

TREATMENT OF ECTOPIC PREGNANCY WITH METHOTREXATE

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SUMMARY – The aim of the present study was to analyze retrospectively the safety and success rates of single- and two-dose methotrexate (MTX) protocols for the treatment of hemodynamically stable cases of ectopic pregnancy at University Department of Gynecology and Obstetrics, Zagreb University Hospital Center, during a five-year period. The study evaluated MTX treatment efficacy in 35 women with ectopic pregnancies in relation to the initial levels of human chorionic gonadotropin (hCG) and progesterone. Successful treatment was recorded in 32/35 women, 24/25 on single dose MTX and 8/10 on double dose MTX, whereas 3/35 patients underwent laparoscopy. The mean initial hCG level in all 35 patients on day 0 was 657.54 ± 592.4 IU/L; 572.99 ± 488.10 IU/L in those successfully treated with MTX and 1560.30 ± 890.70 IU/L in those requiring additional laparoscopy ($p < 0.005$). The mean initial hCG level was 393.10 ± 305.9 IU/L in patients successfully treated with a single dose of MTX and 973.5 ± 722.40 IU/L in those with an additional dose of MTX ($p < 0.002$). The mean initial progesterone level was 16.36 ± 10.70 nmol/L in 35 MTX-treated ectopic pregnancy patients, 13.64 ± 8.89 nmol/L in those with treatment success and 28.45 ± 11.32 nmol/L in cases of treatment failure ($p < 0.05$). The mean level of progesterone on day 0 was 12.74 ± 8.30 nmol/L in patients successfully treated with a single dose of MTX and 26.10 ± 18.80 nmol/L in patients treated with double-dose MTX ($p < 0.006$). It is concluded that pretreatment values of hCG and progesterone are inversely related to medicamentous treatment success in selected cases of hemodynamically stable patients, thus they may be used as an important predictor in the management of ectopic pregnancy treated with MTX.

Key words: *Ectopic pregnancy – medical treatment; Single- and multiple-dose methotrexate – efficacy; Prediction – human chorionic gonadotropin and progesterone*

Introduction

The prevalence of ectopic pregnancy (EP) continues to rise because of the increasing incidence of risk factors and better diagnostic tools¹. Recently, the overall rate of EP among women aged 15-44 was 0.64% and no increasing or decreasing trend has been found.

However, the incidence of EP increased with age, from 0.3% among women aged 15-19 to 1% among women aged 35-44². Due to the availability of expedient serum human chorionic gonadotropin (hCG) assay at most early pregnancy assessment units, EP can now be diagnosed early. Diagnostic capabilities of ultrasound technology to confirm an EP are well founded. Particularly the introduction of high-resolution transvaginal probes has been the driving force behind the revolutionary change towards conservative management strategies in EP care³. Transvaginal ultrasound and assessment of the whole pelvis, even in

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the presence of intrauterine pregnancy, can be an important aid in the diagnosis of heterotopic pregnancy⁴. Surgical treatment of EP is the mainstay of management, and laparoscopic surgery is currently the 'gold standard' because of a higher subsequent intrauterine pregnancy rate after salpingotomy compared with salpingectomy^{5,6}.

Medical treatment with several agents including methotrexate (MTX), hyperosmolar glucose, potassium chloride, prostaglandin F2 alpha, estradiol and trichosanthin has been the subject of numerous trials⁷. It has an established place in the treatment of smaller unruptured EP where tubal integrity is usually preserved, and in selected patients it appears to be as effective as surgery. It is clear, however, that many women with EP are not suitable for medical therapy and recent studies have investigated the possible ways of improving the efficacy of medical therapy and better predicting of cases where medical treatment will be successful⁸. MTX is a folic acid antagonist that binds to the enzyme dihydrofolate reductase, which is involved in the synthesis of purine nucleotides. It is ideally suited for inhibition of rapidly growing cells such as trophoblast. MTX is commonly used as the first-line agent in the treatment of newly diagnosed EP, as it is most thoroughly studied and established for clinical use. MTX can be administered systemically (intramuscular and intravenous injections), orally or by local injection under ultrasound or laparoscopic guidance. Contrary to the multiple-dose schedules that were prevalent in older studies, recent studies used more unified, single-dose MTX⁹. In women with EP, who are hemodynamically stable and wishing to preserve their fertility, medical treatment with single dose MTX tends to be equal to the treatment with laparoscopic surgery regarding success rate, complications, and subsequent fertility. It seems to be a viable alternative to laparoscopic salpingotomy for a selected group of patients with EP¹⁰.

