Methotrexate success rates in progressing ectopic pregnancies: a reappraisal

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OBJECTIVE: The purpose of this study was to determine the success rates of methotrexate in progressing ectopic pregnancies and to correlate them with beta—human chorionic gonadotropin (\(\beta\)-hCG) levels.

STUDY DESIGN: This retrospective cohort study that was carried out in a tertiary university-affiliated medical center included women who had been diagnosed with ectopic pregnancies between January 2001 and June 2013. Daily \(\beta\)-hCG follow-up examinations were performed to determine the progression of the ectopic pregnancy. Women with hemodynamically stable progressing ectopic pregnancies received methotrexate (50 mg/m² of body surface). We measured the success and failure rates for methotrexate treatment in correlation to \(\beta\)-hCG level.

RESULTS: One thousand eighty-three women were candidates for “watchful waiting” (\(\beta\)-hCG follow up). Spontaneous resolution and decline of \(\beta\)-hCG levels occurred in 674 patients (39.5%); 409 women (24.0%) had stable or increasing \(\beta\)-hCG levels and were treated with methotrexate. In 356 women (87.0%), the treatment was successful; 53 women (13.0%) required laparoscopic salpingectomy. Compared with prompt administration of methotrexate, our protocol resulted in lower overall success rates for all levels of \(\beta\)-hCG in women with progressing ectopic pregnancies: 75% in women with \(\beta\)-hCG levels of 2500-3500 mIU/mL, and 65% in women with \(\beta\)-hCG levels >4500 mIU/mL. A mathematical model was found describing the failure rates for methotrexate in correlation with \(\beta\)-hCG levels.

CONCLUSION: The success rates for methotrexate treatment in progressing ectopic pregnancies after daily follow-up evaluation of \(\beta\)-hCG levels are lower than previously reported. This reflects redundant administration of methotrexate in cases in which the ectopic pregnancy eventually will resolve spontaneously.

KEY WORDS: \(\beta\)-hCG, ectopic pregnancy, methotrexate


Patients diagnosed with extraterine pregnancies (EUPs) who are hemodynamically stable are almost universally treated with methotrexate. This treatment has gained popularity because it is effective and the side-effects are minimal in most regimens used. Recent years of research have established the dominance of the levels of beta—human chorionic gonadotropin (\(\beta\)-hCG) as a predictor of methotrexate success rates; other parameters such as the size of the ectopic mass or gestational age have proved less important. Today, the agreed on contraindications for methotrexate use are few and include hemodynamic instability, fetal cardiac activity, and a high level of \(\beta\)-hCG, which is 5,000-10,000 IU/mL in most institutions.

Recently, we have shown that sequential \(\beta\)-hCG level follow up can differentiate true progressing ectopic pregnancies from spontaneously resolving ectopic pregnancies. We previously demonstrated that, in true progressing ectopic pregnancies, the success rates of methotrexate are lower than those reported in the literature. This is merely a reflection of the fact that the group of patients who were treated promptly with methotrexate was composed of patients with progressing and spontaneously resolving ectopic pregnancies. Treatment with methotrexate when ectopic pregnancies are spontaneously resolving will have high success rates at the expense of patients who do not need therapy at all.

The objective of our study was to bring forward the success rates of methotrexate in ectopic pregnancies that are not spontaneously resolving according to \(\beta\)-hCG levels. After monitoring \(\beta\)-hCG levels using our “watchful waiting” protocol, we were able to administer this treatment only in progressing ectopic pregnancies. We also wanted to find out whether \(\beta\)-hCG levels can predict treatment or failure rates.

MATERIALS AND METHODS
This retrospective study was carried out at the Department of Gynecology in a tertiary university-affiliated medical center in Tel Aviv. The institutional review board approved this retrospective study. We reviewed the medical records of all patients who were admitted to our department with hemodynamically stable ectopic pregnancies from January 2001 and June 2013. This reflects an expanded population of patients enrolled in our previous study at the same institution. Both \(\beta\)-hCG level measurements and transvaginal ultrasonography imaging were used to evaluate the condition of women with suspected EUP. Women
with either hemodynamic instability, EUP with cardiac activity, β-hCG levels >10,000 IU/mL, and severe abdominal pain or signs of intraabdominal bleeding were excluded from the study and referred for surgery.

