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ORIGINAL ARTICLE

Single-dose methotrexate for ectopic pregnancy treatment: preliminary data

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Abstract. Background and aim of the work: our purpose was to evaluate the efficacy of a single-dose of MTX for ectopic pregnancy treatment in a sample of patients carefully selected according to strict inclusion criteria. Methods: 11 patients that matched the inclusion criteria were enrolled. Results: β-hCG at diagnosis averaged 1349 mIU/ml out of the 11 treated patients, 10 (90%) received a single dose of MTX and had a time of EP resolution averaging 27,3 days. The remaining patient received an additional dose of MTX, equal to the start dose, with a time resolution of 35 days. Conclusions: This study provides evidence of the efficacy of MTX in EP treatment, both as therapy and as a form of clinical management: the successful medical management of EP, defined as β-hCG levels becoming negative after administration of one or more MTX doses, was obtained in all treated cases.

Key words: MTX, ectopic pregnancy, β-hCG levels

Introduction

Ectopic pregnancy (EP) occurs when the embryo fails to implant in its physiological location within the uterine cavity.

The EP rate in industrialized countries has considerably increased over the last few decades, especially in the United States, where the incidence of EP rose from 4.5 per 1,000 pregnancies in 1970 to 19.7 per1000 in 1992 (1). Only one study carried out in Finland actually showed a decreased incidence of EP in the years 1990-95 (2).

Currently, the use of diagnostic algorithms based on a combination of endocrine and sonographic criteria, enables early diagnosis (at the 5th-6th week of gestation) (3) with a high degree of accuracy (>95% of cases), thus making diagnostic laparoscopy increasingly less necessary.

EP management basically follows a three-pronged approach: expectant management awaiting spontaneous resolution, medical treatment, and surgical treatment by laparoscopy or laparotomy. While expectant management can be applied only in few selected cases, which account for a very small proportion of the female population with ectopic pregnancies, medical treatment is now considered a good alternative to surgery.

Several drugs have been suggested in literature for medical treatment. Among them, methotrexate (MTX) systematically administered seems to offer the greatest benefits in terms of efficacy and tolerability. Since it was first used for EP treatment, it has proved to be a good alternative to laparoscopy in selected cases (4).

In particular, a single-dose of 50 mg/mq of MTX given intramuscularly has been associated with a 94% success rate (5).

Table 1. Inclusion criteria and contraindications of MTX treatment

Inclusion criteria	Contraindications
Baseline β-hCG levels of or below 5000 mIU/ml	Presence of embryonic cardiac activity
Pregnancy diameter < 4 cm as demonstrated by ultrasound	Tubal rupture
Increasing β-hCg levels (<50%) after 48 hours from the previous blood test	Hemoperitoneum > 100ml
Hemochrome, platelets, renal function and liver enzymes in the normal range	Ultrasound pregnancy diameter of 4 cm or larger
	Pain lasting for more than 24 hours
	Diagnosis to be confirmed by laparoscopy

The purpose of our study was to evaluate the efficacy of a single-dose of MTX for EP treatment in a sample of patients carefully selected according to strict inclusion criteria.

Materials and methods

All patients admitted to Department of Gynecology, Obstetrics and Neonatology of Parma Univerity with EP diagnosis between Dec.1st 2002 and Apr.30th 2003 were included in the study, provided that they matched all of the following inclusion criteria: 1) baseline β-hCG levels of or below 5,000 mIU/ml; 2) pregnancy diameter <4 cm as demonstrated by ultrasound; 3) increasing β-hCG levels (<50%) after 48 hours from the previous blood test; and, 4) count blood cells, platelets, renal function, and liver enzymes in the normal range. All patients gave their informed consent before beginning the study.(Table 1)

Exclusion criteria were: 1) presence of embryonic cardiac activity; 2) tubal rupture; 3) hemoperitoneum >100 ml; 4) ultrasound pregnancy diameter of 4 cm or larger; 5) pain lasting for more than 24 hours; and, 6) diagnosis to be confirmed by laparoscopy (Table 1).

The clinical features of patients, and especially any risk factors for EP, are summarized in Table 2. The ultrasound examination was performed using a 7.5-MHz transvaginal probe (Astro-Esaote Genoa).

The patients received a regimen which included the following tests and administration schedules: Day 0, uranalysis and blood tests (β-hCG, count blood cells, serum transaminase activity, uremia, blood creatinine, blood group and RH factor); Day 1, β-hCG test and administration of MTX i.m. in a single dose of 50 mg/m^2; Days 4 and 7, β-hCG tests.

If the β-hCG level on Day 7 was at least 15% lower than that on Day 4, the patients were singled out for biochemical follow-up.

If the β-hCG level on Day 7 was the same as or higher than that on Day 4, the patients received a second 50 mg/m^2 dose of MTX. Repeated MTX administration at the starting dose was considered also for patients whose β-hCG levels remained steady or increased during the follow-up period.

Follow-up β-hCG tests were performed weekly until they were negative (with a value of ≤ 5 mIU/ml).

Single-dose MTX treatment was considered successful when β-hCG levels decreased until they became negative without further administration of MTX doses and without surgery.

Moreover, the medical management of EP was considered successful when β-hCG levels became negative following the administration of one or more MTX doses (6).

The toxicity of MTX treatment was also evaluated considering the rate of treatment-induced complications that required hospitalization.

Finally, the time to EP resolution was also considered, which was defined as the total number of days from the beginning of the treatment until β-hCG levels became negative.