The aim of this study was to assess the initial cut-off values of hCG and progesterone as a predictor of the efficacy of MTX treatment in a single or repeated doses in selected cases of EP.

Patients and Methods

Cases of hemodynamically stable EP were identified retrospectively at University Department of Gy-

necology and Obstetrics, Zagreb University Hospital Center, during a five-year period (2006-2010). Clinical, office and hospital records were reviewed in detail to identify these patients. EP was diagnosed with a non-laparoscopic algorithm combining quantitative hCG and progesterone serum levels, transvaginal sonogram (no intrauterine gestational sac) and curettage (no trophoblastic villi). Total serum hCG and progesterone concentrations were determined by chemiluminescent immunometric assays using hCG-Vitros and progesterone-Vitros, respectively (Ortho Clinical Diagnostics, Johnson&Johnson, USA). Patients with serum hCG level <2000 IU/L and persistently abnormal increase of hCG (<50% increase in 48 hours) underwent curettage. The exclusion criteria were an hCG level >10,000 IU/L, an embryo with cardiac activity, the presence of a yolk sac, adnexal mass >3.5-4 cm in greatest dimension, disturbances in hepatic (aspartate aminotransferase level more than twice the normal level) or renal (serum creatinine value >1.5 mg/dL) function, leukopenia (<2000 cm³), thrombocytopenia (<100,000/cm³), or the patient's inability to comply with treatment protocol. More than 100 of our patients were excluded from the study according to the exclusion criteria. Medical treatment consisted of 50 mg/m² of MTX injected intramuscularly after obtaining the patient's consent. A second identical dose of MTX was administered on day 7 if the hCG level between day 4 and 7 either fell <15% or continued to increase. Patients with favorable results were monitored by weekly repetition of the clinical, laboratory, and ultrasonographic tests until hCG resolution, and adverse effects. Outcome criteria for the failure

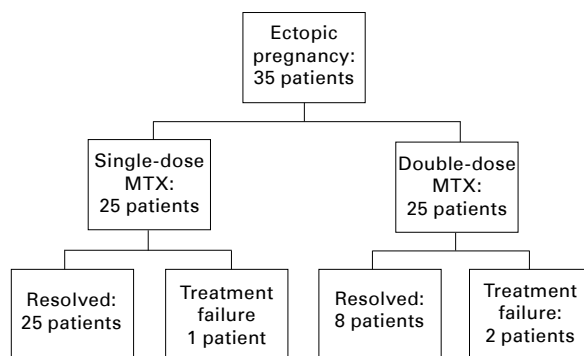


Fig. 1. Outcome of ectopic pregnancy patients treated with methotrexate (MTX)

Table 1. Mean initial hormone levels in ectopic pregnancy patients treated with methotrexate

Hormone	Study patients (n=35)	Treatment success (n=32)	Treatment failure (n=3)
hCG (IU/L)	657.54±592.40	572.99±488.10	1560.30±890.70
Progesterone (nmol/L)	16.36±10.70	13.64±8.89	28.45±11.32

hCG = human chorionic gonadotropin

rate included the need for a second dose of MTX, the time to hCG resolution, adverse effects, and surgical intervention. Laparoscopic treatment was indicated if the hCG level had not decreased sufficiently by day 14 (<15% of day 7 level) or had begun to increase at any point, in case of pelvic pain not manageable by non-opiate analgesics, or signs of internal hemorrhage.

