Non-Surgical Treatment of Ectopic Pregnancy: Three Years Experience

KHALID H. SAIT MBChB, FRCS(C)
Department of Obstetrics and Gynecology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

ABSTRACT. A retrospective chart review was performed of all patients with intact ectopic pregnancies that were treated initially with methotrexate from January 1999 to December 2001. Fifty patients satisfied the inclusion criteria. The presence of an ectopic gestational sac and/or an adnexal mass consistent with an ectopic pregnancy was demonstrated by vaginal ultrasonography in 30 (60%) of 50 women. Methotrexate was successful in 46 (92%) out of 50 patients. The size of the ectopic mass was lower in the successfully treated women. Logistic regression analysis revealed a size of ectopic mass > 3 cm to be the only factor significantly linked to failure of treatment with methotrexate (p = 0.008). Methotrexate achieved a 92% success rate in selected intact ectopic pregnancies. When the ectopic pregnancy mass was > 3 cm in largest diameter, there was a greater probability of requiring either surgical intervention or a second dose of methotrexate. Eight percent of all patients required emergency surgical intervention after methotrexate treatment. Women with intact ectopic pregnancies selected methotrexate treatment must be counseled about success rate, must undergo serial human chorionic gonadotrophin titers, and must be fully compliant with close monitoring for possible emergency surgical intervention.

Keywords: Ectopic pregnancy, Methotrexate, Human chorionic gonadotrophin.

Introduction

Methotrexate (MTX), a well-known chemotherapeutic agent, is effective against trophoblastic tumors. In 1982 Tanaka et al. published the first use of
methotrexate for treatment of an ectopic pregnancy. Since then numerous studies have refined the recommended regimen for Methotrexate as an alternative treatment of ectopic pregnancy[2-7]. Stovall and Ling[8] had achieved a 92% success rate with a single intramuscular dose of Methotrexate at 50 mg / m² (body surface area) with minimal side effects and few complications. This protocol has been utilized to treat selected patients with intact ectopic pregnancies at Dhahran Health Center, a tertiary referral center for over 250,000 Saudi Aramco employees and their dependants. This study reports on the efficacy and safety of methotrexate treatment of intact ectopic pregnancy in a closely monitored population in the eastern province of Saudi Arabia from January 1999 to December 2001.

**Material and Methods**

During the three years study period, there were a total of 11,206 pregnancies: 9,867 (88%) deliveries, 1,191 (10.6%) abortions, and 148 (1.3%) ectopic pregnancies. Diagnosis of ectopic pregnancy was accepted for inclusion in this study only after satisfying the presence of one of the following inclusion criteria as established by the American College of Obstetricians and Gynecologists (ACOG):

1) The absence of an intrauterine gestational sac on transvaginal ultrasonography with either a human chorionic gonadotrophin (ß-hCG) level > 1500 mIU / ml (using the 1st International Reference Preparation) or a well documented gestational age > 35 days with the presence of an adnexial mass.

2) Abnormally rising ß-hCG level > 1500 mIU / ml with no chorionic villi seen histological on curettage followed by persistent ß-hCG levels.

Sixty-two (42%) patients of all ectopic pregnancies received methotrexate as a first line of treatment. Using the above inclusion criteria, 12 (18%) patients were excluded from analysis. Patients that were excluded were as follows: One patient received methotrexate for presumed ectopic pregnancy, and subsequently had a uterine curettage which showed chorionic villi; five patients received methotrexate after a slow decrease in ß-hCG titers with no uterine curettage, four patients were treated with methotrexate for persistent trophoblastic activity after primary salpingostomy and one patient was given methotrexate with a gestational age less than 35 days and ß-hCG of 145 mIU / ml with no documentation of absent villi in curettage. One patient was excluded because of the presence of fetal heart activity.