Patients who were hemodynamically stable and demonstrated no contraindications for methotrexate therapy were treated expectantly, as previously described in our “watchful waiting” protocol. Briefly, patients who demonstrated spontaneous daily fall of β-hCG levels by >15% were considered to be spontaneously resolving ectopic pregnancies and were discharged. Patients who demonstrated a daily increase of ≥15% in β-hCG level were treated with methotrexate. In all other patients whose β-hCG levels were in plateau (daily change of <15%) in-hospital follow up and repeat β-hCG levels were performed daily. This type of serial measurements and decision-making was repeated each day with a 5-day limit at which time we administered methotrexate.

Patients were candidates for methotrexate treatment if the following criteria were met: (1) normal liver and renal function test, (2) absence of intrauterine pregnancy, (3) no known methotrexate allergy, and (4) signed an informed consent form. Methotrexate was given according to the “single dose” protocol at a dose of 50 mg/m² of body surface area. The injection day was considered as day “zero,” and repeated β-hCG measurements were taken on days 4 and 7 in our outpatient clinics with the use of the same hospital laboratory. When β-hCG concentration failed to decline by ≤15% between days 4 and 7, an additional injection of methotrexate was administered. We defined treatment failure when patient returned with severe abdominal pain, hemodynamic instability, or continuous rise in β-hCG level, despite 2 sequential injections of methotrexate. We calculated the success rates for methotrexate and correlated them with the last β-hCG level before treatment.

**Statistical analysis**

We used Shapiro Wilks test to evaluate the distribution of the data. Because data were not normally distributed, we used a Mann-Whitney U test for comparison between continuous variables. Fisher exact and χ² tests (2 by k) were used for proportional comparison. Regression analysis found an exponential model to have a good fit describing the association of β-hCG levels and failures rates. A probability value of < .05 was considered significant.

**Results**

Between January 2001 and June 2013, 1703 women were admitted to our department with the diagnosis of ectopic pregnancy. Immediate surgery was carried out in 620 patients. According to the protocol described earlier, 1083 patients were candidates for β-hCG follow up—“watchful waiting.” None of the patients whom we observed were referred for surgery during this “watchful waiting” period. Spontaneous resolution and decline of β-hCG levels occurred in 674 patients (39.5%); 409 (24.0%) women were candidates for methotrexate treatment. A total of 356 women (87.0%) were treated successfully with methotrexate (group 1); in contrast, 53 women (13.0%) required surgical intervention because of methotrexate treatment failure (group 2; Figure 1).

Table 1 presents the clinical and demographic variables of those women who were treated with methotrexate in both groups. There was no difference between the 2 groups regarding maternal age, parity, gestational age, endometrial thickness, and size of the ectopic mass as determined by ultrasound scanning. Women in the successfully treated group had significantly lower β-hCG concentration when compared with the failure group (1407 IU/mL vs 2664 IU/mL; *P* < .0001). In the successfully treated group, 306 women (86%) required 1 dose of methotrexate, and 50 women (14%) required an additional dose. To investigate whether there were predictive factors for those women who required 2 doses of methotrexate to achieve resolution of the pregnancy, a second analysis was made in the successfully treated group between women who received a single dose and those with an additional dose of methotrexate. We found no difference between the 2 groups regarding demographic and clinical characteristics.

Table 2 demonstrates the success rates for methotrexate treatment in correlation with β-hCG levels.

We used regression analysis as a statistical model to find a mathematic function that could predict the failure rates of methotrexate treatment in ectopic pregnancies. This model is presented in Figure 2.

**Comment**

Medical management of ectopic pregnancies with methotrexate has become the treatment of choice for hemodynamically stable ectopic pregnancies.¹ A great deal of research and effort has been focused in previous years on the criteria for patient selection to augment success rates on one hand and to prevent potentially life-threatening failures on the other hand.

Treatment algorithms that were published >2 decades ago still are accepted commonly in the treatment of EUPs.²⁷⁻¹⁰ Although it has been well-established that methotrexate treatment for ectopic pregnancies with lower β-hCG levels has a higher success rates,¹ there is wide variation regarding the success rate in different studies, and there is no consensus regarding the cutoff value at which methotrexate is contraindicated or less successful. Several reasons that the success rates for methotrexate treatment are still elusive are outlined hereunder.