Table 2. Patients' clinical features

Median age	28,2
Parity	
Parous 0/0/0/0 (n; %)	3
Nonparous (n; %)	3
Primiparous (n; %)	5
Median gestational age at diagnosis	4,7 weeks

Results

During this period, 11 patients with EP and matching the inclusion criteria of our study were treated with MTX.

The clinical features of the patients included in the study are summarized in Table 2. Mean gestational age at EP diagnosis was 6 weeks ± 3 days.

In all patients, ultrasound imaging suggested EP with an average pregnancy diameter smaller than or equal to 3.5 cm. A yolk sac was visible in four cases. No embryonic cardiac activity was detected in any of the patients.

β-hCG levels at diagnosis averaged 1,349 mIU/ml (range, 419-2,979 mIU/ml), mean 768.5 mIU/ml (Table 3).

β-hCG levels, measured on Day 4 and on Day 7, averaged 1446.9 mIU/ml (range, 231-4,128 mIU/ml) and 930 mIU/ml (range, 67-3,974 mIU/ml), respectively, as shown in Table 3. On Day 4, the β-hCG titer was usually elevated, probably as a result of trophoblastic tissue breakdown releasing a huge amount of the hormone into the bloodstream (7).

Out of the 11 treated patients treated, 10 (90%) received a single dose of MTX and had a time of EP resolution averaging 27.3 days (range, 21-35 days); the remaining patient (10%) – who showed steady β-hCG levels throughout the follow-up period – received an additional dose of MTX equal to the starting dose and had a time of EP resolution averaging 35 days. In this patient, β-hCG levels at diagnosis were on average 2,353 mIU/ml – higher than the average levels (1,161 mIU/ml) in patients receiving a single MTX dose (Table 4).

Table 3. Mean β-hCG levels.

Time	Mean β-hCG levels mUI/ml	Range
Diagnosis	1349	419-2979
4° day	1446,9	231-4128
7° day	930	67-3974

Table 4. Treatment's features

Number of patients	Number of MTX doses	β-hCG levels at diagnosis	Time of resolution (days)
36 (90%)	1	1161	27,3
4 (10%)	2	2353	35

The medical treatment with a single-dose of MTX was successful in 10 patients (90%) – success being defined as a decrease in β-hCG levels until they became negative without additional MTX doses and without surgery. The successful medical management of EP, defined as β-hCG levels becoming negative after administration of one or more MTX doses, was obtained in all treated cases, with a 100% success rate.

Four patients (40%) were hospitalized for pelvic pain occurring two days after treatment. The pain in these patients regressed without surgery. One patient developed a mild rash in light-exposed skin areas. No patient reported gastrointestinal side effects. Two patients had a term pregnancy and one of them had a previous monolateral adnexal excision.

Discussion

A review of the studies published so far on single- vs multidose MTX (8) treatment for EP shows a success rate of 89%. Single-dose methotrexate appears to be effective as published multidose regimen with advantages of requiring less methotrexate, not requiring citrovorum recovery, reducing patient hospitalization, and offering more patient acceptance of this form of treatment. The present study, seems offer further data in favour of this schedule of treatment; moreover the success rate is 100%. This might be explained by the very low average serum concentrations of hCG at the time of the treatment were very low in our patients (1349 mIU/ml) –lower than the average hCG concentrations reported in literature Moreover, the detection of embryonic cardiac activity, which seems to be an additional factor of medical treatment failure, was among the exclusion criteria of our study, thus implying a further selection of patients.

The single most important factor in determining the success of treatment, or when multidose MTX needs to be administered instead of single-dose, might be the hCG blood concentration at the time of diagnosis. Particulary, treatment success is inversely correlated to hCG concentrations.

In patients with average β-hCG concentrations of 1,161 mIU/ml at diagnosis, a single dose of MTX was enough and the average time EP resolution was 27.3 days.

In patients with more elevated average β-hCG concentrations at diagnosis (2,353 mIU/ml), two identical doses of MTX were necessary and the average time EP resolution was 35 days. Thanks to improved diagnostics, such as more rapid and sensitive β-hCG assays and transvaginal ultrasound, early detection of EP is possible today.

The medical management by MTX seems to offer several benefits over surgical treatment: it is less invasive, less expensive and can be given on an out-patient basis.

Finally, this study provides further evidence of the efficacy of MTX in EP treatment, both as therapy and as a form of clinical management. The results of our study also seem to suggest that further studies on larger case series might lead to identification of a β-hCG cut-off value at diagnosis, above and below which single- or multidose MTX regimens should be respectively. Recommended.

References

1. From the Centers for Disease Control and Prevention. Ectopic pregnancy-United States, 1990-1992. *JAMA* 1995; 273: 533-3.
2. Mäkinen J. Ectopic pregnancy falls in Finland. *Lancet* 1996; 340: 129-30.
3. Pisarska MD, Carson SA, Buster JE. Ectopic pregnancy. *Lancet* 1998; 351: 1115-20.
4. Tanaka T, Hayashi H, Fujimoto S, Ichinoe K. Treatment of interstitial ectopic pregnancy with methotrexate: report of a successful case. *Fertil Steril* 1982; 37: 851-2.
5. Stovall TG, Ling FW. Single-dose methotrexate: an expanded clinical trial. *Am J Obstet Gynecol* 1993; 168: 1759-65.
6. Stika CS, Anderson L, Frederiksen MC. Single-dose methotrexate for the treatment of ectopic pregnancy: Northwestern Memorial Hospital three-year experience. *Am J Obstet Gynecol* 1996; 174: 1840-6.
7. Pescetto G, De Cecco L, Pecorari D, Ragni N. *Ginecologia e Ostetricia* 2001; 2: 1777-82.
8. Barnhart K.T., 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.

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