwent surgical intervention on the discretion of the physician and patient wishes.

Statistical analysis was done via SPSS software (SPSS, Chicago, IL, USA). Student *t* test was used to compare means, and χ^2 or Fisher exact tests were used when appropriate to compare dichotomous variables. Receiver operator characteristics (ROC) curves for initial β-hCG concentration and longest ectopic mass diameter were created to establish cut-off points associated with success in both groups. A *P* value of less than 0.05 was considered statistically significant.

3. Results

A total of 157 patients were enrolled and randomized to group 1 (n = 79) or group 2 (n = 78). There were no significant difference between the groups in demographic and baseline data (Table 1).

Methotrexate treatment failed for 9 (11%) participants in group 1 and 14 (18%) participants in group 2 (Fig. 1). Among these participants, 2 in group 1 and 3 in group 2 required emergency laparotomy during the first week owing to tubal rupture, corresponding to a tubal rupture frequency of 2.5% (2/79) in group 1 and 3.8% (3/78) in group 2. For these patients, the β-hCG level on day 4 was increased by 20%–50% of the pretreatment level. The remaining 7 participants with failed treatment in group 1 and 8 with failed treatment in group 2 had elective laparoscopic surgery, which showed no tubal rupture. No failed treatments were due to women reaching the 6-week limit without a negative β-hCG level.

Table 1
Demographic and baseline criteria of both groups.[a]

Baseline criteria	Group 1 (n = 79)	Group 2 (n = 78)	*P* value [b]
Patient age, years	23.1 ± 6.5 (19–35)	25.4 ± 4.7 (18–36)	0.3
BMI	25.6 ± 8.4 (20–39)	26.2 ± 7.7 (22–38)	0.6
Parity			
0	29 (36.7)	25 (32.1)	0.6
1	31 (39.2)	36 (46.1)	
≥2	19 (24.0)	17 (21.8)	
History of spontaneous abortion	21 (26.5)	24 (30.7)	0.8
History of previous ectopic pregnancy	7 (8.8)	6 (7.6)	0.2
History of ovulation induction	12 (15.0)	10 (12.8)	0.1
History of IVF	4 (5.0)	6 (7.6)	0.2
Gestational age, days	43.4 ± 17.1(35–58)	45.1 ± 14.9 (37–62)	0.4
β-hCG, mIU/mL	3565.8 ± 1977.6 (550–9200)	3158.4 ± 1462.4 (450–8800)	0.1
Longest ectopic mass diameter, cm	2.7 ± 0.9 (0.5–4.0)	2.6 ± 0.8 (0.8–4.0)	0.6
Patients presented with pelvic pain	16 (20.2)	17 (21.7)	0.7
Patients presented with vaginal bleeding	14 (17.7)	13 (16.6)	0.9

Abbreviation: β-hCG, human chorionic gonadotropin.
[a] Values are given as mean ± SD (range) or number (percentage) unless stated otherwise.
[b] Unpaired Student *t* test was used to compare means; χ^2 or Fisher exact test was used to compare percentages.

