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Medical Management of Ectopic Pregnancy

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology with the assistance of Donald Fylstra, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

In the United States, ectopic pregnancy accounts for 2% of all first-trimester pregnancies and 6% of all pregnancy-related deaths; it is the leading cause of maternal death in the first trimester (1). Early detection of ectopic pregnancy can lead to successful management without surgery. Methotrexate, a folic acid antagonist, can be used successfully to treat early, nonruptured ectopic pregnancy. The purpose of this document is to review the risks and benefits of the use of methotrexate in the management of ectopic pregnancy.

Background

Incidence

The true incidence of ectopic pregnancy is difficult to estimate because many patients are treated in an outpatient setting. In 1992, ectopic pregnancies accounted for 2% of pregnancies (2). The prevalence of ectopic pregnancy among women presenting to an emergency department with first-trimester vaginal bleeding, abdominal pain, or both has been reported to be as high as 18% (3).

Etiology

Nearly all ectopic pregnancies (97%) are implanted within the fallopian tube, although implantation can occur within the abdomen, cervix, ovary, or uterine cornua. One common factor for the development of an ectopic pregnancy is a pathologic fallopian tube. Causes for such pathology include tubal surgery, genital tract infections leading to pelvic inflammatory disease, previous ectopic pregnancy, and in utero exposure to diethylstilbestrol (4). One third of pregnancies that occur after sterilization failure are ectopic implantations (5, 6), and such pregnancies account for 10% of all ectopic pregnancies (7). Additionally,

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one third of pregnancies after an ectopic pregnancy are also ectopic implantations (7). Other risk factors for the development of ectopic pregnancy include infertility, use of assisted reproductive technologies, previous pelvic or abdominal surgery, and smoking.

Diagnosis

Traditionally, the diagnosis of ectopic pregnancy has been based on the clinical signs and physical symptoms of tubal rupture. However, if ectopic pregnancy is diagnosed before rupture, conservative treatment is an option. By measuring serial human chorionic gonadotropin (hCG) levels and using serial ultrasonography, ectopic pregnancy can be diagnosed before rupture. At least one half of women in whom ectopic pregnancy is diagnosed have no identifiable risk factors or initial definitive physical findings. Early diagnosis is aided by a high index of suspicion. Every sexually active reproductive-aged woman who presents with abdominal pain or vaginal bleeding should be screened for pregnancy (8, 9).

Transvaginal ultrasonography should be considered for all women with suspected early gestational pathology. An initial transvaginal ultrasound examination can be used to visualize an intrauterine pregnancy or a definite extrauterine gestation, or it can be nondiagnostic (10). The woman with a nondiagnostic ultrasound examination result (nothing seen to confirm a gestation inside or outside the uterus) requires further evaluation, including measurement of serum hCG levels. Accurate gestational age calculation, rather than an absolute level of hCG, is the best determinant of when a normal pregnancy should be seen within the uterus with transvaginal ultrasonography. Therefore, if the precise gestational age is known, as in the case of patients conceiving with ovulation induction or embryo transfer, the failure to detect a gestational sac within the uterus by 24 days or later after conception is presumptive evidence of an abnormal pregnancy (13). Without such precise gestational dating, the serum level of hCG must be used in order to interpret a nondiagnostic ultrasonogram. The “discriminatory zone” of hCG is that level of hCG, generalized 1,500–2,000 mIU/mL (International Reference Preparation) (11, 12), which when reached is associated with the appearance, on transvaginal ultrasonography, of a normal singleton intrauterine gestation.

Historically, detection of an intrauterine sac has led to the presumptive exclusion of ectopic pregnancy. However, the incidence of heterotopic pregnancy appears to have increased with the use of assisted reproductive techniques. It has been reported to be as high as 1% in some series (14), although the overall incidence of heterotopic pregnancy probably is much lower.

If the hCG level is higher than the discriminatory zone, and the transvaginal ultrasound examination result is nondiagnostic, ectopic pregnancy is likely (15). However, multiple gestations have higher hCG levels than singletons at any given gestational age and may lead to hCG levels well above 2,000 mIU/mL before ultrasound recognition (13). Therefore, if a multiple gestation is likely, such as in a woman who has conceived with assisted reproductive technology, the discriminatory zone should be reevaluated.

