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## OBSTETRICS

# Single-Dose Systemic Methotrexate Therapy in Patients with Suspected Ectopic Pregnancy: Two- year Experience

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### ABSTRACT

**Objective** To evaluate the safety and efficacy of single-dose systemic methotrexate in the treatment of ectopic pregnancy.

**Setting** Department of Obstetrics and Gynecology, Nopparat Rajathanee Hospital, Bangkok, Thailand.

**Design** Prospective study.

**Subjects** Thirty-four inpatients with an unruptured ectopic pregnancy who met the criteria for methotrexote therapy, from October 1998 to December 2000.

**Intervention** Single dose of methotrexate 50 mg/m$^2$ intramuscular injection. Blood samples for β-hCG titer were collected weekly until the β-hCG titer became normal (0-10 mIU/ml).

**Results** Patients had a mean age of 26.15±5.73 years, a mean gravidity of 2.06±1.04, and a mean parity of 0.74±0.83. The mean human chorionic gonadotropin titer before treatment initiation was 2990.24±3076.55 mIU/ml. One (2.9%) patient of 34 failed medical therapy and required surgery. One (2.9%) patient required a second methotrexate dose. The mean time to resolution for the 34 subjects successfully treated was 4.32±1.97 weeks. No biochemical or clinical side effect occurred. Post-treatment hysterosalpingograms demonstrated tubal patency on the ipsilateral side in 6 of 7 (85.7%) patients. To date, 5 pregnancies have occurred in this group , all of which were intrauterine.

**Conclusion** Single-dose systemic methotrexate in the treatment of ectopic pregnancy is safe, effective and can preserve reproductive capability when used in carefully selected patients.

**Key words:** ectopic pregnancy, methotrexate

The combination of sensitive human chorionic gonadotropin (hCG) assays and ultrasonography assists in early diagnosis of unruptured ectopic pregnancies. Early diagnosis and treatment may reduce morbidity and mortality and continue fertility. In the past, after laparoscopy confirmed the diagnosis of ectopic pregnancy, patients underwent laparotomy to complete the surgical treatment. Recent modifications in operative laparoscopic instrumentation and technique have permitted the endoscopic approch to ectopic pregnancy, with potential reduction in morbidity and duration of hospitalization.[1]

If the necessity for laparoscopy to diagnose ectopic pregnancy is eliminated, treatment with intramuscular methotrexate can offer the advantages of decreased cost, avoidance of anesthetic and laparoscopic-related morbidity, and less time lost from the patient's daily activities. Variable dose methotrexate for treatment of ectopic pregnancy have been reported.[2,3,4] Stovall et al[4] reported their experience in treatment of ectopic pregnancy with minimally invasive diagnostic techniques combined with a single-dose (50 mg/m$^2$) intramuscular methotrexate treatment protocol. The purpose of this study was to evaluate the safety and efficacy of single-dose intramuscular methotrexate in the treatment of unruptured ectopic pregnancies at Nopparat Rajathanee Hospital.

## Materials and methods

Between October 1, 1998, and December 31, 2000, all patients presenting to the Emergency Department, Nopparat Rajathanee Hospital, and those in the out patient clinics with suspected of ectopic pregnancy underwent a urine pregnancy test. If the results of the urine pregnancy tests were positive, the patients were managed according to their conditions. Patients with signs and symptoms of ruptured ectopic pregnancy who were hemodynamically unstable underwent an emergency laparotomy. If the patients were clinically stable and without signs of hemoperitoneum they were admitted and transabdominal ultrasonography were evaluated to rule out an intrauterine pregnancy and look for pathological signs of ectopic pregnancy. In cases of suspected unruptured ectopic pregnancy, diagnosis were confirmed by transvaginal ultrasonography, then β-hCG (First International Preparation) and serum progesterone were measured. Patients were diagnosed as having an ectopic pregnancy by means of a nonlaparoscopic diagnostic algorithm (Fig.1) that combines the use of serial β-hCG titers, serum progesterone, transvaginal ultrasonography, and endometrial curettage. The sensitivity and specificity of this diagnotic algorithm is well established.[4,5,8,9]

Patients with β-hCG level <2000 mIU/ml and a serum progesterone level <5.0 ng/ml underwent endometrial curettage and were followed according to the diagnostic algorithm. In this situation without histologic evidence of chorionic villi, ectopic pregnancy was considered. Patients with a rising β-hCG titer ≥2000 mIU/ml without an associated intrauterine sac visualized by transvaginal ultrasonography did not require pretreatment curettage.