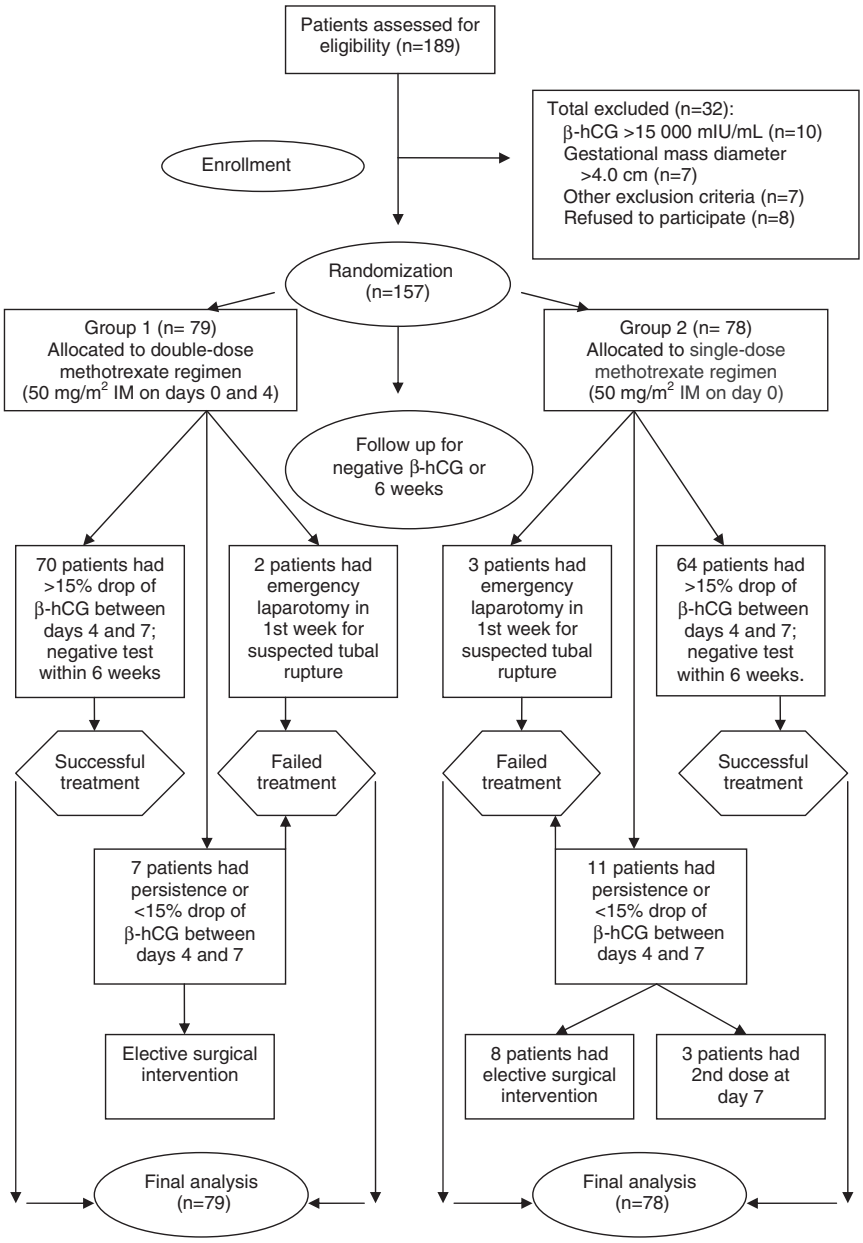

Fig. 1. Flow of participants through the study.

The overall success rate was comparable between the 2 groups ($P=0.1$) (Table 2). The duration of follow up until a negative β-hCG level in responding patients was significantly shorter in group 1 ($P=0.001$). ROC curve analysis (Fig. 2) showed that the sensitivity and specificity of success in group 1 were 81% and 89% at a β-hCG cut-off of 5500 mIU/mL (area under curve, 0.822), whereas in group 2 they were 75% and 86% at a β-hCG cut-off of 3600 mIU/mL (area under curve, 0.768). In addition, the sensitivity and specificity of success in group 1 were 73% and 78% at a mass diameter cut-off of 3.5 cm (area under curve, 0.813), whereas in group 2 they were 72% and 71% at a mass diameter cut-off of 2.7 cm (area under curve, 0.79).

There were also higher success rates in group 1 among patients with β-hCG levels of 3600–5500 mIU/mL ($P=0.03$) and an ectopic mass diameter of 2.7–3.5 cm ($P=0.055$). The overall incidence of adverse effects of treatment was comparable in both groups ($P=0.5$). The most common adverse effects recorded were new-onset abdominal pain; gastrointestinal symptoms including nausea, vomiting, and mucositis; and a transient decrease in leukocyte ($<4000/cm^3$) and platelet ($<120\,000/cm^3$) counts. All adverse effects were mild and transient, and responded well to expectant or symptomatic treatment.

4. Discussion

The present study demonstrated a comparable overall success rate for the double- and the single-dose methotrexate regimens (88% versus 82%). The success rate for the double-dose regimen (88%) was higher than that of Barnhart et al. [11] who first described this protocol, reporting a rate of 76% in a study that included 101 patients of 5 different ethnicities. The heterogeneity of their study population and the counting of 4 patients who chose to have surgery after starting methotrexate treatment as failed treatments could be possible explanations for this difference. By contrast, the overall success rate of the single-dose treatment (82%) is comparable to other reports (65%–96%), which vary depending on the number of repeated doses and initial β-hCG concentration [7,9,16]. In terms of failed treatments, the double-dose protocol had a tubal rupture rate of 2.5%, which is

Table 2
Outcome in both groups.[a]

