Safety and efficacy of systemic methotrexate in the treatment of unruptured tubal pregnancy

Khaled B. Soliman, MD, Nisreen M. Saleh, MD, Allaa A. Omran, MD.

ABSTRACT

Objectives: To evaluate the safety and efficacy of single dose intramuscular methotrexate (MXT) as a treatment option for early unruptured ectopic pregnancies, and to compare the results with those of previously published studies.

Methods: We performed a prospective study on 30 patients with small unruptured ectopic pregnancies treated with a single dose of MXT therapy in the Department of Obstetrics and Gynecology, Maternity and Children Hospital, Buraidah, Qassim, Kingdom of Saudi Arabia from January 2002 to June 2004.

Results: The mean pretreatment level of β-human chorionic gonadotropin (β-hCG) was 2209 ± 1381 mIU/ml. Only 22 women (73.3%) were successfully treated with a single dose of MXT. Five women required a second injection, and one woman required a third dose.

The combined success rate for medical management of ectopic pregnancy with 1-3 doses of MXT was 86.7% (26 women). Pretreatment β-hCG levels were significantly lower in women who responded to single dose therapy than in those who required either multiple doses or who had failure of medical management ($p<0.001$). The mean time to resolution of β-hCG was 32.5 ± 17 days. Higher pretreatment levels correlated with longer resolution time ($p<0.001$). Four women (13.3%) had a failure of medical management and required surgery.

Conclusion: In our series, MXT was successful in 26 women (86.7%). Women with a pretreatment β-hCG level of 3000-4000 mIU/ml had a greater probability of requiring either surgical intervention or multiple doses of MXT. The potential for emergency surgery remains an important risk.

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Methotrexate (MXT), a well-known chemotherapeutic agent, is particularly effective against trophoblastic tumors. In 1982, Tanaka et al[1] published the first use of MXT for the treatment of an ectopic pregnancy. Since that report the use of MXT for ectopic pregnancy has been widely described in the literature as an effective treatment for tubal, ovarian, and cervical pregnancies.[2] Also, MXT has been used successfully, to treat selected patients with early ectopic pregnancies when given systemically,[3] or locally.[4] With the advent of sensitive tests for human chorionic gonadotropin (β-hCG), high resolution ultrasonography, laparoscopy, and office curettage, physicians have been able to diagnose early ectopic pregnancies. Stovall and Ling,[5] have reported a high success rate, for patients who were treated with a single dose of intramuscular MXT at 1 mg/kg or 50 mg/m^2. A single-dose MXT treatment proved to be effective as multidose therapy for treatment of unruptured ectopic pregnancy.[6] Medical treatment with systemic MXT is an alternative treatment option but only in hemodynamically stable women with an unruptured tubal pregnancy and no signs of active bleeding, presenting with low serum β-hCG concentrations

From the Department of Obstetrics and Gynecology, Maternity and Children Hospital, Qassim, *Kingdom of Saudi Arabia*.

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Address correspondence and reprint request to: Dr. Khaled B. Soliman, Department of Obstetrics and Gynecology, King Abdul-Aziz Specialist Hospital, PO 10127, Taif, *Kingdom of Saudi Arabia*. Tel. +966 508219100. Fax. +966 (2) 7310801. E-mail: khaled_b_s@yahoo.com

and in the absence of cardiac activity.[7] Medical management plays an increasing role in ectopic pregnancy, but patient compliance is essential,[8] it avoids the inherent morbidity of anesthesia and surgery and is cost-effective.[9] Overall, the treatment of a woman with a small unruptured ectopic pregnancy with intramuscular MXT is successful and associated with only minor side effects.[7] It offers success rates comparable to surgical management, with no loss in future potential fertility.[10] With increasing experience and success using MXT to treat ectopic pregnancy, conservative medical treatment is gaining more popularity.[11]

The purpose of this study was to prospectively evaluate the safety and efficacy of single dose intramuscular MXT, and to investigate the need to receive second or multiple doses, as a treatment option for early, unruptured ectopic pregnancies in a tertiary teaching hospital.