Serum progesterone level determination may help confirm an ectopic pregnancy diagnosis. Serum progesterone values are independent of hCG levels, and an abnormal progesterone level is consistent with an abnormal, failing pregnancy but does not identify the site of the pregnancy (failed intrauterine or ectopic pregnancy). A serum progesterone level less than 5 ng/mL has a specificity of 100% in confirming an abnormal pregnancy (16). Serum progesterone levels higher than 20 ng/mL usually are associated with normal intrauterine pregnancies, and levels between 5 ng/mL and 20 ng/mL are considered equivocal. Most ectopic pregnancies are associated with a serum progesterone level between 10 ng/mL and 20 ng/mL, limiting the clinical utility of this assessment.

In the absence of a diagnostic ultrasound examination result or a low serum progesterone level consistent with a failed pregnancy, serial hCG levels must be used to evaluate an ongoing pregnancy. With 99% sensitivity in early pregnancy, an increase in serum hCG of less than 53% in 48 hours confirms an abnormal pregnancy (17). Therefore, a nondiagnostic ultrasound examination result with a serum progesterone level less than 5 ng/mL and an inappropriate increase in hCG are each associated with an abnormal pregnancy. If necessary, endometrial sampling can be used to differentiate between a failed intrauterine pregnancy and ectopic pregnancy by confirming the presence or absence of intrauterine chorionic villi.

If a woman has an initial nondiagnostic ultrasound examination result, an equivocal or normal serum progesterone level, and an appropriately increasing hCG level, and she remains clinically stable, a transvaginal ultrasound examination should be repeated when the hCG reaches the discriminatory zone. The same diagnostic possibilities then should be considered.

Methotrexate

Methotrexate is an antimetabolite that binds to the catalytic site of dihydrofolate reductase, interrupting the synthesis of purine nucleotides and the amino acids serine and methionine, thus inhibiting DNA synthesis and repair and cell replication. Methotrexate affects actively

proliferating tissues such as bone marrow, buccal and intestinal mucosa, respiratory epithelium, malignant cells, and trophoblastic tissue. Systemic methotrexate has been used to treat gestational trophoblastic disease since 1956 and was first used to treat ectopic pregnancy in 1982 (18). The overall success for treatment of ectopic pregnancy using systemic methotrexate in observational studies ranges from 71.2% to 94.2% (7, 19). Success depends on the treatment regimen used, gestational age, and hCG level. A systematic review of several observational studies reported a failure rate of 14.3% or higher with single-dose methotrexate when pretreatment hCG levels are higher than 5,000 mIU/mL, compared with a 3.7% failure rate for hCG levels less than 5,000 mIU/mL (20). If hCG levels are higher than 5,000 mIU/mL, multiple doses may be appropriate (21).

Clinical Considerations and Recommendations

► *Who are candidates for treatment with methotrexate?*

Methotrexate therapy can be considered for those women with a confirmed, or high clinical suspicion of, ectopic pregnancy who are hemodynamically stable with an unruptured mass. A candidate for methotrexate treatment must be able to comply with follow-up surveillance. Because methotrexate affects all rapidly dividing tissues within the body, including bone marrow, the gastrointestinal mucosa, and the respiratory epithelium, it should not be given to women with blood dyscrasias or active gastrointestinal and respiratory disease. Methotrexate is directly toxic to the hepatocytes and is cleared from the body by renal excretion; therefore, it should not be used in women with liver or kidney disease. Contraindications for the use of methotrexate are listed in the box, "Contraindications to Methotrexate Therapy." Before administering methotrexate, a woman should have a confirmed normal serum creatinine level, normal liver transaminases, and no bone marrow dysfunction indicated by significant anemia, leucopenia, or thrombocytopenia. Typically, these laboratory tests are repeated 1 week after administering methotrexate to evaluate any possible impact on renal, hepatic, and hematologic function.

► *How is methotrexate used in the management of ectopic pregnancy?*

Three protocols are published for the administration of methotrexate to treat ectopic pregnancy: 1) single dose,

Contraindications to Medical Therapy

Absolute contraindications

- Breastfeeding
- Overt or laboratory evidence of immunodeficiency
- Alcoholism, alcoholic liver disease, or other chronic liver disease
- Preexisting blood dyscrasias, such as bone marrow hypoplasia, leukopenia, thrombocytopenia, or significant anemia
- Known sensitivity to methotrexate
- Active pulmonary disease
- Peptic ulcer disease
- Hepatic, renal, or hematologic dysfunction

Relative contraindications

- Gestational sac larger than 3.5 cm
- Embryonic cardiac motion

Methotrexate Treatment Protocols

Single-dose regimen:*

Single dose MTX 50 mg/m² IM day 1
 Measure hCG level on posttreatment days 4 and 7
 Check for 15% hCG decrease between days 4 and 7.
 Then measure hCG level weekly until reaching the nonpregnant level.