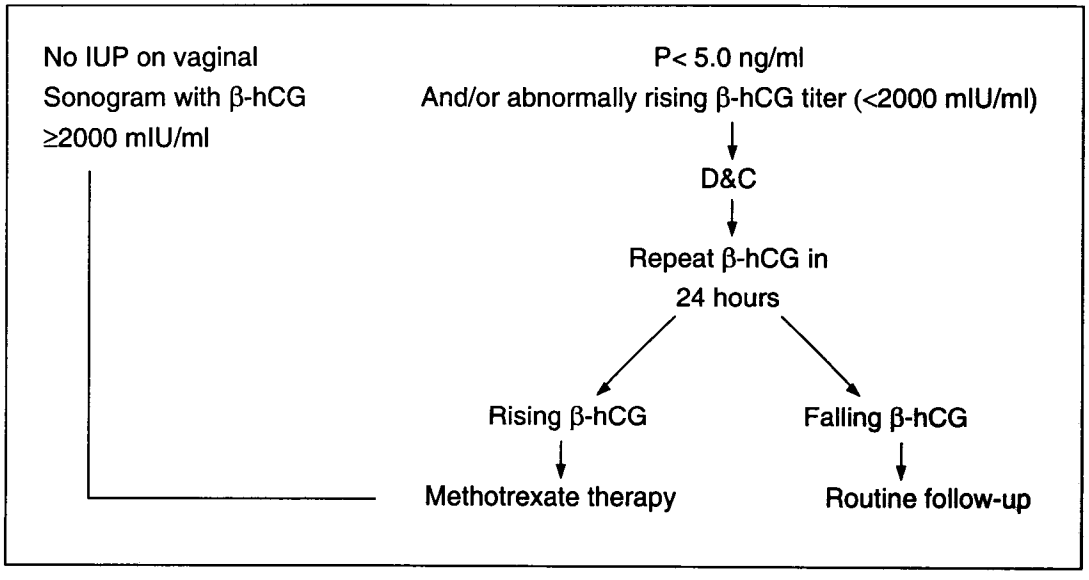


**Fig. 1.** Diagnostic algorithm for ectopic pregnancy.

Inclusion criteria for methotrexate therapy included (1) β-hCG titer ≥2000 mIU/ml with no intrauterine gestational sac detected by transvaginal ultrasonography, (2) the β-hCG titers increased after curettage, if performed, (3) they were hemodynamically stable, (4) transvaginal ultrasonography demonstrated an unruptured ectopic pregnancy ≤3.5 cm in greastest dimension and/or absent of fetal cardiac activity in an extrauterine gestrational sac, (5) β-hCG titer <10000 mIU/ml, (6) no biochemical evidence of hepatic, renal, or hematologic dysfunction, (7) no evidence of HIV infection (8) they signed an informed consent agreement after clearly counselling.

All patients were treated as inpatients with a single-dose intramuscular injection of methotrexate (50 mg/m$^2$). Patients were informed that pelvic discomfort after treatment required re-examination to rule out possible tubal rupture and intra-abdominal hemorrhage. Re-examination included a transvaginal ultrasonography, physical examination, and a CBC. Patients were instructed to abstain from alcohol or intercourse until complete resolution of ectopic pregnancy. Patients were instructed to use oral contraceptive pills for at least 3 months after treatment completion. Serum β-hCG was repeated on days 4 and weekly there after until β-hCG titer <10 mIU/ml. Patient received additional doses of methotrexate if β-hCG levels demonstrated (1) <15% decrease between approximately posttherapy day 4 or (2) a rise or plateauing between subsequent weekly levels.