Outcome	Group 1 (n = 79)	Group 2 (n = 78)	Odds ratio (95% CI)	*P* value [b]
Overall success rate	70/79 (88.6)	64/78 (82.1)	1.70 (0.68–4.2)	0.1
Success relative to baseline β-hCG, mIU/ml				
<3600	33/35 (94.3)	48/50 (96.0)	0.68 (0.09–5.1)	1.0
3600–5500	24/27 (88.9)	11/19 (57.9)	5.80 (1.29–26.2)	0.03
>5500	13/17 (77.5)	5/9 (55.6)	2.60 (0.46–14.6)	0.3
Success relative to ectopic mass diameter, cm				
<2.7	37/40 (92.5)	45/46 (95.7)	0.56 (0.08–3.5)	0.6
2.7–3.5	21/23 (91.3)	12/19 (63.2)	6.12 (1.09–34.3)	0.055
>3.5	12/16 (75.0)	8/13 (61.5)	1.87 (0.38–9.1)	0.6
Follow up duration in successful patients, days [c]	20.3 ± 4.8 (15–32)	31.0 ± 6.7 (21–42)	–	0.001
Adverse effects				
Overall complication rate [d]	24/79 (30.4)	20/78 (25.6)	0.79 (0.39–1.58)	0.5
New-onset abdominal pain	7 (8.8)	6 (7.7)	–	–
Gastrointestinal symptoms	6 (7.5)	4 (5.1)	–	–
Mucositis	4 (5.0)	3 (3.8)	–	–
Loss of hair	1 (1.3)	2 (2.6)	–	–
Elevated liver enzymes [e]	4 (5.0)	3 (3.8)	–	–
Thrombocytopenia/ leucopenia	2 (2.5)	2 (2.6)	–	–

[a] Values are given as mean ± SD (range) or number (percentage) unless stated otherwise.
[b] Student t test was used to compare means; χ^2 or Fisher exact test was used to compare percentages.
[c] Duration of treatment and follow up until β-hCG <15 mIU/mL.
[d] Some adverse effects overlapped in some patients.
[e] Counted as abnormal when it was at least double the normal value.

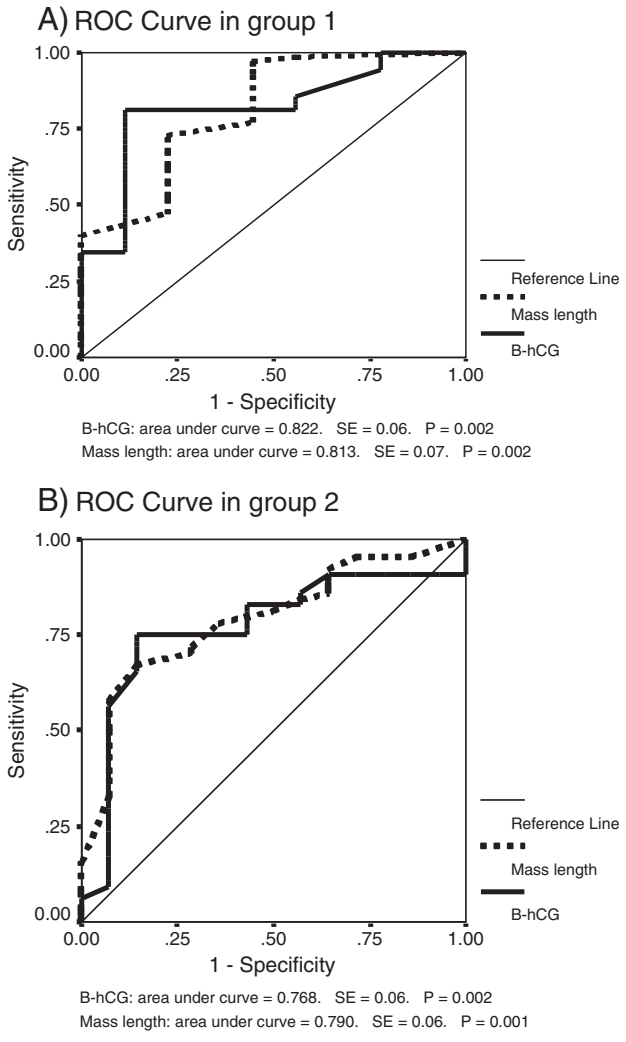

Fig. 2. ROC curves for the effect of initial serum β-hCG level and longest gestational mass length on successful outcome. A. Group 1; B. Group 2.

comparable to a previous report (3%) [11]. The observed early rise in β-hCG levels in affected patients despite being given methotrexate has been described as an indicator for treatment failure and tubal rupture [18].

