Medical treatment of ectopic pregnancy

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Appropriate use of medical therapy of early ectopic pregnancies is discussed. (Fertil Steril® 2008;90:S206–12. ©2008 by American Society for Reproductive Medicine.)

Ectopic pregnancy is a significant cause of morbidity and mortality in the first trimester of pregnancy (1). Currently, a high index of suspicion, serial hormone assays, and transvaginal ultrasonography (TVU) facilitate the diagnosis and treatment of ectopic pregnancy before rupture occurs. Early nonsurgical diagnosis and timely treatment have resulted in a dramatic decline in mortality due to ectopic pregnancy (1).

Treatment with methotrexate (MTX), a folic acid antagonist highly toxic to rapidly replicating tissues, now reportedly achieves results comparable to surgery for the treatment of appropriately selected ectopic pregnancies and is used commonly (2). An unruptured ectopic pregnancy can be managed with either surgery or methotrexate. Surgery is specifically indicated in cases of suspected tubal rupture and when MTX is contraindicated.

PREVALENCE

There are more than 100,000 ectopic pregnancies reported per year in the United States, but the actual number is almost certainly much greater because only cases managed surgically are reported (3, 4). At least 90% of all ectopic pregnancies are located in the fallopian tube, and 80% of those are located in the ampullary segment of the tube (5).

RISK FACTORS

Any pregnant woman can potentially have an ectopic pregnancy. Damage to the fallopian tubes predisposes a woman to ectopic pregnancy. Knowledge of risk factors can help identify women who may benefit from close monitoring and early treatment. High-risk conditions include [1] previous ectopic pregnancy; [2] history of tubal surgery, including a previous tubal sterilization; [3] history of sexually transmitted infection, tubal infection, or pelvic adhesions; [4] current use of an intrauterine device; [5] conception resulting from assisted reproduction; [6] cigarette smoking; and [7] in utero exposure to diethylstilbestrol (6–8).

DIAGNOSIS

Timely diagnosis of ectopic pregnancy is important to reduce risk of rupture and improve the success of medical management. Diagnosis of all women at risk for ectopic pregnancy should be prompt but is not always an emergency. Any reproductive age woman experiencing abnormal vaginal bleeding with or without abdominal pain is at risk for ectopic pregnancy. Such women should be followed closely until a diagnosis is made. Given the high risk of recurrence, women with history of a previous ectopic pregnancy should be followed carefully, even in the absence of symptoms. A hemodynamically stable woman at risk for an ectopic pregnancy should be diagnosed before rupture, a goal that often can be accomplished without laparoscopy. For women who present in shock, immediate surgery is both diagnostic and therapeutic.

Diagnostic approaches that use serial hCG, ultrasonographic examinations, and sometimes uterine curettage facilitate the early diagnosis of ectopic pregnancy (9–11). A gestational sac (or sacs) should become visible by TVU between 5.5 and 6.0 weeks gestational age (12, 13). In sequence, structures such as a gestational sac ("double decidual sign"), yolk sac, and fetal pole with later cardiac motion become visible by TVU. When gestational age is not known, hCG levels can provide alternate criteria for timing and interpretation of TVU (14, 15).

It now is widely accepted that above the discriminatory zone of 1,500 IU/L–2,500 IU/L, a normal intrauterine pregnancy (IUP) should be visible by TVU. The absence of an intrauterine gestational sac when the hCG concentration is above the discriminatory zone implies an abnormal gestation. The specific cutoff value for hCG used at each institution will depend on clinical expertise and the specific characteristics of the hCG assay used. A more conservative discriminatory zone, that is, higher hCG level, may be used to minimize the risk of terminating a viable pregnancy (16). In the case of multiple pregnancy, hCG levels are higher at an early stage of development than in singleton intrauterine gestations, but the rate of increase remains similar (17).

If the initial hCG level is below the discriminatory zone, and TVU cannot identify definitively an intrauterine or extrauterine gestation, then serial hCG measurements are needed to document either a growing, potentially viable or a nonviable pregnancy. The minimum rise for a potentially viable pregnancy in women who present with symptoms of pain and/or vaginal bleeding is 53% per two days, based on the 99th percent confidence interval (CI) around the mean of the curve for β-hCG rise (up to 5,000 IU/L) over time (16). Intervention when the β-hCG level rises less than 66% over

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2 days, a practice supported by previous data, potentially may result in the interruption of viable pregnancies (18). When the hCG levels have risen above the discriminatory zone, ultrasound should be used to document the presence, or absence, of an IUP.

