Suspected Ectopic Pregnancy

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Abstract: Women who present with pain and bleeding in the first trimester are at risk for ectopic pregnancy, a life-threatening condition. Conditions that predispose a woman to ectopic pregnancy are damaged fallopian tubes from prior tubal surgery or previous pelvic infection, smoking, and conception using assisted reproduction. Many women without risk factors can develop an ectopic pregnancy. A diagnostic algorithm that includes the use of transvaginal ultrasonography, human chorionic gonadotropin (hCG) concentrations, and, sometimes, uterine curettage can definitively diagnose women at risk in a timely manner. The absence of an intrauterine pregnancy above an established cut point of hCG is consistent with an abnormal pregnancy but does not distinguish a miscarriage from an ectopic pregnancy. When the initial hCG value is low, serial hCG values can be used to determine whether a gestation is potentially viable or spontaneously resolving. The minimal rise in hCG for a viable pregnancy is 53% in 2 days. The minimal decline of a spontaneous abortion is 21–35% in 2 days, depending on the initial level. A rise or fall in serial hCG values that is slower than this is suggestive of an ectopic pregnancy. Women diagnosed with an unruptured ectopic pregnancy are potential candidates for medical management with methotrexate. Intramuscular injection with methotrexate can be used to safely treat an ectopic pregnancy with success rates, tubal patency rates, and future fertility that are similar to those obtained with conservative surgery. Success rates using methotrexate are inversely rated to baseline hCG values and are higher using "multidose" compared with "single-dose" regimens. Surgical treatment may be conservative or definitive and should be attempted in most cases via laparoscopy. (Obstet Gynecol 2006;107:399–413)
dence of sexually transmitted infections, earlier diagnosis of pelvic inflammatory disease resulting in tubal damage but not complete blockage, and the rise in the number of ectopic pregnancies resulting from assisted reproductive technologies (ART) may account for the overall increase. The advent of radioimmunoassay (RIA) and specific antiserum to the β-subunit of human chorionic gonadotropin (hCG) has allowed for the accurate quantification of β-hCG and the ability to closely follow trends in hormonal rise and fall. Currently, hCG is almost exclusively assayed by using chemiluminescence and third International Reference Preparation. This standard is very similar to the original 1st International Reference Preparation.

Likewise, high resolution, transvaginal ultrasonography with Doppler flow imaging has improved visualization of adnexal masses, including ectopic pregnancies, at earlier gestational ages. As discussed by Maymon and Shulman, the incidence of tubal pregnancy after oocyte retrieval/embryo transfer may be as high as 4.5%, although this may be due to already existing tubal pathology in these patients and not solely to the ART intervention.

The incidence of heterotopic pregnancy is now believed to be about 1:4,000 in the general population and 1:100 in in vitro fertilization (IVF) pregnancies—much higher than the originally described prevalence of 1:30,000 in the late 1940s. This phenomenon may be due to the increasing use of ovulation induction agents that increase the chance of twinning and may cause hormonal fluctuations affecting tubal motility, and also due to the invasive nature of ART. Although in the past the diagnosis of an intrauterine pregnancy effectively ruled out an ectopic, it is important for clinicians to be aware of the chances of a dual pregnancy and thoroughly evaluate symptomatic patients.

Risk Factors
The risk factors for ectopic pregnancy were summarized by Ankum et al. in a meta-analysis that included 36 prior studies. There is a strong association between ectopic pregnancy and conditions that are thought to impede the migration of the fertilized ovum to the uterus. These include damage to the fallopian tube from prior pelvic inflammatory disease, history of ectopic pregnancy, and previous tubal surgery, including previous tubal ligation. This same pathophysiologic mechanism of altered tubal integrity may be the cause of an increased number of ectopic pregnancies seen in patients with infertility or previous pelvic surgery. Cigarette smoking (thought to affect tubal motility), increasing age, and having more than one lifetime sexual partner have also been weakly linked to an increased risk of ectopic pregnancy. No clear association has been documented between ectopic pregnancy and oral contraceptive use, previous elective pregnancy termination, spontaneous miscarriage, or cesarean delivery. Women with an intrauterine device in place and those who have undergone tubal ligation are more likely to have an ectopic pregnancy than an intrauterine one if conception occurs, but their baseline risk of pregnancy is far lower than that of women not using family planning.

Studies have not supported the theory that certain embryo factors, for example ones found in abnormal gestations, may lead to erroneous implantation at an ectopic site. Karyotype analysis of excised tubal pregnancies has shown a rate of chromosomal abnormalities comparable to that expected for the maternal and gestational age of the cases. More recent studies have focused on molecular level factors, based on the theory that alterations in the molecular dialog between the implanting blastocyst and the site of implantation may make ectopic pregnancy more likely. Some plausible candidates responsible for this cell-cell and cell-extracellular matrix interaction include lectin, integrin, matrix-degrading cumulus and their inhibitors, prostaglandins, as well as a host of growth factors, cytokines, and their receptors and modulator proteins.