Fifty patients met the ACOG’s criteria for the diagnosis of ectopic pregnancy that was treated with methotrexate was included in this study. After 1-2 days admission to the hospital for diagnostic evaluation, selected patients for me-
methotrexate treatment of an intact ectopic pregnancy received a single intra-muscular dose of methotrexate with close follow-up in the out-patient clinic with serial titers of β-hCG on days 4 and 7 of methotrexate injection and weekly titers after that until titer becomes negative. β-hCG titer does not drop by at least 15% from day 4 to day 7, the patient is reevaluated, transvaginal ultrasonography is repeated and a second methotrexate dose is administered in the asymptomatic patients. In the presence of increasing abdominal pain, the patient is re-evaluated with transvaginal ultrasonography and/or laparoscopy. Out- and in- patients’ medical records for the 50 patients were reviewed. Data were collected and entered into a study data base for analysis.

The data collected included patient demographics, vaginal ultrasonography findings, pre- and post- treatment β-hCG levels and the number of methotrexate doses administered. Data for patients who required surgery included symptoms, surgical procedure, operative findings, and hospital admissions for pain. Successful response to methotrexate treatment was defined as the resolution of β-hCG level after one or more doses of methotrexate without surgery. Data are presented as mean ± SD. "T's" test was used to compare between mean and Chi-square statistics was used to compare proportions. Statistical significance was defined as a p-value < 0.05.

Methotrexate Protocol for treatment of ectopic pregnancy (modified from Stovall and Ling)\[8\].

Indications:
- Hemodynamically stable patient
- Ectopic pregnancy mass < 3.5 cm in largest diameter
- β-hCG level < 10,000 mIU / ml
- Patient is able to return for follow-up

Contraindications:
- Breast feeding
- Chronic liver disease
- Pre-existing blood dyscrasias, such as bone marrow hypoplasia, leucopenia, thrombocytopenia or significant anemia
- Active peptic ulcer

Relative Contraindications:
- Un-ruptured ectopic pregnancy mass 3.5 cm or greater
- Presence of fetal heart rate activity

Monitoring after treatment:
- Quantitative β-hCG on day 4 and 7 after methotrexate administration (day 1)
• If ß-hCG titer shows a 15% or more drop on day 7, continue weekly monitoring until ß-hCG < 25 mIU / ml
• Failure of this decrease indicates the need for reevaluation of the patient for an additional dose of methotrexate
• Increasing abdominal pain indicates the need for reevaluation of the patient with transvaginal ultrasonography for possible laparoscopy

Dosing Regimen:
• Single dose intramuscular methotrexate (50 mg / m²) without citrovorum rescue
• m² (body surface area) = 4 X WT (kg) + 7 / WT (kg) + 90

Possible Side Effects:
• Gastritis, nausea, stomatitis, elevated hepatic transaminase levels, leucopenia, thrombocytopenia and alopecia.

Results

The characteristics of the 50 patients with ectopic pregnancy who satisfied our inclusion criteria for initial treatment with methotrexate are presented in Table 1. Two thirds of these patients had identifiable ectopic pregnancy on vaginal ultrasonography with a gestational mean age of 6.7 weeks. Current or past use of an intrauterine contraceptive devices (IUCD) were present in 16% of these cases. Current or past use of fertility drugs was also present in 16% of these patients.

Table 1. Characteristics of 50 women treated with methotrexate.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (year) ± SD</td>
<td>32.7 ± 5.3</td>
</tr>
<tr>
<td>Mean gravidity (No) ± SD</td>
<td>5.7 ± 3.2</td>
</tr>
<tr>
<td>Free fluid in the peritoneal cavity no (%)</td>
<td>15.0 (3.2)</td>
</tr>
<tr>
<td>Identified ectopic mass no. (%)</td>
<td>33.0 (66)</td>
</tr>
<tr>
<td>History of fertility drug use (%)</td>
<td>8.0 (16)</td>
</tr>
<tr>
<td>IUCD use (%)</td>
<td>13.0 (16)</td>
</tr>
<tr>
<td>Current</td>
<td>8.0 (16)</td>
</tr>
<tr>
<td>Past</td>
<td>5.0 (10)</td>
</tr>
<tr>
<td>Previous ectopic no. (%)</td>
<td>4.0 (8)</td>
</tr>
<tr>
<td>Site of ectopic no. (%)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>15.0 (30)</td>
</tr>
<tr>
<td>Right</td>
<td>18.0 (36)</td>
</tr>
<tr>
<td>Unknown</td>
<td>17.0 (34)</td>
</tr>
<tr>
<td>Mean gestational age at diagnosis - weeks ± SD</td>
<td>Mean 6.7 ± 1.6</td>
</tr>
</tbody>
</table>
Pre-treatment β-hCG levels were available in 49 out of 50 women with a mean (SD) of 1,924 (2333) mIU/ml and a range of 109-10,699 mIU/ml. Two patients had levels > 5,000 mIU/ml and two patients had levels > 10,000 mIU/ml. Forty-four (88%) patients had ectopic masses < 3 cm. No patient had an ectopic mass greater than 4.5 cm.