Methods. This prospective study was conducted in the Department of Obstetrics and Gynecology of the Maternity and Children Hospital, a tertiary referral hospital, Buraidah, Qassim, Kingdom of Saudi Arabia. Between January 2002 and June 2004, 30 women with an early, unruptured ectopic pregnancy, either referred directly or attended the Emergency Unit, were prospectively enrolled in the study. All subjects gave informed written consent to participate in the study. Diagnosis of ectopic pregnancy was based on: 1. thorough history taking including obstetric history, especially last menstrual period (LMP), reproductive and surgical history; 2. physical examination; 3. quantitative serum level of β-hCG measurement; 4. absence of intrauterine gestational sac, or presence of any adnexal mass by transvaginal ultrasonography (TVS).[12] Patients with a serum β-hCG level of ≥2000 mIU/ml, and no intrauterine sac seen by ultrasonography, did not have a curettage. This diagnostic method for ectopic pregnancy avoids any intervention in a viable pregnancy and has a sensitivity of 100%.[5] In cases of suspected ectopic pregnancy, patients were counseled and an informed consent for MXT treatment was obtained. This treatment policy was approved by the hospital ethical committee.

The inclusion criteria for medical treatment were: 1. progressing, unruptured ectopic pregnancy (of any dimension ≤4 cm, by TVS); 2. β-hCG level ≥2000 or ≤4,000 mIU/ml; and 3. stable hemodynamic condition.[7,11,13] The exclusion criteria were: 1. β-hCG level ≤2000 or ≥4000 mIU/ml; 2. an embryo with cardiac activity; 3. disturbances in hepatic (aspartate aminotransferase level more than twice the normal level) or renal function (serum creatinine value >1.5 mg/dL), leucopenia (<2000/cm^3), thrombocytopenia (<100,000/cm^3); or 4. if the patient cannot comply with treatment.

Medical treatment only began after the progress of the ectopic pregnancy was verified (increase in the serum β-hCG level after 48 hours). Patients were considered candidates for MXT if hemodynamically stable, did not desire surgical therapy and agreed to appropriate follow up.[14] The medical treatment consisted of 50 mg/m^2 of methotrexate injected intramuscularly on the basis of actual body weight. This day was considered as day one. Serum β-hCG levels were repeated on days 4 and 7. If β-hCG levels failed to decline by 15% between days 4 and 7, a second dose of MXT was administered. If β-hCG levels fell by 15%, levels were followed up weekly. Failure of β-hCG levels to fall by 15% on each successive week also resulted in repeat dosing of MXT. If repeat dosing of MXT was performed, the protocol was restarted with a new day one. All patients were followed with serial TVS and an additional ultrasonography was carried out if severe abdominal pain occured.[7,14] A sample for serum β-hCG measurement and complete blood cell count was drawn from each patient on days one, 4, 7, 10, and then weekly. Measurement of blood urea nitrogen, creatinine, and aspartate aminotransferase were carried out on day 7.[15] Laparoscopic treatment was indicated if β-hCG level had not decreased sufficiently by day 14 (<15% of the day 7 level) or had begun to increase and at any point in case of pelvic pain was not manageable by non-opiate analgesics or signs of internal hemorrhage (acute drop in blood pressure, anemia, or hemoperitoneum visible on ultrasonography).[5]

The protocol for monitoring patients required: 1. checking for clinical signs of hemoperitoneum; 2. performing ultrasonography (fluid in the pouch of Douglas); and 3. monitoring the quantitative serum β-hCG levels.

The MXT toxicity was evaluated by clinical surveillance (checking for signs of gastritis, stomatitis, headaches, nausea, and vomiting), and additional laboratory tests (blood count, with platelets, alanine aminotransferase, and aspartate aminotransferase). Patients with favorable results were then monitored by weekly repetition of the clinical, laboratory, and ultrasonographic tests until the β-hCG levels were resolved (<10 mIU/ml).[14] Methotrexate success is defined as successful resolution of the ectopic pregnancy, without surgery, regardless of how many doses of MXT were administered. Conversely, MXT failure is defined as abandonment of medical treatment in favor of surgical management. Time to

complete resolution was defined as the number of days from the initiation of treatment to a β-hCG level <10 mIU/ml.[15,16]

Statistical analysis. Collection of data included patient demographics, vaginal ultrasonographic findings, pretreatment and post-treatment β-hCG levels, the number of MXT doses administered, need of surgery, operative findings and occurrence of any MXT side effects were also noted. Data entry and analysis were carried out using the Statistical Package for Social Sciences version 10 software package. The level of significant was set at $p<0.05$.