If results are less than the expected 15% decrease, re-administer MTX 50 mg/m² and repeat hCG measurement on days 4 and 7 after second dose. This can be repeated as necessary.

If, during follow-up, hCG levels plateau or increase, consider repeating MTX.

Two-dose regimen:†

Administer 50 mg/m² IM on day 0.
 Repeat 50 mg/m² IM on day 4.
 Measure hCG levels on days 4 and 7, and expect a 15% decrease between days 4 and 7.
 If the decrease is greater than 15%, measure hCG levels weekly until reaching nonpregnant level.
 If less than a 15% decrease in hCG levels, readminister MTX 50 mg/m² on days 7 and 11, measuring hCG levels.

(continued)

Methotrexate Treatment Protocols (continued)

Two-dose regimen:[‡] (continued)

If hCG levels decrease 15% between days 7 and 11, continue to monitor weekly until nonpregnant hCG levels are reached.

If the decrease is less than 15% between days 7 and 11, consider surgical treatment.

Fixed multidose regimen:[‡]

Administer MTX 1 mg/kg IM (on days 1, 3, 5, 7), alternate daily with folinic acid 0.1 mg/kg IM (on days 2, 4, 6, 8).

Measure hCG levels on MTX dose days and continue until hCG has decreased by 15% from its previous measurement.

The hCG level may increase initially above pretreatment value, but after 15% decrease, monitor hCG levels weekly until reaching the nonpregnant level.

If the hCG level plateaus or increases, consider repeating MTX using the regimen described.

MTX, methotrexate; IM, intramuscular; hCG, human chorionic gonadotropin.

*Stovall TG, Ling FW. Single-dose methotrexate: an expanded clinical trial. *Am J Obstet Gynecol* 1993;168:1759–62; discussion 1762–5. (Level II-3)

[‡]Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Chakhtoura N. Use of “2-dose” regimen of methotrexate to treat ectopic pregnancy. *Fertil Steril* 2007;87:250–6. (Level III)

[‡]Rodi IA, Sauer MV, Gorrill MJ, Bustillo M, Gunning JE, Marshall JR, et al. The medical treatment of unruptured ectopic pregnancy with methotrexate and citrovorum rescue: preliminary experience. *Fertil Steril* 1986;46:811–3. (Level III)

2) two dose, and 3) fixed multidose (see the box, “Methotrexate Treatment Protocols”). The single 50 mg/m² dose regimen is the simplest and has been shown by some to be as effective as the fixed multidose regimen, eliminating the need for folinic acid rescue to minimize side effects (22). However, a recent meta-analysis has shown the fixed multidose regimen to be more effective, especially in treating women with more advanced gestations and those with embryonic cardiac activity (19). A recent prospective study evaluating a two-dose regimen found high patient satisfaction, few side effects, and 87% treatment success (23).

Methotrexate also can be used after surgical management of an ectopic pregnancy. Treatment failure (persistent ectopic pregnancy) ranges from 2% to 11% after laparotomy and salpingostomy, and from 5% to 20% after laparoscopic salpingostomy (7). A nonruptured,

persistent ectopic pregnancy after salpingostomy diagnosed by monitoring serial hCG levels almost uniformly resolves with a single dose of methotrexate. In one randomized trial, the empiric administration of a single dose of methotrexate immediately after laparoscopic salpingostomy essentially eliminated the risk of subsequent persistent ectopic pregnancy (24). However, many women would need to be treated with methotrexate to prevent one persistent ectopic pregnancy; therefore, monitoring with serum hCG levels may be more useful (25).

► **What surveillance is needed after methotrexate treatment?**

With any conservative surgical or medical treatment of ectopic pregnancy, women require close monitoring to ensure disappearance of trophoblastic activity and elimination of the possibility of persistent ectopic pregnancy after treatment with methotrexate. Persistent trophoblastic activity is confirmed by serially measuring hCG levels. The hCG level may increase initially to levels higher than the pretreatment level, but then should progressively decrease to reach a nonpregnant level (26). Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is considered treatment failure. Therapy with either additional methotrexate administration or surgical intervention is required. Posttreatment hCG levels should be monitored until a nonpregnancy level is reached.