Two months after complete treatment, 7 patients were allocated for performing a hysterosalpingogram. All patients were contacted by telephone or letter every 6 months to seek information regarding any conception that had occurred after treatment.

**Table 1.** Patient characteristics

| Patient characteristics | Ranges | Mean ± SD |
|---|---|---|
| 1. Age (yr.) | 17-39 | 26.15 ± 5.73 |
| 2. Gravida | 1-5 | 2.06 ± 1.04 |
| 3. Parity | 0-3 | 0.74 ± 0.83 |
| 4. Abortion | 0-2 | 0.32 ± 0.54 |
| 5. Gestational age (day) | 28-107 | 49.06 ± 15.03 |
| 6. Hematocrit (%) | 28-42 | 34.53 ± 3.35 |
| 7. Initial β-hCG (mIU/ml) | 175-9951 | 2990.24 ± 3076.55 |
| 8. β-hCG resolution (wks) | 2-11 | 4.32 ± 1.97 |
| 9. Hospital stay (day) | 2-8 | 3.62 ± 1.58 |

**Table 2.** Initial β-hCG titers

| β-hCG titer (mIU/ml) | Number of patient (%) |
|---|---|
| <1000 | 14 (41.18%) |
| 1000-1999 | 4 (11.77%) |
| 2000-3999 | 5 (14.71%) |
| 4000-5999 | 5 (14.71%) |
| 6000-7999 | 2 (5.88%) |
| 8000-9999 | 4 (11.77%) |
| **Total** | **34 (100%)** |

**Table 3.** Ultrasound findings

| Ultrasound findings | Number of patient (%) |
|---|---|
| 1. Adnexal sac | 1 (2.9%) |
| 2. Adnexal mass | 7 (20.6%) |
| 3. Fluid in cul de sac | 2 (5.9%) |
| 4. Sac with fetal echo and fluid in cul de sac | 2 (5.9%) |
| 5. Adnexal sac and fluid in cul de sac | 2 (5.9%) |
| 6. Adnexal mass and fluid in cul de sac | 20 (58.8%) |
| **Total** | **34 (100%)** |

## Results

During the study period, there were 24,013 deliveries and 248 cases of ectopic pregnancy, giving an overall incidence of 10.33 ectopic pregnancies per 1,000 deliveries. In accordance with protocol, 34 patients (13.71%) were included for medical treatment by intramuscular injection of methotrexate (50 mg/m$^2$), 214 patients (86.29%) were treated surgically. Patients had mean age of 26.15±5.73 years, a mean gravidity of 2.06±1.04 and mean parity of 0.74±0.83 (Table 1). The pretreatment β-hCG titer ranged from 175-9951 mIU/ml (Table 2), with a mean of 2990.24±3076.55 mIU/ml. The mean time to resolution of β- hCG was 4.32±1.97 weeks (range 2-11 weeks). In 18 of 34 (52.94%) patients treated with methotrexate, the diagnosis of ectopic pregnancy was established by rising β-hCG concentration after negative endometrial curettings. Villi was not demonstrated by histologic pathology in all curetting endometrium.

All patients demonstrated the pathologic finding by vaginal ultrasonography (Table 3). Most of them were adnexal masses with fluid in cul de sac. The 34 women treated by methotrexate included 2 patients where transvaginal ultrasonography demonstrated ectopic pregnancy at the cornu, and one of these received a second dose of methotrexate.