Results. The 30 women included in this study who received MXT as a primary treatment for ectopic pregnancy had a mean age of 27.1 ± 5.6 years (range 16-41years). Thirty percent was primigravida (range 0-8). The estimated mean gestational age was 56.8 ± 11.7 days (range 32-77 days). Pretreatment β-hCG levels ranged from 2109-3570 mIU/ml and a mean of 2209 ± 1381 mIU/ml. The diagnosis of an ectopic pregnancy was established for all women, who had abnormal β-hCG levels ≥2000 mIU/ml with no identifiable intrauterine pregnancy by TVS. The presence of an ectopic gestational sac or an adnexal mass was demonstrated by TVS in 23 of 30 women (76.7%). None of them had fetal cardiac activity identified in the adnexa. Twenty-six (86.7%) women were successfully treated by MXT therapy and 4 (13.3%) treated surgically (**Table 1**).

Table 1 - Clinical data of the studied women with early ectopic pregnancies treated with methotrexate (N=30).

Characteristics	Number of patients (%)
Gestational age (days, mean ± SD)	56.8 ± 11.7
Clinical symptoms	
None	3
Abdominal pain	9
Vaginal bleeding	7
Abdominal pain and vaginal bleeding	11
Admission ultrasound findings	
Adnexal mass on ultrasound scan	23 (76.7)
Free fluid on ultrasound scan	18 (60)
Laboratory parameters	
Mean pretreatment β-hCG	2209 ± 1381 mIU/ml.
15% fall of β-hCG day 4	22 (73.3)
Treatment outcome	
Success	26 (86.7)
Failure	4 (13.3)
Appropriate follow up	28 (93.3)
Days to resolution (mean ± SD)	32.5 ± 17
Third dose methotrexate	1 (3.3)
Underwent surgery	4 (13.3)

β-hCG - beta-human chorionic gonadotropin

Table 2 - Pretreatment level of β-hCG levels between women treated with one and multiple doses of methotrexate.

Pretreatment β-hCG levels (mIU/ml)	One dose of MTX (N=24/30)	Two and 3 doses of MTX (N=6/30)	Significance
Mean ± SD	2105.3 ± 920	3882 ± 3221	$p<0.001$
Median	2039	3538	

MXT - methotrexate, β-hCG - beta-human chorionic gonadotropin.

Of the 30 patients treated with MXT, 24 women (80%) received one dose of MXT, 5 women (16.7%) received a second dose and one (3.3%) woman required a third dose. Complete resolution was achieved in 22 out of 24 women who received one dose of MXT, 3 out of 5 women who had a second dose of MXT and also, for the only patient who required a third dose. The additional doses of MXT were all administered according to the guidelines of Stovall et al.[12] Three out of the 5 patients required a second dose at the end of the first week of therapy, one woman received the second injection at the end of the second week and one at the beginning of the third week. One woman received a third dose at the beginning of the fourth week (**Table 1**).

Table 2 shows that women who required additional doses of MXT had significantly higher pretreatment β-hCG levels than women who responded to a single dose therapy ($p<0.001$). Four out of 30 women (13.3%) required surgical treatment for ectopic pregnancy either due to occurrence of severe abdominal pain or the presence of a significant amount of free fluid in pouch of Douglas seen by ultrasonography. Characteristics of these patients are shown in (**Table 3**). One woman was operated on the fourth day after the first MXT injection, one at the end of the first week and 2 at the end of the second week. Pretreatment serum β-hCG levels were significantly higher in women who required surgical intervention than in those who successfully responded to medical therapy ($p<0.001$). Other reported side effects included 3 patients who had mild pelvic pain with mild nausea and dehydration that required intravenous therapy and analgesia but did not have surgery. One had mild attack of diarrhea and dizziness who was evaluated and treated conservatively.

Discussion. Our data support the use of systemic MXT in the treatment of an early and unruptured ectopic pregnancy. A comparison of our results with those reported by Catherine et al,[17] Stovall and Ling[5] and Glock et al[18] show that there are no statistical

Table 3 - Details of patients who had a failure of medical treatment and required surgery.