Diagnostic Approach
The symptoms of abdominal or pelvic pain and vaginal bleeding in the first trimester of pregnancy are the most common complaints suggestive of ectopic pregnancy. The multiple potential sites of ectopic pregnancies add to the complexity of the diagnosis (Fig. 1). These symptoms may be erratic and variable, and, in some cases, absent. Likewise, such symptoms are nonspecific and also have been associated with spontaneous miscarriage, cervical irritation or trauma, and infection. Therefore, patients may delay reporting these symptoms to their physicians. On physical examination, hypotension and tachycardia with rebound tenderness and guarding alert the clinician to likely tubal rupture with immediate need for surgical intervention. However, the majority of patients present with less severe symptoms and more subtle signs on examination. For these patients, early diagnosis is imperative. In fact, for those with a high risk of ectopic pregnancy, some clinicians advocated screening as soon as these women report a positive pregnancy test. However, because of the high false-positive rate of screening, there is little medical economic benefit to screening asymptomatic women, and we do not do so in our practice.
Steps to Diagnosis

The diagnostic work-up for ectopic pregnancy requires the exclusion of a normal intrauterine pregnancy, bearing in mind the incidence of heterotopic pregnancy of about 1 in 4,000 (Fig. 2). For gestations greater than 5½ weeks, a transvaginal ultrasound examination should identify an intrauterine pregnancy with near 100% accuracy.17 Because of the inaccuracies of pregnancy dating, \( \beta \)-hCG is often used as a surrogate for gestational age. Sequentially, structures become visible by transvaginal ultrasonography, including a gestational sac (“double decidual sign” at 4½–5 weeks after the last menstrual period), yolk sac (at 5 weeks), and fetal pole with later cardiac motion (at 5½–6 weeks). A pseudosac is a collection of fluid within the endometrial cavity that occurs due to bleeding from the decidualized endometrium when an extrauterine gestation is present. Although it may sometimes be mistaken for a gestational sac, it can be distinguished from one by its central location, filling the endometrial cavity itself. However, the identification of a presumed pseudosac on ultrasonography should not be interpreted as diagnostic of ectopic pregnancy because it has been shown to have a high false-positive rate for ectopic pregnancy diagnosis.18

Discriminatory Cutoff

Critical to the diagnosis and management of suspected ectopic pregnancy is the concept of the “discriminatory cutoff” of \( \beta \)-hCG. This cutoff is defined as that level of \( \beta \)-hCG at which a normal intrauterine pregnancy can be visualized by ultrasonography with sensitivity approaching 100%.19 Although the concept was originally established using abdominal ultrasonography, it is now widely accepted that, above the discriminatory cutoff of 1,500–2,500 IU/L, using transvaginal ultrasonography, a normal intrauterine pregnancy should always be visualized. The absence of such implies an abnormal gestation.2–4

The discriminatory cutoff should be set by each institution based on that hospital’s success in correctly identifying ectopic pregnancies, based mostly on equipment used and expertise of the sonographers. Varying the discriminatory cutoff will affect the sensitivity (positively identifying an ectopic gestation) and specificity (correctly excluding an ectopic when none exists) for diagnosis. Some clinicians may choose a low discriminatory cutoff, for example a \( \beta \)-hCG of 1,500 IU/L. Such a cutoff would have high sensitivity for ectopic but at the cost of low specificity. This increases the possibility of misclassifying a developing intrauterine pregnancy as an abnormal gestation. Conversely, some clinicians may choose a high discriminatory cutoff, for example a \( \beta \)-hCG of 3,000 IU/L. In this situation a clinician would be provided with “extra” reassurance that lack of visualization of an intrauterine pregnancy did not miss an early viable gestation. Using this approach, however, may delay the diagnosis of ectopic pregnancy, decreasing the initial sensitivity and resulting in the possibility of...
rupture. In our view, it is better to set the discriminatory cutoff high, especially in a population of stable patients who maintain close medical follow-up. Such a principle would minimize the risk of interrupting a viable pregnancy, a very costly error, at the expense of initially delaying the diagnosis of a woman with an ectopic pregnancy by a few days.

**Human Chorionic Gonadotropin Above Discriminatory Cutoff**

If no intrauterine pregnancy is visualized above the discriminatory cutoff, we strongly advocate evacuating the contents of the uterus to differentiate an abnormal intrauterine gestation (spontaneous abortion) from an ectopic pregnancy. This management is based on findings that the presumption that an ectopic pregnancy exists when there is no evidence of an intrauterine pregnancy by ultrasonography and the β-hCG is above the discriminatory cutoff is incorrect in up to 54% of cases. Similarly, diagnosing an ectopic pregnancy based solely on serial β-hCG levels that are declining abnormally below the discriminatory zone is inaccurate in up to 31% of cases.

Following the evacuation of the uterus, if intrauterine chorionic villi are not confirmed by pathological examination, then treatment for ectopic pregnancy needs to be instituted. Alternatively, if pathological examination is not available at the time of tissue procurement, then the patient’s β-hCG may be checked approximately 12–24 hours later. If the level does not drop significantly on the day after uterine evacuation, then an extrauterine gestation is diagnosed. We use a drop of 15% as the minimal needed but normally see a much steeper drop if the pregnancy tissue has been successfully removed.