The definition of success is sometimes ambiguous and needs clarification. It is easy to define successful treatment when levels of methotrexate are declining to zero and the patient is asymptomatic. Although this is a common occurrence, it is certainly not the rule. When a patient has severe abdominal pain or intraperitoneal bleeding, despite medical treatment even if levels of β-hCG are declining, it is more difficult to define this as successful treatment. Lipscomb et al.,¹ as an example of this notion, defined treatment failure in the following manner: persistent β-hCG levels, despite 3 doses of methotrexate, suspected tubal rupture defined by declining hematocrit levels or hemodynamic instability or the
presence of peritoneal fluid extending into the flanks. The American Society for Reproductive Medicine's criteria regarding medical treatment with methotrexate regards the presence of severe abdominal pain, which alerts the presence of imminent tubal rupture, as an indication for abandoning medical management. Our definition of failure was similar to the 1 used by the American Society for Reproductive Medicine. Previous years of research have failed to demonstrate a clear benefit of conservative medical treatment for ectopic pregnancies, compared with surgical treatment in terms of future success in reproduction. We believed that putting patients at risk of hemorrhage or even allocating resources for careful follow up or having patients endure significant pain are unnecessary under these circumstances. We therefore defined treatment as failure after 2 trials of methotrexate or in circumstances in which the patient was in severe pain or in danger because of acute blood loss.

Another consideration is the timing of methotrexate administration because there are no specific guidelines for \( \beta\)-hCG follow up before medical treatment for ectopic pregnancies. Methotrexate usually is administered immediately in hemodynamically stable patients who received a diagnosis of ectopic pregnancies with \( \beta\)-hCG levels >2000 IU/mL and an ectopic pregnancy mass <3.5 cm on ultrasound examination.

Prompt administration of methotrexate will yield high rates of success, because patients with both true progressing ectopic pregnancies and spontaneously resolving ectopic pregnancies will be treated. Withholding methotrexate, especially in women with plateau in \( \beta\)-hCG level eventually will single out patients with a spontaneous resolution and declining \( \beta\)-hCG level without need for intervention. This follow up in turn will result in fewer patients being medically treated at the expense of lower success rates. This notion was demonstrated in our previous work. In our study, the “watchful waiting” approach with daily repeated \( \beta\)-hCG testing reduced significantly the number of women who were treated. Up to 46.4%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methotrexate successful (n = 356)</th>
<th>Methotrexate failure (n = 53)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31.2 ± 5</td>
<td>30.4 ± 4</td>
<td>.2</td>
</tr>
<tr>
<td>Parity, n</td>
<td>0.6 ± 0.8</td>
<td>0.5 ± 0.7</td>
<td>.3</td>
</tr>
<tr>
<td>Gravidity, n</td>
<td>2.3 ± 1.3</td>
<td>2 ± 0.9</td>
<td>.4</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>6.6 ± 1.2</td>
<td>6.5 ± 1.6</td>
<td>.5</td>
</tr>
<tr>
<td>Extrauterine mass, mm²</td>
<td>412.3 ± 446.8</td>
<td>379.2 ± 607.3</td>
<td>.1</td>
</tr>
<tr>
<td>Pretreatment ( \beta)-hCG, IU/mL</td>
<td>1407.3 ± 1420.8</td>
<td>2664.2 ± 1772.3</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Data are presented as mean (±SD).
\( \beta\)-hCG, \( \beta\)-human chorionic gonadotropin level.

The number that is given in each box represents the number of women involved (% of total). \( \beta\)-hCG, \( \beta\)-human chorionic gonadotropin; EUP, extrauterine pregnancies.
of the women who were candidates for methotrexate treatment eventually were discharged without the need for any treatment because of spontaneous ectopic resolution. We were able to reduce significantly the number of patients who were treated at the expense of reduced success rates of 73.8% for methotrexate (for progressing ectopic pregnancies).