Patient	Doses of MTX	Preoperative β-hCG (mIU/ml)	Adnexal mass (cm)	Clinical presentation	Procedure
1	1	2914	3.5 × 3.4	Acute, severe abdominal pain; large amount of free fluid on US	Laparoscopic salpingectomy
2	1	3107	3.4 × 3.6	Sudden, severe abdominal pain; hemodynamically unstable	Laparotomy and salpingectomy
3	2	3972	3.6 × 2.9	Acute abdominal pain	Laparoscopic salpingostomy
4	2	3787	3.3 × 3.6	Acute abdominal pain; free fluid on US	Laparoscopic salpingostomy

β-hCG - beta-human chorionic gonadotropin, US - ultrasound scan, MXT - methotrexate

Table 4 - Comparison of results among 4 studies treated with systemic methotrexate for selected ectopic pregnancies.

Variables	Current study (%)	Catherine et al[17] (%)	Stovall and Ling[5] (%)	Glock et al[18] (%)
No. of women	30	50	120	35
Age (year)	27.1 ± 5.6	32 ± 5.6	26.1 ± 6.2	30.8 ± 0.9
Gravidity	3.9 ± 2.2	2.9 ± 2.0	3.2 ± 1.6	2.5 ± 0.3
Parity	1.4 ± 1.3	0.8 ± 1.3	0.97 ± 1.0	0.5 ± 0.2
β-hCG levels mIU/ml	2209 ± 1381	1896 ± 2399	3950.6 ± 1193	1388.1 ± 464
No. of women with adnexal mass or sac seen with vaginal probe US	23 (76.7)	13 (26)	113 (94.2)	6 (17.1)
No. of women with fetal cardiac activity	0	1 (2)	14 (11.7)	0
No. of women receiving				
1 dose MTX	24 (80)	39 (78)	116 (96.7)	33 (94.3)
2 doses MTX	5 (16.7)	10 (20)	4 (3.3)	2 (5.7)
3 doses MTX	1 (3.3)	1 (2)	0	0
Success rates				
1 dose MTX	22 (73.3)	32 (64)	(1 and 2 doses together)	30 (85.7)
1-3 doses MTX	26 (86.7)	39 (78)	113 (94.2)	(2 doses 0% success)
No. of days until β-hCG resolved, (All doses MTX)	32.5 ± 17	26.9 ± 17	35.5 ± 12	23.1 ± 2.9
No. of women required surgery	4 (13.3)	11 (22)	7 (5.8)	5 (14.3)

β-hCG - beta-human chorionic gonadotropin, US - ultrasound scan , MXT - methotrexate

significant differences regarding age, gravidity or parity between the different studies (**Table 4**). However, when characteristics of the ectopic pregnancies are examined, striking differences became apparent. In the current study, the mean pretreatment β-hCG level (2209.4 ± 1381 mIU/ml) was higher than that reported by Catherine et al[17] (1896 ± 2399 mIU/ml) and Glock et al[18] (1388.1 ± 464 mIU/ml), but less than that noted by Stovall and Ling[5] (3950.5±1193 mIU/ml). The percentage of ectopic adnexal masses visualized by TVS in our population was 76.7% compared to 94.2%.[5] The current study and the study reported by Glock et al[18] had no cases with identifiable fetal cardiac activity (0% versus 11.7%,[5] 2%,[17]), which suggests that the women treated in our study had ectopic pregnancies of a younger gestational age than those treated by Stovall and Ling[5] and Catherine et al.[17]

Our study population had an overall success rate of (86.7%), which is almost equal to that reported by Glock et al[18] (85.7%) compared to Catherine et al[17] (78%), Stovall and Ling[5] (94.2%) and Kumtepe and Kadanali[19] (81%) and a higher incidence of women requiring additional doses of MXT (20%) in

comparison with that reported by Stovall and Ling[5] (3%), Glock et al[18] (5.7%), while it was lower than reported by Catherine et al[17](22%). Banhart et al,[20] in a meta analysis of MXT therapy, reported 20 studies, which examined the single dose regimen, and 6 examined multidose regimen. They reported a crude overall success rate of 88%, for single dose regimen compared with multidose regimen 93%. They also concluded that MXT regardless of the regimen, had an overall 89% crude success rate.