Data were analyzed using SPSS ver. 17.0. Values are given as percentage or mean ± SD, unless otherwise indicated. Statistical comparison and analysis of hormonal levels and efficacy of treatment were done by using one-way ANOVA, two-tailed t-test or χ^2 -test when appropriate. Post-hoc tests of ANOVA were used to determine the specific groups that were significantly different from each other. The level of significance was set at $p < 0.05$.

Results

A total of 35 ectopic gestations treated with MTX were identified retrospectively during the five-year period. The overall successful rate of 91.43% was recorded in 32/35 MTX-treated ectopic pregnancies; 24/25 in the single dose group and 8/10 in the group requiring an additional dose of MTX. The treatment

was considered unsuccessful in 3/35 women administered MTX, who had to undergo laparoscopic surgery for pain or suspected rupture, or if the patient declined to continue the treatment protocol (Fig. 1).

The mean initial hCG level of all the 35 patients on day 0 was 657.54±592.4 IU/L; 572.99±488.10 IU/L in those successfully treated with MTX and 1560.30±890.70 IU/L in those requiring additional laparoscopy ($p < 0.005$). The mean initial progesterone level was 16.36±10.70 nmol/L in the 35 MTX-treated ectopic pregnancies; 13.64±8.89 IU/L in those with treatment success and 28.45±11.32 IU/L in cases of treatment failure ($p < 0.05$) (Table 1).

In 32/35 successfully treated patients with MTX, the mean initial hCG level was 393.10±305.9 IU/L in 24/32 patients treated with a single dose and 973.5±722.40 IU/L in 8/32 patients treated with an additional dose of MTX ($p < 0.002$). The mean hCG level in patients treated with a single dose of MTX on days 0 and 7 was lower (476.56±410.28 *vs.* 176.32±102.78 IU/L) compared with patients treated with 2 doses of MTX (1101.810.70 *vs.* 363.33±184.70 IU/L) ($p < 0.05$ *vs.* $p < 0.0005$). The mean initial progesterone level in patients treated with a single dose and two doses of MTX was 13.10±9.20 nmol/L and 26.10±18.80 nmol/L, re-

Table 2. Efficacy of medical treatment of ectopic pregnancy in relation to hormone levels

Methotrexate	Single dose	Double dose	* p value
Initial hCG	476.56±410.28	1101±810.7	0.0046
hCG (day 7)	176.32±102.78	363.33±184.7	0.0005
Initial hCG level in successful treatment	393.1±305.9	973.5±722.4	0.0019
Initial hCG level in treatment failure	1831±980.9	2213.5±1826.5	0.2922
Initial progesterone	13.1±9.2	26.1±18.8	0.0093
Progesterone (day 7)	7.8±1.6	15.1±4.8	0.0001
Progesterone level in successful treatment (day 0)	12.74±8.3	26.1±18.8	0.0058
Surgical treatment (laparoscopy)	1 (4%)	2 (20%)	0.7435**

*two-tailed t-test; ** χ^2 -test; hCG = human chorionic gonadotropin

spectively ($p < 0.009$). In patients successfully treated with a single dose and two doses of MTX, the mean level of progesterone on day 0 was 12.74 ± 8.30 nmol/L and 26.10 ± 18.80 nmol/L, respectively ($p < 0.006$). The mean progesterone level on day 7 in patients treated with a single dose and two doses of MTX was 7.80 ± 1.60 IU/L and 15.10 ± 4.80 nmol/L, respectively ($p < 0.0001$). The cutoff value of hCG and progesterone for the use of a double dose of MTX was 363.33 IU/L and 15.10 nmol/L, respectively (Table 2).