Declining hCG values suggest a failing pregnancy. Serial hCG levels can be used to show that the gestation is regressing spontaneously. After a complete abortion, hCG levels decline at least 21%–35% every 2 days, depending on the initial value (19). However, a decline in hCG concentrations at this rate, or faster, does not exclude entirely the possibility of a resolving ectopic pregnancy or its rupture.

The absence of a gestational sac with an hCG above the discriminatory zone, or an abnormally rising or declining hCG level, suggests an abnormal pregnancy but does not distinguish an ectopic pregnancy from a failed intrauterine gestation. The presumption of an ectopic pregnancy in such circumstances can be incorrect in up to 50% of cases (20). A uterine curettage and evaluation of uterine contents may be helpful to differentiate an abnormal IUP from an ectopic pregnancy (20). Limited endometrial biopsy, such as may be performed with a pipelle suction cannula or similar instrument, is insufficient (21, 22). Alternatively, if hCG levels continue to rise after curettage, the diagnosis of ectopic pregnancy is established.

Effort should be made to diagnose ectopic pregnancy definitively before medical treatment with MTX. Medical treatment for a suspected ectopic pregnancy without a definitive diagnosis does not reduce complication rates or cost because many women with undiagnosed miscarriage would otherwise be exposed to MTX and its side effects unnecessarily (20, 23). Potential consequences of medical management of a presumed ectopic pregnancy include [1] subsequent pregnancies will be viewed as high risk for recurrent ectopic pregnancy resulting in repeated, costly, and anxiety-provoking diagnostic evaluations; [2] apparent efficacy of MTX to treat ectopic pregnancy will be artificially increased; and [3] an IUP may be exposed to a known teratogen and abortifacient (24–26). Exposure of a viable pregnancy to MTX may result in embryopathy, a very serious and avoidable complication that is being reported with increasing frequency (24).

TREATMENT

Medical treatment protocols for MTX were established in the late 1980s and have become a widely accepted primary treatment for ectopic pregnancy (27–31). MTX is a folic acid antagonist (26, 32). Folic acid normally is reduced to tetrahydrofolate by the enzyme dihydrofolate reductase (DHFR), a step in the synthesis of DNA and RNA precursors. MTX inhibits DHFR, causing depletion of cofactors required for DNA and RNA synthesis. Folinic acid (leucovorin) is an antagonist to MTX that can help reduce otherwise prohibitive side effects, particularly when higher doses of MTX are used (26, 32).

TABLE 1

Contraindications to MTX therapy (25, 26, 29–31).

Absolute contraindications
Intrauterine pregnancy
Evidence of immunodeficiency
Moderate to severe anemia, leukopenia or thrombocytopenia
Sensitivity to MTX
Active pulmonary disease
Active peptic ulcer disease
Clinically important hepatic dysfunction
Clinically important renal dysfunction
Breast feeding
Relative contraindications
Embryonic cardiac activity detected by transvaginal ultrasonography
High initial hCG concentration (>5,000 mIU/mL)
Ectopic pregnancy >4 cm in size as imaged by transvaginal ultrasonography
Refusal to accept blood transfusion
Inability to participate in follow-up

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Ideally, a candidate for medical management with MTX should meet the following criteria: [1] hemodynamic stability, [2] no severe or persistent abdominal pain, [3] commitment to follow-up until the ectopic pregnancy has resolved, and [4] normal baseline liver and renal function tests. Contraindications to MTX treatment are listed in Table 1.

Prior to the first dose of MTX, women should be screened with a complete blood count, liver function tests, serum creatinine and blood type and Rh. Women having a history of pulmonary disease also should have a chest x-ray because of the risk of interstitial pneumonitis in patients with underlying lung disease.

There are two commonly used MTX treatment regimens: "multiple dose" and "single dose." Schema for treatment and follow-up for the two regimens are summarized in Tables 2 and 3, respectively. The multiple-dose protocol is a regimen adapted from early experience with MTX treatment for trophoblastic disease and was the regimen first used to treat ectopic pregnancy (27, 28). The multiple-dose protocol alternates MTX treatment with leucovorin therapy. MTX is continued until hCG falls by 15% from its peak concentration. Approximately 50% of patients so treated will not require the full 8-day regimen (29, 30). The term "single dose" actually is a misnomer. Whereas it describes the number of MTX injections planned, the regimen includes provisions for additional doses of MTX when the response is inadequate (33–35).

TABLE 2

Multiple-dose MTX treatment protocol (28, 29).