Forty-three (86%) patients were treated with single doses of methotrexate and 7 (14%) patients were treated with double doses of methotrexate. Forty (80%) patients were successfully treated with single doses of methotrexate. Six additional patients were successfully treated with double doses of methotrexate. Four (8%) patients required surgical intervention for an overall success rate of methotrexate treatment of 92% (46/50 patients).

Thirteen (26%) patients required re-admission after methotrexate treatment: 3 patients were hospitalized for pelvic pain requiring analgesics only, 4 patients required immediate surgical intervention by salpingectomy with ruptured ectopic in two patients. No patient had any side effects from methotrexate. There was no statistically significant difference between patients who were successfully treated with methotrexate and those who failed this treatment with regard to age, gravidity, presence of free fluid in the pelvis and pre-treatment β-hCG levels (Table 2). The size of the ectopic mass was smaller in the successfully treated patients (Table 2). Logistic – regression analysis identified ectopic mass to be the only factor significantly linked to failure of methotrexate treatment (p = 0.008, Table 2).

**Table 2.** Analysis of factors related to the efficacy of methotrexate therapy in women with ectopic pregnancies.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Success</th>
<th>Failure</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age - Yr ± SD</td>
<td>32.7 ± 5.4</td>
<td>31.8 ± 4.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean Gravidity No. ± SD</td>
<td>5.7 ± 3.3</td>
<td>5.0 ± 2.1</td>
<td>0.65</td>
</tr>
<tr>
<td>Mean Pre Mtx Serum β hCG mIU / ml ± SD</td>
<td>1774.3 ± 2031.5</td>
<td>3611.0 ± 4738.7</td>
<td>0.65</td>
</tr>
<tr>
<td>Mean Size of Mass (cm.) ± SD</td>
<td>2.3 ± 0.6*</td>
<td>3.5 ± 1.0**</td>
<td>0.008</td>
</tr>
<tr>
<td>Presence of Free Fluid No. (%)</td>
<td>13.0 (26)</td>
<td>2.0 (4)</td>
<td>0.36</td>
</tr>
<tr>
<td>Need Admission No. (%)</td>
<td>9/46 (19.5)</td>
<td>4/4 (100.0)</td>
<td>.0004</td>
</tr>
</tbody>
</table>

Table 3 shows the characteristics of the four patients who required surgery after methotrexate therapy. Two of these patients presented with shock and ruptured ectopic pregnancy.
Discussion

Using a single-treatment protocol, we had 92% success rate with methotrexate treatment of ectopic pregnancy. This rate compares favorably with the reported result (94%) by Stovall and Ling[9]. The clinical decision to abandon medical therapy is critical to the determination of the overall success rate. The development of worsening pain after administration of methotrexate is common; it occurred in up to 35/50 (70%) of patients in this present study; this compares with 59% reported by Stovall and Ling[9]. Only 13 of those patients in this study required hospitalization; 3/13 women were managed conservatively; in only two of those patients was the pain so severe, with signs and symptoms of acute abdomen pain, that immediate laparotomy was performed. As long as the β-hCG is decreasing appropriately and the patient is hemodynamically stable, the patient may be followed up closely and surgery avoided.