► **What are the potential side effects from systemic methotrexate administration?**

Methotrexate morbidity usually is dose and treatment duration dependent. Because methotrexate affects rapidly dividing tissues, gastrointestinal side effects, such as nausea, vomiting, and stomatitis, are the most common. Therefore, women treated with methotrexate should be advised not to use alcohol and nonsteroidal antiinflammatory drugs (NSAIDs). Elevation of liver enzymes usually is seen only with multidose regimens and resolves after discontinuing methotrexate use or increasing the rescue dose of folinic acid (27). Alopecia is a rare side effect with the doses used to treat ectopic pregnancy. Women should report any fever or respiratory symptoms because pneumonitis has been reported.

It is not unusual for women treated with methotrexate to experience abdominal pain 2–3 days after administration, presumably from the cytotoxic effect of the drug on the trophoblast tissue, causing tubal abortion. In the absence of signs and symptoms of overt tubal rupture and significant hemoperitoneum, this pain usually can be

managed expectantly by monitoring a woman's hemoglobin level and intraperitoneal fluid amount with transvaginal ultrasonography.

► ***How should women be counseled regarding immediate and long-term treatment effects of methotrexate?***

Patients should receive information about the types of side effects they might experience and about activity restrictions during treatment. They should be informed of the ongoing risk of tubal rupture during treatment. It is important to educate patients about symptoms of tubal rupture and to emphasize the need to seek immediate medical attention if these symptoms occur. The patient should be advised during therapy not to use folic acid supplements, NSAIDs, or alcohol, to avoid sunlight exposure, and to refrain from sexual intercourse or vigorous physical activity (27).

Methotrexate is one of the most studied drugs in pregnant women, with an extensive history of use in treating gestational trophoblastic disease. Methotrexate therapy has not been associated with any additional congenital anomalies in future offspring. Comparing systemic methotrexate with tube-sparing laparoscopic surgery, randomized trials have shown no difference in overall tubal preservation, tubal patency, repeat ectopic pregnancy, or future pregnancies (25).

► ***Is there a role for expectant management of ectopic pregnancy?***

Distinguishing patients who are experiencing spontaneous resolution of their ectopic pregnancies from patients who have proliferating ectopic pregnancies and require active intervention is difficult. Candidates for successful expectant management must be willing to accept the potential risks of tubal rupture and hemorrhage; they should be asymptomatic and have objective evidence of resolution (generally manifested by decreasing hCG levels). In general, patients with early tubal gestations with lower hCG levels are the best candidates for observation. Approximately 20–30% of ectopic pregnancies are associated with decreasing hCG levels at the time of presentation (28). If the initial hCG level is less than 200 mU/mL, 88% of patients experience spontaneous resolution, and lower spontaneous resolution rates can be anticipated with higher hCG levels (29). Reasons for abandoning expectant management include intractable or significantly increased pain, failure of hCG levels to decrease, and tubal rupture with hemoperitoneum.

Summary of Recommendations and Conclusions

The following conclusion is based on good and consistent evidence (Level A):

- In comparing systemic methotrexate with tube-sparing laparoscopic surgery, randomized trials have shown no difference in overall tubal preservation, tubal patency, repeat ectopic pregnancy, or future pregnancies.

The following recommendations and conclusions are based on limited or inconsistent evidence (Level B):

- An increase in serum hCG of less than 53% in 48 hours confirms an abnormal pregnancy.
- With an hCG level of 5,000 mIU/mL or higher, multiple doses of methotrexate may be appropriate.
- Methotrexate can be considered in those women with a confirmed, or high clinical suspicion of, ectopic pregnancy who are hemodynamically stable with an unruptured mass.
- Failure of the hCG level to decrease by at least 15% from day 4 to day 7 after methotrexate administration is considered treatment failure requiring therapy with either additional methotrexate administration or surgical intervention.
- Posttreatment hCG levels should be monitored until a nonpregnancy level is reached.

The following conclusion is based primarily on consensus and expert opinion (Level C):

- If the initial hCG level is less than 200 mU/mL, 88% of patients experience spontaneous resolution.

Performance Measure

Percentage of women with an ectopic pregnancy in whom hCG levels are monitored to a nonpregnant level

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and May 2007. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician-gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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