A technique to identify villi, such as floating tissue in saline solution, is not as accurate as microscopic examination, with data showing that the surgeon was
only able to identify villi in this manner in about 50% of cases.\textsuperscript{21} To definitively confirm resolution of the pregnancy in the absence of tissue diagnosis, β-hCG values should be followed at least weekly until undetectable, a process that may take up to several weeks. Currently we perform a dilation and curettage (D&C) or a manual vacuum extraction because these are the only reliable methods of determining the presence of intrauterine products of conception. Office endometrial biopsy has been demonstrated not to be helpful in the discrimination of a miscarriage from an ectopic pregnancy.\textsuperscript{22}

**Human Chorionic Gonadotropin Below Discriminatory Cutoff**

If the initial β-hCG is below the discriminatory zone, then serial β-hCG measurements are needed to document a growing (potentially viable) or a nonviable pregnancy. The minimum rise for a potentially viable pregnancy that presents with pain and/or vaginal bleeding is 53%, based on the 99th percentile confidence interval (CI) around the mean of the curve of β-hCG rise over time.\textsuperscript{23} This curve was derived from data from 287 subjects with vaginal bleeding or pain complicating an early pregnancy. These women were followed with serial β-hCG levels until an intrauterine pregnancy was confirmed. Intervention for a β-hCG rise of less than 66% over 2 days, a practice supported by previous data, would potentially result in the interruption of many viable pregnancies.\textsuperscript{24–26} Ultrasonography should be used to document the presence, or absence, of an intrauterine pregnancy when the β-hCG levels have risen above the discriminatory zone.

If the β-hCG does not rise appropriately, or declines, a nonviable pregnancy has been diagnosed. A rapid decline in β-hCG value is consistent with a miscarriage that may resolve spontaneously. If the β-hCG does not fall 21–35% in 2 days (depending on the initial value), the presence of an ectopic pregnancy should be suspected.\textsuperscript{27} These figures were derived from standard curves for expected β-hCG decline for gestations subsequently confirmed to have resulted in completed spontaneous abortion. These were based on data from over 700 women whose β-hCG was falling and who were subsequently diagnosed with a miscarriage. The 90% CIs around the mean for the curves were used to define the minimal decline.

**Definitive Diagnosis**

In the absence of definitive ultrasound diagnosis of an ectopic pregnancy, we strongly feel that the new guidelines for minimal rise and fall of β-hCG as described above should be used in the diagnostic work-up of ectopic pregnancy. These guidelines are based on recent data from large numbers of women and use conservative confidence intervals to minimize the error of misdiagnosing an intrauterine pregnancy as abnormal. More than 70% of women who have an ectopic pregnancy will have a rise in hCG that is slower than the minimal rise for a viable pregnancy or a decline that is slower than the minimal rate of fall in a spontaneous abortion (Fig. 3). However, there are cases when the rise, or fall, in serial hCG values can mimic that of a viable gestation or completed miscarriage.

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**Fig. 3.** Hypothetical illustration of the rise, or fall, of serial hCG values in women with an ectopic pregnancy. A total of 71% of women with an ectopic pregnancy (EP) will have a rise in hCG slower than the 1 percentile of women with a viable intrauterine pregnancy (IUP) and slower than the 90% for women with a spontaneous completed miscarriage (SAB). However, 21% of ectopic pregnancies have an hCG rise that mimics an intrauterine pregnancy; 8% have a fall in hCG similar to a spontaneous completed miscarriage.

riage. In these cases, the use of ultrasonography and the serial evaluation of patient’s symptoms are paramount.

A rise (or fall) in $\beta$-hCG of less than the value described above strongly suggests an abnormal pregnancy but does not distinguish a miscarriage from an ectopic pregnancy. A D&C or manual vacuum extraction should be used to obtain tissue diagnosis of products of conception, differentiating an abnormal intrauterine pregnancy from an ectopic pregnancy before subsequent management.30

**Erroneous Use of Methotrexate**

Unless a definitive diagnosis of an ectopic pregnancy is made, the use of methotrexate as medical therapy should not be undertaken. The use of methotrexate in circumstances where the patient actually has a miscarriage may unnecessarily expose the woman or the embryo to a chemotherapeutic agent. Moreover, the presumptive treatment of a woman with an abnormal pregnancy of unknown location with methotrexate instead of first performing a D&C to obtain tissue diagnosis does not reduce the complications or cost of treatment.28

Such management is in concordance with the conclusion of a decision analysis by Gracia and Barnhart,17 Using a hypothetical cohort of 10,000 women and previously published probabilities for pregnancy outcome, these authors compared 6 diagnostic strategies commonly employed in the evaluation of patients with suspected ectopic pregnancy. The strategies included the use of different combinations of serial physical examination, $\beta$-hCG, ultrasonography, and progesterone level.19,29–32 They found that the best strategy was transvaginal ultrasound examination performed on all women presenting with symptomatic pregnancy. If the ultrasound examination was nondiagnostic, then $\beta$-hCG should be measured. With this algorithm, no ectopic pregnancies were missed, few potential intrauterine pregnancies were interrupted, and a timely diagnosis was achieved.