The result of Natale et al.[10] demonstrated that 23.1% of patients undergoing resolution of methotrexate-treated ectopics showed an immediate increase β-hCG value with Day 4 after a single dose of methotrexate. According to the literature[9,11,12] this justifies that in a clinically stable patient expectant management is indicated despite increase in β-hCG until a week from the methotrexate dose. Figure 1 showed this increase in day 4 β-hCG from the available data. However, since only 10 patients in this study’s population had Day 4 β-hCG done, it will be difficult to estimate what percentage of patients will have a rise in β-hCG and relate that to success of treatment. We are currently conducting a similar study in order to explain this particular phenomenon in more detail. It is still to be clarified why an initial increase of β-hCG titer can be observed before a complete resolution and why it is present only in specific patients, some hypotheses have addressed the interpretation of this issue: 1) the long half life (36 h) of β-hCG must be considered for the initial lag time in serum β-hCG clearance. 2) It is possible, but not unequivocally demonstrated yet, that the initial response of the trophoblast to the cytotoxic effect of methotrexate results in the release of additional β-hCG into the circulation. 3) It is

<table>
<thead>
<tr>
<th>No.</th>
<th>Doses of MTX</th>
<th>Pre-MTX β hCG</th>
<th>Pre-OP β hCG</th>
<th>Pre-OP Symptoms &amp; Signs</th>
<th>Findings / Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1566</td>
<td>NA</td>
<td>Acute abdomen pain &amp; shock</td>
<td>Ruptured ectopic / open salpingectomy</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>750</td>
<td>746</td>
<td>Severe lower abdomen pain</td>
<td>Intact ectopic / open salpingectomy</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1429</td>
<td>960</td>
<td>Severe lower abdomen pain</td>
<td>Intact ectopic / laparoscopic salpingectomy</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>10699</td>
<td>2600</td>
<td>Acute abdomen pain &amp; shock</td>
<td>Ruptured ectopic / open salpingectomy</td>
</tr>
</tbody>
</table>
possible that although methotrexate is arresting mitosis in cytotrophoblasts, the syncytiotrophoblast mass may still be increasing and producing β-hCG\textsuperscript{[11]}.

![HCG levels diagram](image)

**Fig. 1.** Level of Beta HCG in response to Methotrexate (10 Patients). Each line in the graph shows serial of Beta HCG level in 10 patients, pre-treatment (D1) with raise in D4 and subsequent drop. The arrows indicates the time of methotrexate administered.

Most studies, including this one, have enrolled carefully selected women who were managed uniformly according to an established protocol. We have an advantage of treating our patients in a close community with very close follow-up of patients, and our patients can access our medical service 24-hours per day, seven days a week.

The use of methotrexate for treatment of ectopic pregnancy is a great advance in gynecology. The benefits include decreased cost of treatment, and avoidance of surgery with its inherent risks and complications; however strict criteria, close follow-up, and patient compliance are a must for safe and successful management.

**Comments**

Methotrexate regimen developed by Stovall and Ling for treatment of selected ectopic pregnancy offers patients a simple non-surgical alternative with a high success rate and minimal side effects.

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and not necessarily of SAMSO. My many thanks to Dr. Abdualaziz Boker from Department of Anesthesia for his great help for the statistical analysis of the data.

References


علاج الحمل الهاجر بطرق غير جراحية
(ثلاث سنوات خبرة)

خالد حسين سبتم
قسم أمراض النساء والتوليد، كلية الطب، جامعة الملك عبدالعزيز، جدة - المملكة العربية السعودية

المستخلص: كانت الغاية من الدراسة تقديم الفعالية لعلاج الحمل الهاجر عن طريق جرعة من العلاج الكيميائي (سبوتوبوتريكسات) خلال ثلاث سنوات في المركز الواحد. تم تطبيقه على 50 حالة حمل هاجر وجدت بالميتوتركسات حسب بروتوكول فريق سنت فعال الطبي في الفترة ما بين بداية عام 1999م إلى نهاية عام 2001م. كان متوسط عمر المرضى 22 سنة، ومتوسط عدد الحمل 0.68. وتم تشخيص الحمل الهاجر بواسطة الأشعة فوق الصوتية لثلاثين مريضة من أصل 50.92٪ تمكنت فرق رئيسيين من خلال التجربة، وجد أن حجم كتلة الحمل الهاجر في العامل الوحيد الذي يؤثر في معدل فشل العلاج (0.86). في هذه الدراسة، كان معدل نجاح العلاج غير الجراحي للحمل الهاجر 98٪. المريضات اللواتي لديهن كتلة حمل هاجر بمقدار 3 سم قد يحتاجن إلى تدخل جراحي، أو جرعة ثانية من العلاج الكيميائي.