Three out of 5 women who required 2 doses, and also the one who received a third dose of MXT achieved complete resolution without surgery. Kurt et al[7] reported that some patients need to receive more than one dose of MXT in order to maximize the success rates. They concluded that the optimal treatment dosing for MXT has not yet been elucidated, but are more than one dose and not more than 4 doses. In our study, pretreatment β–hCG levels in women who required 2 or 3 doses of MXT were significantly higher than those women who responded to a single injection (**Table 2**). In addition, an even greater significant difference was observed when pretreatment β-hCG levels, in women who successfully responded to single dose therapy, were compared with levels in women who either failed to medical management or required additional doses (**Table 3**). This result agreed with that reported by Lipscomp et al[21] who concluded that the lower the β–hCG levels at initiation of treatment, the higher the success rate of MXT therapy. Also, it agreed with the report of Dudley et al[22] who reported that the increase in β-hCG before and after MXT administration was positively associated with tubal rupture and it can be used as predictor factors. The successful response to single dose therapy appeared to correlate with the absolute β–hCG level. Our study, as well as Catherine et al[17] and Glock et al[18] studies, demonstrated a positive correlation between pretreatment β-hCG level and resolution time, with correlation coefficient of ($r=0.83$, $p<0.001$). This correlation is apparent across all 4 studies when the mean values are compared. This correlation is also evident within our study when the mean values are compared between the women who responded successfully to one dose of MXT and those who required 2 or 3 doses for successful therapy. Hung et al[23] concluded that a higher failure rate of medical treatment is associated with a gestational age of ≥9 weeks, a fetal pole >10 mm, the presence of embryonic cardiac activity and a serum β-hCG concentration of ≥10000 mIU. The development of severe abdominal pain associated with significant hemoperitoneum was unpredictable and, in 2 of the women, occurred in the presence of falling β-hCG levels. Stovall and Ling[5] reported that some physicians decide to operate prematurely, physician concern and patient anxiety cannot be discounted in patients with severe abdominal pain. Gary et al[24] stated that with careful selection, the majority of patients with separation pain, even if rebound or free fluid is noted, can be managed successfully without surgery. Kurt et al[7] reported that the etiology of such abdominal pain may be due to abortion of a tubal pregnancy from the fallopian tube or may be directly related to MXT. Interestingly, the presence of side effects is associated with a lower chance of treatment failure. It is possible that the therapeutic window for successful management with MXT is narrow, and some side effects are therefore, to be expected. We believe that pain developing after MXT therapy for ectopic pregnancy should not be the sole indication for surgical intervention, specially if it is mild as 3 patients (10%) had mild abdominal pain, were evaluated and treated conservatively and did not have surgery. Iacob and Bert[25] reported a case of MXT failure, 4 days after treatment with a single dose of MXT as the patient had to undergo tubal surgery in the presence of an acute abdomen and syncope, due to the rarity of bilateral ectopic pregnancy. They concluded that it is difficult to establish an effective dosage of MXT in such rare condition.

The significant difference between the pretreatment β-hCG levels in women who responded to a single dose MXT therapy and those who required 2 or 3 doses suggests that there may be an upper limit of trophoblastic mass that is sensitive to this particular MXT dosage. However, the large overlap in β-hCG ranges between these groups also suggests an unpredictable, idiosyncratic response in cytotoxic sensitivity to a given dose of MXT. Also, interpersonal differences in plasma concentration of MXT and renal clearance may be less important than the differences in delivery of the drug to the ectopic site, and most important, differences in the cellular response to MXT. Schäfer et al[26] has shown that trophoblastic tissue cultures from intrauterine and ectopic pregnancies respond differently to in-vitro exposure to MXT. Ectopic trophoblast required concentrations approximately 10 fold higher to demonstrate the same suppression of β-hCG levels. Methotrexate cytotoxicity and resistance, in general, are not clearly understood. Alterations in cellular response can occur at multiple points: changes in transport in and out of the cell, which affects its intracellular concentration; differences in the binding affinity and intracellular concentration of its target enzyme dihydrofolate reductase; and differences in the production of MXT polyglutamates, which have enhanced cytotoxicity.[27] Additional studies examining the response of ectopic

trophoblast to MXT are needed so that we can better counsel our patients and provide an optimal medical regimen.

In conclusion, in our presented report a single dose of MXT therapy may be an option for some patients with a small unruptured ectopic pregnancy, but more studies are needed to establish the safety and effect on fertility. Selection of women for treatment with a low β-hCG concentration, and the absence of cardiac activity will enhance success. Efficacy of treatment should not be sacrificed for convenience. Counseling and patient desire will ultimately affect choice of protocol. Also needed are more studies to better predict those patients who are likely to have failure of medical treatment.

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