**Progesterone**

The use of serum progesterone levels to diagnose ectopic pregnancy is still debated. Although it has been shown that progesterone levels are higher in intrauterine pregnancies than in ectopics, there is no well-established upper cutoff to use to discriminate between the two.33 A recent meta-analysis of 26 studies examined the accuracy of single serum progesterone measurement and concluded that, although serum progesterone measurement can identify patients at risk for ectopic pregnancy, this test alone is insufficient to diagnose ectopic pregnancy with certainty.33 Algorithms using progesterone can be problematic because they are associated with some missed ectopic pregnancies, especially among high-risk women.30 A study evaluating the diagnostic accuracy of 5 gynecologists to correctly identify ectopic pregnancies out of a cohort of pregnancies of unknown location using $\beta$-hCG and progesterone (48 hours apart) resulted in misdiagnoses of 35% of ectopic pregnancies.34 A low progesterone level of less than 5 ng/mL can rule out a normal pregnancy with almost complete certainty (99.8% accuracy) but does not discriminate between an abnormal intrauterine gestation and an ectopic pregnancy.32 For these reasons, we do not use progesterone levels in our diagnostic algorithm.

**Novel Diagnostic Methods**

The search for novel methods for the diagnosis of ectopic pregnancy with the most precision continues. The goal of such research is to develop a serum-based test that relies on placental or pregnancy-specific markers. Elevated levels of vascular endothelial growth factor (VEGF) have been described in ectopic gestations and have been noted 11 days after embryo transfer during IVF cycles in ectopic gestations, but with rather lower predictive values.35,36 Other putative markers have included pregnancy-associated plasma protein A (PAPP-A), pregnancy-specific B1-glycoprotein, human placental lactogen, and hCG, as well as the nonplacental markers, glycodelin, VEGF, and progesterone.37 One study found that a combination of VEGF, PAPP-A, and progesterone was able to discriminate ectopic pregnancy from intrauterine pregnancy with 97.7% sensitivity and 92.4% specificity, although this discriminative power was lower for early gestations. Gerton et al38 set out to identify serum markers of ectopic pregnancy with a proteomic approach. In a publication of some preliminary findings, they were able to identify several proteins that may potentially discriminate between an ectopic pregnancy and an intrauterine pregnancy. The next step requires the characterization of these proteins. Such promising results now require validation in a prospective population. Other markers that have been considered, but do not appear useful in the clinical setting at this point, include creatinine kinase, fetal fibronectin, leukemia inhibitory factor, smooth muscle heavy-chain myosin, and CA 125.39–45

**Modeling Risk**

As an alternative approach, investigators have attempted to optimize the diagnosis of women at risk for ectopic pregnancy by using decision rules and mathematical models.46 Condous et al,47 using logistic
regression models to predict outcome of pregnancies of unknown location, found that a model based on the β-hCG ratio at 0 and 48 hours was best at predicting subsequent outcomes of a pregnancy with an initial unknown location. However, with a minimum rise of 66% over 48 hours needed to classify a pregnancy as an intrauterine pregnancy, those women whose β-hCG level rose more slowly would have been misclassified with an abnormal gestation. Conversely, there are cases of ectopic pregnancy whose β-hCG curve mimics that of an intrauterine pregnancy, with a rapid initial rise giving erroneous reassurance that an ectopic pregnancy is absent.

**THERAPEUTIC APPROACH**

The primary goal of accurate and early diagnosis of ectopic pregnancy is to limit morbidity and eliminate mortality resulting from this condition. If diagnosed early, at a clinically stable state, the patient with an ectopic pregnancy is a likely candidate for either minimally invasive surgery or medical therapy. These treatment modalities have been shown to have success rates comparable to the gold-standard treatment of laparotomy with salpingectomy, but with the potential benefit of fallopian tube conservation. Laparotomy is still the mainstay of therapy for hemodynamically unstable patients with high suspicion of tubal rupture.48

**Methotrexate**

Medical treatment with methotrexate (MTX) has become a safe and effective means of treating ectopic pregnancy without the risks associated with surgery. It was first introduced as a novel therapy for ectopic pregnancy in 1982. In many centers and among many clinicians, it has become the primary treatment. The goal of medical management with MTX is to selectively kill the cytrophoblasts, the rapidly dividing cells at the fallopian tube implantation site. The body will then spontaneously resorb the remaining products of conception and blood clot that constitute the ectopic pregnancy. It is important for clinicians who use this chemotherapeutic agent to be well versed with its mechanism of action, dosing regimens, and adverse effects.