The larger the size of ectopic mass, the higher the possibility of β-hCG production and the higher methotrexate dose required to control active trophoblasts. This is the rational for using the multi-dose regimen or repeating dosages in the single-dose protocol. The Royal College of Obstetricians and Gynecologists describe only the single-dose regimen in its recommendations for the medical treatment of EP [19]; this recommendation is based on several studies demonstrating that only 15%–25% of women will require more than 1 dose [3,10,13,20]. However, there is a problem in that this group of patients cannot be accurately anticipated and hence cannot be counseled for the multi-dose protocol or for repeating single dosages. Indeed, the term "single-dose protocol" is a misnomer because it includes the possibility of repeating the dose at weekly intervals in poor responders. The cumulative success rate after 1, 2, 3, and 4 single doses has been reported as 77%, 92%, 93%, and 94%, respectively [14]. Repeating dosages are associated with longer treatment and follow up duration, more adverse effects, and less compliance—disadvantages that are typical disadvantages of the multi-dose regimen [7,10]. By contrast, the double-dose protocol has the advantage of the close proximity of the second to first dose, a factor that is suggested to enhance the drug's effect on patients with high trophoblastic-cell load [10]. This postulation was supported in the present trial by the finding that the higher cut-off levels of β-hCG and gestational mass size were associated with successful treatment by the double-dose regimen.

There was no significant difference between the 2 regimens in subgroups of patients with an initial β-hCG level of less than 3600 mIU/mL and a gestational mass diameter of less than 2.7 cm. When these values were exceeded, however, there was a tendency for better outcome with the double regimen that achieved statistical significance only in patients with β-hCG levels between 3600 and 5500 mIU/mL ($P = 0.03$). Among patients with an ectopic mass diameter between 2.7 and 3.5 cm, the higher success rate for the double-dose regimen was approaching significance ($P = 0.055$). A larger sample size might demonstrate a significant difference for this subgroup. By contrast, the lack of significant difference between the 2 regimens among patients with β-hCG levels greater than

5500 mIU/mL could suggest the possibility of an upper limit of trophoblastic mass that is sensitive to methotrexate treatment [12]. This was previously reported by Cho et al. [21], who showed for the single-dose protocol a success rate of 58% for β-hCG levels greater than 6000 mIU/mL and 96% for levels less than 6000 mIU/mL. In addition, others have recommended the use of careful methotrexate treatment because there is an increased risk of failure when the initial β-hCG level is more than 4000 mIU/mL, when patients present with pelvic pain or vaginal bleeding [12], or when a yolk sac [22] or large ectopic mass (>3 cm) [23] is present.

The types and frequency of adverse effects in the present study were comparable in both groups (30% versus 26%) and similar to other reports (25%–32%) [1,4,11,15,24,25]. The most frequent adverse effect was pelvic pain (8.8% versus 7.7%), which is mostly caused by resolution of EP rather than methotrexate itself [11]. The present rates of pain were lower than the previously reported values of 27% for the double-dose [11] and 20% for the single-dose [4] protocols. This could be because only patients who developed symptoms after treatment, and not those presenting with pain, were counted. The next common adverse effect for the double-dose regimen was nausea and vomiting (7.5%), a value that is comparable to the present single-dose protocol (5.1%) but lower than that of Barnhart et al. [11], who reported a rate of 16% for the double-dose regimen. This difference might be explained by different study protocols because Barnhart et al. [11] repeated the double-dose regimen twice. Further studies are needed to ensure the safety of the administration of 2 methotrexate doses, 4 days apart, without folinic acid.

In summary, the double-dose protocol was found to be an efficient and safe alternative to the single-dose regimen. It has the advantage of a shorter follow-up duration that improves patient compliance, treatment satisfaction, and costs. It is also more effective for patients with moderately high initial β-hCG levels up to 5500 mIU/mL. Randomized trials with adequate power to compare the 2 regimens on a selected population at potential risk of methotrexate failure, such as those with a high β-hCG level and/or large gestational mass, are recommended in order to establish an effective management protocol for these patients.

Conflict of interest

The authors have no conflicts of interest.

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