Discussion

Medical treatment with MTX for extrauterine gestations was initially used in cases of abdominal pregnancy¹¹. Prompt deterioration of the placenta produced by MTX administration may bring about resolution without sequels, whereas surgical manipulation of the placenta has generally resulted in profuse hemorrhage. Similar trials undertaken for cervical and interstitial pregnancies also indicated effectiveness of this therapy¹². The rationale for the use of MTX in these instances was to bring about prompt destruction of placental trophoblastic activity, with the assumption that this would be associated with a concomitant decrease in placental vascularity and thereby marked restriction of the potential of hemorrhagic complications of the retained placenta. MTX therapy for tubal pregnancies has also been based on the expectation of similar effects. The erosive action of trophoblast and the separation of the ovum from the tubal wall may be responsible for bleeding into oviducts and from the fimbriated orifice, which may be filled with clots. Although the causal factors resulting in subsequent tubal pregnancy should be accounted for, it is likely that such bleeding into the oviduct gives rise to either peritubal adhesions or obstruction. This would suggest that MTX administration should be initiated earlier at a stage before the occurrence of bleeding into the oviduct¹³.

MTX therapy for EP of all routes and doses combined has an overall success rate ranging between 73% and 97%^{14,15}. Success rates between a single-dose and two-dose MTX protocols are usually comparable (80.6%–87% *vs.* 89%–90%)^{16,17}. Among predictive factors of failure in the management of EP with MTX is establishing hCG cutoff values in pretreatment and

after one MTX dose, which is the most important predictive variable for treatment success. Successful medical management of EP with MTX is inversely associated with initial hCG level. MTX should not be used to treat EP when initial hCG is > 4000 IU/L. Caution should also be exercised in using MTX for EP when the patient presents with bleeding or pain even without tenderness¹⁸. Recently, several investigators reviewed their experience with MTX and confirmed these findings. The risk of single-dose MTX failure increases significantly in patients with initial hCG levels > 1300 IU/L and/or in women who report having ever used combined oral contraception before pregnancy¹⁹. Results support a substantial increase in failure of medical management with single-dose MTX when the initial hCG is above 5000 mIU/mL and MTX should be used with caution in patients with EP who present with hCG levels above this level²⁰. In a retrospective study of patients with EP who had been treated with single-dose MTX therapy it was evaluated that post-treatment hCG levels decreased between days 0 and 4 in 40% of cases, and 100% of these cases had treatment success. hCG levels increased in 60% of cases, and 61.8% of these cases had treatment success. It seems that decreasing hCG level is highly predictive of treatment success. The hCG difference variable is a reliable predictor of success in cases with rising hCG levels after MTX therapy²¹. In a recent study of women who received MTX for EP, treatment success was defined as a clinically stable patient whose day-7 hCG level decreased by $>$ or $= 50\%$ compared with the day-of-treatment (DOT) beta-hCG. This model was 100% sensitive and 57.4% specific in predicting the need for a second MTX dose in women whose DOT hCG was < 2000 mIU/mL and was 100% sensitive and 37.9% specific in women whose DOT hCG was $>$ or $= 2000$ IU/L. In comparison to the standard MTX monitoring protocol, this model represents an alternative for single-dose MTX in EP²². In a recent study of double- and single-dose MTX protocols for treatment of EP, it was found that double-dose MTX had efficacy and safety (82%) comparable to that of single-dose (88.6%) MTX; it had better success among patients with moderately high hCG and led to a shorter follow up²³. However, in a recent prospective study of patients with EP it was reported that multiple-dose MTX treatment had a low success rate, and that it was

not associated with initial hCG value, but rather to the size of gestational mass before treatment²⁴.

It has been recently demonstrated that the low initial progesterone cutoff values (<10 nmol/L) found in pregnancies of unknown location are at a low risk of requiring medical intervention with MTX, and may benefit from attending routine follow-up visits²⁵. In addition, serum progesterone concentrations were significantly lower (7.93 nmol/L) in patients with EP treated with single-dose MTX than in the failure group (14.53 nmol/L). The recommended critical level of assessing the effect of MTX treatment for EP patients was 11 nmol/L, and the time for serum progesterone to decrease below the normal level was significantly shorter than for hCG. It was concluded that serum progesterone could be used as an index for selecting candidate EP patients for MTX treatment, and also as a good indicator for assessing the therapeutic effect after treatment²⁶.