Methotrexate belongs to the class of drugs called folic acid antagonists.49 Initially used for treating leukemia, it gained wide use in gynecology for the treatment and cure of choriocarcinoma.50 Methotrexate acts by inactivating the enzyme dihydrofolate reductase (DHFR), leading to depletion of the cofactors required for DNA and RNA synthesis. Leucovorin, a folic acid, has been used as a “rescue” medication that allows for higher MTX dose administration by preventing some of the otherwise prohibitive adverse effects.50 Leucovorin enters cells via a carrier-mediated system and does not require reduction by DHFR for conversion to active folate cofactors, preventing some of the adverse effects of methotrexate.49

Methotrexate may be administered orally, intramuscularly, intrathecally, or by continuous infusion. For the treatment of ectopic pregnancy, the intramuscular injection is preferred, although there have been reports of success with the oral route.51 It may be used as primary treatment, treatment of persistent ectopic pregnancy after salpingostomy, prophylaxis for suspected persistent products of conception after conservative surgery, and in cases of unusually located ectopic pregnancies. If large MTX doses are used, as in a “multidose” regimen to be discussed below, leucovorin rescue should be used to salvage normal cells and prevent cell toxicity. The 2 most common regimens employed for the treatment of ectopic pregnancy are the “multidose” protocol and the “single-dose” administration.

**Methotrexate Dosing Regimens**

The “multidose” regimen administers MTX as the sodium salt (1 mg/kg per day intramuscularly) on days 1, 3, 5, and 7; leucovorin as a calcium salt (0.1 mg/kg intramuscularly) is given on days 2, 4, 6, and 8. Patients are given up to 4 doses (1 MTX, 1 leucovorin) until the β-hCG decreases by at least 15% on 2 consecutive days52 (Table 1). A second course after one week may be given if there is an increase or plateau in 2 consecutive β-hCG values (Table 1).

A single-dose regimen was introduced to enhance patient compliance and simplify administration. The “single-dose” regimen uses 50 mg/m² given by intramuscular injection after calculating the patient’s body surface area, and does not use leucovorin rescue. Although called “single-dose,” under this protocol, a second dose may be administered after 1 week if β-hCG values do not decline by at least 15% between days 4 and 7 after treatment (Table 2). Using the “single-dose” protocol, approximately 20% of women require more than one treatment cycle.54 It is difficult to predict which patients may need more than a single MTX dose.

Regardless of the MTX regimen used, patients need to be followed weekly with surveillance β-hCG after their treatment until β-hCG is undetectable in serum. This is the only way to confirm complete resolution of the ectopic pregnancy. It is important to be aware that ectopic pregnancies may cause tubal rupture even when the β-hCG levels are on their way down.56,57 This may also be the case in situations...
where MTX has already been administered for treatment. Specifically, in situations where the β-hCG increased at least 66% over 48 hours before MTX administration and in cases where the β-hCG continues to rise after MTX administration, the tubal rupture risk may be as high as 20%.

Effectiveness of Methotrexate

The overall effectiveness of MTX was reviewed by Pisarska et al. Based on 12 studies with at least 20 patients each, the authors concluded that MTX treatment has been shown to be successful in 78−96% of selected patients, that posttreatment hysterosalpingogram-documented tubal patency approached 78%, and that 65% of patients who attempted a subsequent pregnancy succeeded, with a 13% incidence of recurrent ectopic pregnancy. Hajenius et al confirmed the comparable effectiveness of MTX therapy and laparoscopic salpingostomy in the only randomized, prospective trial published on the subject.

### Single Dose Versus Multidose

Single-dose MTX therapy has been advocated by some authors as preferable to the multidose protocol. However, these 2 regimes have never been directly compared. Although there have been no randomized trials directly comparing the 2 treatment protocols, they were compared in a recent meta-analysis by our group. Barnhart et al included data from 26 articles that met their search criteria, reviewing 1,327 cases of women diagnosed with ectopic pregnancy who were treated with MTX. They found that the overall success rate for the use of methotrexate was 89%. Considering each regimen separately, the success rate of “multidose” therapy was 92.7%, with a 95% CI of 89−96%; for “single-dose,” 88.1%,

Table 1. Multidose Methotrexate Protocol

<table>
<thead>
<tr>
<th>Treatment Day</th>
<th>Lab Test</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>β-hCG, CBC with differential,LFTs, creatinine, type, and screen</td>
<td>Rule-out SAB</td>
</tr>
<tr>
<td>1</td>
<td>β-hCG</td>
<td>MTX 1.0 mg/kg</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>LEU 0.1 mg/kg</td>
</tr>
<tr>
<td>3</td>
<td>β-hCG</td>
<td>MTX 1.0 mg/kg if &lt; 15% decline day 1 to day 3. If β-hCG &gt; 15%, stop treatment and start surveillance.*</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>LEU 0.1 mg/kg</td>
</tr>
<tr>
<td>5</td>
<td>β-hCG</td>
<td>MTX 1.0 mg/kg if &lt; 15% decline day 3 to day 5. If β-hCG &gt; 15%, stop treatment and start surveillance.*</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>LEU 0.1 mg/kg</td>
</tr>
<tr>
<td>7</td>
<td>β-hCG</td>
<td>MTX 1.0 mg/kg if &lt; 15% decline day 5 to day 7. If β-hCG &gt; 15%, stop treatment and start surveillance.*</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>LEU 0.1 mg/kg</td>
</tr>
</tbody>
</table>

CBC, complete blood cell count; LFTs, liver function tests; SAB, spontaneous completed miscarriage; MTX, methotrexate; LEU, leucovorin.