In our view, another major drawback of a great deal of studies that define the success rates for methotrexate is the fact that, although there is a good correlation between lower \( \beta \)-hCG levels and successful treatment, the mean \( \beta \)-hCG levels are presented for successful and unsuccessful treatment groups instead of presenting success rates according to categoric ranges of \( \beta \)-hCG levels.13-15

In our present study, we used a “watchful waiting” approach to single out patients with progressing ectopic pregnancies. To the best of our knowledge, this represents the largest group of patients with true progressing ectopic pregnancies to be studied. In accordance with our past findings, 39.5% of our patients were discharged home after spontaneous decline of \( \beta \)-hCG levels. Also, we were able to bring forward the success rates of methotrexate in hemodynamically stable, progressing ectopic pregnancies. It is seen clearly that this protocol results in lower success rates for all levels of \( \beta \)-hCG, with an overall success rate of 88%, a 75% success rate in patients with \( \beta \)-hCG levels from 2500-3500 IU/mL, and a 65% success rate for patients with \( \beta \)-hCG level of >4500 IU/mL. Our single-dose methotrexate protocol proved to be less successful with higher failure rates than was reported previously. This again is a reflection of the fact that we treat only progressing, as opposed to spontaneously resolving, ectopic pregnancies.

Additionally, we were able to correlate the failure rates of methotrexate treatment to the levels of \( \beta \)-hCG with a mathematical model. This exponential function of \( \beta \)-hCG, as depicted in Figure 1, gives an accurate estimation of the failure rates for methotrexate in progressing ectopic pregnancies. Being able to estimate our chances of failure or success can help us and our patients make wiser decisions regarding treatment plans.

We used a cutoff of 5 days before we decided to administer therapy with methotrexate. In fact, longer periods of waiting might have revealed more

### TABLE 2

<table>
<thead>
<tr>
<th>( \beta )-hCG level, IU/mL</th>
<th>Cases, n</th>
<th>Failures, n</th>
<th>Success rate, %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-500</td>
<td>106</td>
<td>4</td>
<td>96.23</td>
</tr>
<tr>
<td>500-1000</td>
<td>82</td>
<td>5</td>
<td>93.90</td>
</tr>
<tr>
<td>1000-1500</td>
<td>54</td>
<td>5</td>
<td>90.74</td>
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<tr>
<td>1500-2000</td>
<td>43</td>
<td>5</td>
<td>88.37</td>
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<td>2000-2500</td>
<td>37</td>
<td>9</td>
<td>75.68</td>
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<td>2500-3500</td>
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<td>9</td>
<td>75.00</td>
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<tr>
<td>3500-4500</td>
<td>22</td>
<td>6</td>
<td>72.73</td>
</tr>
<tr>
<td>&gt;4500</td>
<td>29</td>
<td>10</td>
<td>65.52</td>
</tr>
<tr>
<td>Total</td>
<td>409</td>
<td>53</td>
<td>87.04</td>
</tr>
</tbody>
</table>

\( \beta \)-hCG, beta-human chorionic gonadotropin level.  

a \( p < .0001 \).


### FIGURE 2

Treatment failure rate according to \( \beta \)-hCG level in women with progressing ectopic pregnancies

Each point represents average failure rates for respective levels of beta-human chorionic gonadotropin (\( \beta \)-hCG; Table 2). With the equation, an estimation of methotrexate treatment failure (percentage) according to \( \beta \)-hCG level (international units per liter) can be made. Correlation coefficient (\( r \)) = 0.929574.

patients with spontaneous resolution of the ectopic. Although longer hospitalization and repeated β-hCG testing incur additional costs, in this project, we were interested in the medical benefits of the “watchful waiting” protocol, and the economic implications were not calculated. This in no doubt will be studied in the future. Also, the rate of β-hCG rise was not determined but may have an important role on decision-making and better understanding of the biologic properties of the ectopic pregnancy. This, in turn, may have important implications on therapy success or failure.

This study was limited because of its retrospective nature. Also, the decision for intervention in cases in which patients had pain were clinically based regardless of hemoglobin level or hemodynamic instability, as outlined earlier.

In conclusion, this work provides the success rates for methotrexate treatment in progressing ectopic pregnancies after careful β-hCG follow up. This represents a large body of data for clinicians who are willing to use a “watchful waiting” protocol of treatment in an effort to reduce unnecessary treatment with methotrexate. Using the mathematic model we describe, clinicians will be able to estimate failure rates and use this information wisely with their patients.

REFERENCES