In our series of 35 ectopic pregnancies, we recorded an overall success rate of 91.43% (32/35) using single-dose MTX in 25 cases and double-dose MTX in 10 cases for the treatment of EP, which is comparable with those reported by other investigators^{13,14}. The relatively high success rate of 96% (24/25) using single-dose MTX in our study could have mainly be ascribed to the significantly lower mean levels of initial hCG (393.1 IU/L) and progesterone (12.74 nmol/L), in comparison to the lower success rate of 80% (8/10) using double-dose MTX and the levels of hCG (973.5 IU/L) ($p < 0.002$) and progesterone (26.1 nmol/L) ($p < 0.006$). These observations are in agreement with the results of the majority of other studies that pretreatment values of hCG and progesterone are inversely related with treatment success and that they are important predictive variables or indicators for EP management with MTX^{18-20,21,25,26}.

In conclusion, medical therapy with MTX has an established place in the treatment of early EP in selected patients with hemodynamic stability and lower initial levels of hCG and progesterone as the most reliable predictors of treatment outcome.

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Sažetak

LIJEČENJE IZVANMATERNIČNE TRUDNOĆE METOTREKSATOM

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Cilj ove studije bio je retrospektivno analizirati uspješnost i pouzdanost liječenja metotreksatom (MTX) kroz protokole pojedinačne i dvostruke doze u slučajevima hemodinamski stabilnih izvanmaterničnih trudnoća u Klinici za ženske bolesti i porode, KBC Zagreb tijekom petogodišnjeg razdoblja. U radu se procjenjivala učinkovitost liječenja 35 izvanmaterničnih trudnoća pomoću MTX u odnosu na početne razine humanog korionskog gonadotropina (hCG) i progesterona. Uspješno liječenje zabilježeno je kod 32/35 žena, od kojih 24/25 uz pojedinačnu dozu, a 8/10 uz dvostruku dozu MTX, dok su 3/35 bolesnica podvrgnute laparoskopiji. Prosječna početna razina hCG nultoga dana u svih 35 bolesnica bila je $657,54 \pm 592,4$ IU/L, $572,99 \pm 488,10$ IU/L kod bolesnica izliječenih pomoću MTX i $1560,30 \pm 890,70$ IU/L kod žena u kojih je bilo potrebno dodatno načiniti laparoskopiju ($p < 0,005$). U bolesnica uspješno liječenih pomoću MTX prosječna početna razina hCG bila je $393,10 \pm 305,9$ IU/L kod žena s pojedinačnom dozom i $973,5 \pm 722,40$ IU/L kod žena s dvostrukom dozom lijeka ($p < 0,002$). Prosječna početna razina progesterona u svih 35 žena liječenih pomoću MTX bila je $16,36 \pm 10,07$ nmol/L, $13,64 \pm 8,89$ nmol/L kod izliječenih žena i $28,45 \pm 11,32$ nmol/L u slučajevima izostanka uspješnosti ($p < 0,05$). Kod bolesnica izliječenih jednom dozom MTX prosječna početna razina progesterona bila je $12,74 \pm 8,30$ nmol/L, a kod onih s dvije doze lijeka $26,10 \pm 18,80$ nmol/L ($p < 0,006$). Može se zaključiti da su početne vrijednosti hCG i progesterona bile obrnuto proporcionalne s uspješnošću medikamentnog liječenja u odabranoj skupini hemodinamski stabilnih bolesnica i da su važni prediktori u liječenju izvanmaternične trudnoće pomoću MTX.

Ključne riječi: Ektopična trudnoća – medikamentno liječenje; Pojedinačne ili višestruke doze metotreksata – učinkovitost; Prognoza – humani korionski gonadotropin i progesteron