Of the 34 patients treated with methotrexate, 33 women (97.1%) were successfully treated with a single dose of methotrexate. Only one women, who's initial hCG titer was 2949 mIU/ml, required surgical intervention. Two patients were rehospitalized because of an increase in abdominal pain. None of these patients had a significant change in hematocrit, and transvaginal ultrasonography did not demonstrate evidence of tubal rupture. The abdominal and pelvic pain in these patients resolved without surgical intervention. There were no biochemical or clinical side effects noted. Hysterosalpingograms were obtained in 7 patients. Tubal patency was demonstrated on the ipsilateral side in 6(85.71%). Five patients had intrauterine pregnancies, 4 patients had delivered of viable infants, and a one has continuing pregnancy.

## Discussion

The ability to diagnose ectopic pregnancy without laparoscopy coupled with single-dose methotrexate appears to be as effective as the previously studied multidose regimen[3,4] but has the advantages of requiring less methotrexate, eliminating side effects, increasing the safety and patient's acceptance, and with less cost. In this study, no side effects were detected in any patient, and abdominal pain was spontaneously resolved without any intervention.

Stovall et al[5] confirmed that most gestational sac were visualized at an β-hCG titer of 1,000 mIU/ml, but all were visualized at a level of ≥2,000 mIU/ml. Some investigators[6,7] reported that the β-hCG level between 1,000-1,500 mIU/ml intrauterine gestational sacs could be detected by using transvaginal ultrasonography. In this study we used the discriminatory β-hCG zone at a level of 2,000 mIU/ml to add a

considerable safety margin. Thus, patients with no evidence of an intrauterine pregnancy and β-hCG level ≥2,000 mIU/ml were given a diagnosis of ectopic pregnancy, and did not require pretreatment curettage. The others had β-hCG level <2,000 mIU/ml and progesterone level <5.0 ng/ml and were given the pretreatment curettage. According to Stovall's algorithm,[8,9] the patients having unchanged or persistently rising β-hCG (24 β-hCG after curettage was performed) were identified as ectopic pregnancies and treated medically.

Some authors[10,11] do not recommend the use of methotrexate when an ectopic pregnancy is associated with a serum β-hCG concentration exceeding 10,000 mIU/ml. The risk of tubal rupture or bleeding in cases of unruptured tubal pregnancy with initial serum β-hCG concentrations >10,000 mIU/ml treated with methotrexate is 32 percent, whereas the risk is only 3 percent when the initial β-hCG concentration is <10,000 mIU/ml. Stovall et al[2] suggested that the presence of fetal cardiac activity is a relative contraindication because the successfull treatment rate was 80 percent. In this study, we recommend surgical intervention for those patients with presence of cardiac activity in the ectopic pregnancy as well as those with greater than 3.5 cm in greatest dimension[2] to improve the safety and efficacy of methotrexate therapy.

Although overall success of treatment, measured as no surgical intervention, was 87-95%,[10] the risk of secondary surgical intervention after methotrexate therapy was related to the initial β-hCG concentration, the method of methotrexate administration, methotrexate dosage and presence of fetal cardiac activity. In this study, with more strict inclusion criteria, 33(97.1%) of the 34 patients were successfully treated, included the one who had cornual pregnancy and required two doses of methotrexate. Tubal patency was found 6 of the 7 (85.71 per cent) patients evaluated, compared with 82.3 per cent reported by Stovall and Ling.[4]

The potential advantages of systemic methotrexate therapy are a completely nonsurgical management of ectopic pregnancy, if no diagnostic laparoscopy is performed to establish the diagnosis, and an improved homolateral tubal patency rate through avoidance of surgical trauma to the tube. However, the clinicain should consider the psychological consequence of methotrexate therapy, especially with patients' health-related quality of life. Methotrexate treated patients had more limitations in physical functioning, role functioning, and social functioning; had worse health perceptions, less energy, more pain, more physical symptoms, and a worse overall quality of life, and were more depressed than surgically treated patients.[12,13]

The results of our study support the use of single-dose methotrexate for treatment of ectopic pregnancy in carefully selected patients. The key to successful medical therapy and improved reproductive outcome is early diagnosis, which is critical to reducing morbidity and mortality and provides the option of using non surgical therapy.

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