* Surveillance: β-hCG should be checked every 7 days until β-hCG < 5.


Table 2. Single-Dose Methotrexate Protocol

<table>
<thead>
<tr>
<th>Treatment Day</th>
<th>Lab Test</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>β-hCG, CBC with differential,LFTs, creatinine, type, and screen</td>
<td>Rule out SAB</td>
</tr>
<tr>
<td>0</td>
<td>β-hCG</td>
<td>MTX 50 mg/m² IM*</td>
</tr>
<tr>
<td>4</td>
<td>β-hCG</td>
<td>MTX 50 mg/m² IM† If β-hCG &lt; 15%, decrease day 4 to day 7. If &gt; 15%, stop treatment and start surveillance.†</td>
</tr>
<tr>
<td>7</td>
<td>β-hCG</td>
<td>MTX 50 mg/m² IM† If β-hCG &lt; 15%, decrease day 4 to day 7. If &gt; 15%, stop treatment and start surveillance.†</td>
</tr>
</tbody>
</table>

CBC, complete blood cell count; LFTs, liver function tests; SAB, spontaneous completed miscarriage; MTX, methotrexate; IM, intramuscularly.

* Dose calculated by body surface area using nomogram.
† Surveillance: β-hCG should be checked every 7 days until β-hCG < 5.

with a 95% CI of 86–90%, a statistically significant difference. Importantly, when the frequency of failure was compared, controlling for initial hCG value and the presence of embryonic cardiac activity, the failure rate with single-dose therapy was almost 5 times greater (odds ratio [OR] 4.75, 95% CI 1.77–12.62). Success and failure were calculated for each protocol on an intention-to-treat basis, regardless of whether one dose was used in the “multidose” protocol or multiple doses were given as part of the “single-dose” protocol. The frequency of actual dosing with the 3 protocols was also recorded, with 15% of patients under a single-dose protocol actually receiving more than one dose of methotrexate. Conversely, under the “multidose” protocol, 54% of patients actually received 4 or more doses, while 10% received only 1, 23% received 2, and 14% received 3.

The above findings are consistent with other review papers that have examined the success of “single-dose” MTX administration and found a range of success between 64% and 89%. However, not all the studies included in these reviews accounted for how many subjects required more than one MTX dose, making the exact success rate imprecise. These findings about actual dosing support the idea that the ideal dosing regimen may lie somewhere in between these 2 protocols. A new protocol giving 2 doses of MTX (on day 1 and day 4) without leucovorin rescue and using the follow-up of the single-dose protocol may more optimally balance convenience and efficacy. Ultimately, the success of any medical management regime should be compared with the conservative surgical approach of laparoscopic salpingostomy, whose failure rate ranges from 3% to 20%.

Medical management with MTX is reserved for compliant patients who agree to return for follow-up. They should be hemodynamically stable, with no evidence of active bleeding, especially hemoperitoneum. Relative contraindications, as outlined by the American College of Obstetricians and Gynecologists (ACOG), are a gestational sac 3.5 cm or greater and absence of cardiac activity, and presence or absence of free peritoneal blood. Of these, β-hCG levels are most predictive. Tawfiq et al found that treatment failure occurred in 65% of cases when the β-hCG level was greater than 4,000 IU/L, compared with 7.5% when the level was less than 4,000 IU/L. Potter et al found that the median pretreatment serum β-hCG level was lower in women in whom treatment was successful compared with women with treatment failures (793 versus 3,802 mIU/mL). Elito et al found greater success with lower β-hCG level (especially < 1,500 mIU/mL). A recent review of 350 women treated with single-dose MTX for ectopic pregnancy found that the only factor that contributed significantly to the failure rate was serum β-hCG level before treatment. Above 5,000 mIU/mL, the failure rate rose to about 13%. However, there is no absolute level at which medical management is contraindicated. We currently use the multidose protocol or the new “2-dose protocol” to treat women with a hCG above 1,000 mIU/mL.

### Post-Methotrexate Follow-up

It is important that both patients and physicians are aware of the course of the ectopic pregnancy after MTX treatment. Thirty-three to almost 60% of pa-
Methotrexate for Extratubal Ectopics

Methotrexate has also been used for ectopic pregnancies located outside the fallopian tube, for example cervical, interstitial, ovarian, or abdominal gestations. Methotrexate is often considered a first-line treatment in these complicated pregnancies because of the difficulty and risk of surgical resection. Although experience with MTX use for cervical ectopic is limited, one review included 36 women treated with systemic MTX, local injection of MTX or potassium chloride (KCl), or a combination of these therapies and found an 80–90% success rate.24 The estimated success rate for medical treatment of interstitial pregnancy is 83%,75 Medical treatment of the rare ovarian ectopic has also been undertaken with success.26 Multiple studies have suggested that systemic MTX administration considerably reduces costs when compared with surgical treatment.5,77–81

Complications of Methotrexate

Methotrexate, like most medications, has adverse effects. As a folic acid analogue, MTX affects rapidly dividing cells, especially those of the gastrointestinal tract and the bone marrow. Consequently, the major adverse effects include impaired liver function, stomatitis, gastritis-enteritis, and bone marrow suppression.2,48 Hemorrhagic enteritis of the intestinal tract leads to nausea, vomiting, stomatitis, elevated liver enzymes, weight loss, and bloody diarrhea.2 Destructive bone marrow blood precursors puts patients at risk of developing thrombocytopenia, reticulocytopenia, lymphopenia, and granulocytopenia. Thrombocytopenia predisposes patients to life-threatening hemorrhage and lymphopenia and granulocytopenia that predispose patients to systemic infections. There is also the potential for nephrotoxicity, interstitial pneumonitis, alopecia dermatitis, and an anaphylactic reaction.49,82,83

Fortunately, the adverse effects reported with MTX use for ectopic pregnancy have mostly been minor and the medication has been well tolerated. Stovall et al25 reported on the adverse effects of 100 patients treated with the multidose regimen; 2 patients had stomatitis and 3 had elevated liver transaminases, all of which spontaneously resolved. In a follow-up study of 120 patients receiving a single-dose regimen, one patient was reported to have nausea and vomiting.53 In their meta-analysis, Barnhart et al88 reported the prevalence of adverse effects of about 30–40% using the “single-dose” and “multidose” regimens, finding no difference between the two once they adjusted for β-hCG values (Table 3). A summary of adverse effects and treatment effects of methotrexate administration are listed in the box, “Adverse Effects Associated With Methotrexate Treatment.”

Surgical Resection

Historically, laparotomy with tubal excision (salpingectomy) was not only the treatment for ectopic pregnancy but often the diagnostic procedure as well. Today, with the advent of ultrasonography for diagnosis and laparoscopy for treatment, the minimally
invasive approach has become the preferred surgical approach. Laparotomy is reserved for cases of extensive intraperitoneal bleeding with intravascular compromise due to active bleeding, where hypovolemic shock must be prevented. In such cases, laparotomy via a Pfannenstiel incision allows prompt access to the pelvic structures and identification of the ectopic pregnancy. Other situations in which the open surgical approach may be preferable include extensive pelvic adhesions where adequate visualization of the ectopic is impossible or extra-tubal, intra-abdominal ectopic gestations where risk of injury to other pelvic structures is high.

Compared with open surgery, the laparoscopic approach has been associated with a decreased surgical blood loss, a decrease in the amount of analgesic used, and shorter postoperative hospital stay.\(^8^4\)–\(^8^6\) Not only has the laparoscopic approach been shown to be safe and effective, it is also less costly.\(^8^7\)

Salpingostomy Versus Salpingectomy

Removal of the ectopic pregnancy can be accomplished by resection of the involved fallopian tube with the implanted trophoblastic tissue (salpingectomy) or by dissection and removal of only the ectopic pregnancy with tubal conservation (salpingostomy). Segmental resection of the involved tube with subsequent reanastomosis and tubal reconstruction has fallen out of favor because of the success of bypassing the fallopian tube altogether by using in vitro fertilization. If conservation of the fallopian tube resulted in improved future reproductive success with an equal success rate of treatment of the ectopic pregnancy, then we would recommend salpingostomy for all patients. However, the data to support this contention are not clear-cut. Yao and Tulandi\(^6\) reviewed the data from 9 studies to examine the reproductive outcomes after salpingostomy and salpingectomy. The follow-up period in these studies ranged from 3 months to 15 years. Although the approximately 50% subsequent intrauterine pregnancy rate was similar in patients who had been treated with salpingostomy and those treated with salpingectomy, the rate of a subsequent ectopic appeared higher in the salpingostomy group (15% versus 10%). Other studies have suggested a higher intrauterine pregnancy rate in women after salpingostomy (almost double that of salpingectomy), but at the cost of a 2-fold risk of recurrent ectopic after 3 years of follow-up.\(^3^3\) Another recent study found a high rate of successful pregnancy after salpingostomy (88%) compared with salpingectomy (66%), with an equal recurrent ectopic rate of about 16% after at least 18 months of follow-up and, in some cases, up to 8 years posttreatment.\(^8^8\)

The concern with conservative treatment via salpingostomy is that of the persistence of trophoblast tissue due to incomplete removal from the fallopian tube. This problem has been reported as complicating about 5–20% of cases treated with tubal conservation.\(^8^9\)–\(^9^1\) It has been reported as being higher in those patients treated with laparoscopy than with laparotomy.\(^\star\) It is, therefore, very

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**Table 3. Prevalence of Adverse Effects From Use of “Single-Dose” and “Multidose” Regimens**

<table>
<thead>
<tr>
<th></th>
<th>Single Dose [% (95% CI)]</th>
<th>Multidose [% (95% CI)]</th>
<th>Crude OR</th>
<th>Adjusted OR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effect</td>
<td>31.3 (27.3–35.6)</td>
<td>41.2 (34.8–47.8)</td>
<td>0.44 (0.31–0.63)</td>
<td>0.79 (0.21–3.01)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21.5 (18.0–25.4)</td>
<td>25.6 (19.2–32.8)</td>
<td>0.80 (0.53–1.19)</td>
<td>1.11 (0.83–1.47)</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>12.4 (10.2–14.8)</td>
<td>11.0 (7.2–15.9)</td>
<td>1.11 (0.83–1.47)</td>
<td>1.02 (0.65–1.58)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
* Adjusted for actual hCG value given in original articles.


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**Adverse Effects Associated with Methotrexate Treatment**

**Drug Adverse Effects**

- Nausea
- Vomiting
- Stomatitis
- Gastric Distress
- Dizziness
- Severe neutropenia (rare)
- Reversible alopecia (rare)
- Pneumonitis

**Treatment Effects**

- Increase in abdominal pain
- Increase in βhCG levels during first 1–3 days of treatment
- Vaginal bleeding or spotting

important to document a complete resolution of the ectopic pregnancy by monitoring the β-hCG values until they return to zero. Levels that fail to drop, or ones that plateau, indicate a likely persistent ectopic pregnancy that should be treated. This can be accomplished successfully in almost all cases where tubal rupture is not present by the administration of MTX, with a single dose usually being sufficient. Some clinicians elect to give the MTX immediately after salpingostomy as a prophylactic measure against persistent tissue, especially in cases where incomplete resection is more probable. Very early gestations, ectopic pregnancies less than 2 cm in size, and those with high starting β-hCG levels are at increased risk of persistence.

The decision to perform a salpingostomy as opposed to a salpingectomy is often made intraoperatively. In cases of tubal rupture or obvious severe damage, tubal conservation is not indicated. Likewise, if tubal bleeding is encountered that requires extensive coagulation to achieve hemostasis, then future tubal function would likely be compromised, and salpingectomy may be the appropriate intervention. Recurrent ectopic pregnancy in a previously incised tube should also be treated with salpingectomy.

Complications of Surgery
Complications of surgical treatment of ectopic pregnancy include the usual operative risk factors as well as those associated with anesthesia. Postoperative adhesion formation is more likely after laparotomy than laparoscopy. Postoperative adhesion formation may be reduced by minimizing desiccation and manipulation of pelvic and abdominal structures during surgery, as well as by using barrier agents such as oxidized regenerated cellulose (Interceed; Johnson and Johnson Medical, New Brunswick, NJ).

FOLLOW-UP
Reproductive Outcome
Because ectopic pregnancy occurs mostly as a result of fallopian tube pathology, there is a substantial risk of recurrence, both at a previously operated tubal site and in the contralateral tube. Thus, women who have undergone salpingectomy still have an increased risk of developing an ectopic pregnancy in the remaining tube.

The risk of recurrent ectopic pregnancy after MTX treatment is similar to that after salpingostomy, about 10%. Butts et al found that the risk of a recurrent ectopic pregnancy increased with a history of surgery, history of live birth, and history of spontaneous miscarriage, and not with history of gonorrhea, chlamydia, pelvic inflammatory disease, cesarean delivery, or pregnancy termination. They also found that patients with a recurrent ectopic pregnancy were less likely to bleed on initial presentation, had similar complaints of pain, and like primary ectopic patients, the majority had nondiagnostic initial ultrasound evaluations.

Tubal patency after MTX treatment is best assessed with hysterosalpingography (HSG), and this has been compared with patency after conservative surgery. Stovall summarized the results of his group’s studies. Although we do not know the pre-treatment tubal patency rates, 58 women of 100 study participants who had received multidose MTX for an ectopic pregnancy underwent HSG, and of these, 84.5% had tubal patency and 89.7% had at least one patent tube. After single-dose MTX therapy, 62 patients underwent HSG, with 82.3% showing ipsilateral tubal patency. Hajenius et al found that ipsilateral tubal patency was equal in the groups of patients treated with MTX and salpingostomy. However, they found much lower overall patency rates, 62% in the MTX group and 66% in the salpingostomy group, compared with previous reports.

One group from Sweden followed 89 women who had been treated for ectopic pregnancy with expectant management, MTX, or salpingostomy and found that an equal number in each group had an intrauterine pregnancy within 2½ years. Of those who had been treated with MTX, 64% attained a pregnancy. Dias Pereira et al found that the cumulative spontaneous intrauterine pregnancy rate at 18 months posttreatment for ectopic was 36% in the MTX group and 43% in the laparoscopic salpingostomy group, a difference that was not statistically significant.

Reproductive outcome after a previously treated ectopic pregnancy appears to be similar, whether the treatment method had been MTX or conservative surgery. Intrauterine pregnancy rates seem to be comparable in both of these groups, with a possible slightly lower risk of recurrent ectopic seen in the medically treated group. Women who have had a previous ectopic pregnancy should be followed closely during their subsequent pregnancy to ensure its proper site of implantation. However, even among a population of women at increased risk for ectopic, screening them with transvaginal ultrasonography and performing β-hCG testing when they are asymptomatic does not appear to have much benefit in decreasing morbidity.
REFERENCES