Treatment day	Laboratory evaluation	Intervention
Pretreatment	hCG, CBC with differential, liver function tests, creatinine, blood type and antibody screen	Rule out spontaneous Ab Rhogam if Rh negative
1	hCG	MTX 1.0 mg/kg IM
2		LEU 0.1 mg/kg IM
3	hCG	MTX 1.0 mg/kg IM if <15% decline day 1–day 3 If >15%, stop treatment and start surveillance
4		LEU 0.1 mg/kg IM
5	hCG	MTX 1.0 mg/kg IM if <15% decline day 3–day 5 If >15%, stop treatment and start surveillance
6		LEU 0.1 mg/kg IM
7	hCG	MTX 1.0 mg/kg IM if <15% decline day 5–day 7 If >15%, stop treatment and start surveillance
8		LEU 0.1 mg/kg IM

Note: Surveillance every 7 days (until hCG <5 mIU/mL).

Screening laboratory studies should be repeated 1 week after the last dose of MTX. LEU = leucovorin; IM = intramuscularly.

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In both single- and multiple-dose MTX treatment protocols, once hCG levels have met the criteria for initial decline, hCG levels are followed serially at weekly intervals to ensure that concentrations decline steadily and become undetectable. Complete resolution of an ectopic pregnancy usually takes between 2 and 3 weeks but can take as long as 6 to 8 weeks when pretreatment hCG levels are in higher ranges (29, 30, 35). When declining hCG levels again rise, the diagnosis of a persistent ectopic pregnancy is made.

When the criteria described earlier are fulfilled, treatment with MTX yields treatment success rates comparable to those achieved with conservative surgery (2, 30, 31). Numerous open-label studies have been published demonstrating the efficacy of both MTX treatment regimens. One review concluded that MTX treatment was successful in 78%–96% of selected patients. Post-treatment hysterosalpingography documented tubal patency in 78% of cases; 65% of patients who attempted subsequent pregnancies succeeded, and the

TABLE 3

Single-dose MTX treatment protocol (33).

Treatment day	Laboratory evaluation	Intervention
Pretreatment	hCG, CBC with differential, liver function tests, creatinine, blood type and antibody screen	Rule out spontaneous Ab Rhogam if Rh negative
1	hCG	MTX 50 mg/m^2 IM
4	hCG	
7	hCG	MTX 50 mg/m^2 IM if β-hCG decreased <15% between day 4 and day 7

Note: Surveillance every 7 days (until hCG <5 mIU/mL).

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TABLE 4

Caveats for physicians and patients regarding the use of MTX (25, 26, 30, 31, 33, 44).

Avoid intercourse until hCG is undetectable.
Avoid pelvic exams and ultrasound during surveillance of MTX therapy.
Avoid sun exposure to limit risk of MTX dermatitis.
Avoid foods and vitamins containing folic acid.
Avoid gas-forming foods because they produce pain.
Avoid new conception until hCG is undetectable.

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TABLE 5

Predictors of MTX treatment failure (38–41, 45).

Adnexal fetal cardiac activity
Size and volume of the gestational mass (>4 cm)
High initial hCG concentration (>5,000 mIU/mL)
Presence of free peritoneal blood
Rapidly increasing hCG concentrations (>50%/48 hours) before MTX
Continued rapid rise in hCG concentrations during MTX

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incidence of recurrent ectopic pregnancy was a relatively low 13% (29, 31).

There have been no randomized trials directly comparing the two different MTX treatment protocols. In a meta-analysis including data from 26 articles and 1,327 cases, the overall success rate for MTX treatment was 89% (35). The success rate of the multiple-dose regimen was 92.7% (95% CI, 89–96), which was statistically significantly higher than that achieved with the single-dose regimen (88.1%; 95% CI, 86–90) (35). After controlling for initial hCG values and the presence of embryonic cardiac activity, the failure rate for single-dose therapy was higher than that for multiple-dose treatment (odds ratio 4.75, 95% CI, 1.77–12.62) (33). A small randomized clinical trail also noted that single-dose therapy has a higher failure rate, but the difference was smaller (RR = 1.50; 95% CI, 0.44–5.01) (36). It is possible, but not established, that the difference in failure rates between the two protocols may not be as dramatic in women with an overall good prognosis for successful medical treatment.

A hybrid protocol, involving two equal doses of MTX (50 mg/m^2) administered on days 1 and 4 without leucovorin rescue and follow-up as described previously for the single-dose protocol, may offer a more optimal balance between convenience and efficacy (37). The protocol also allows for more than 2 doses of MTX when hCG values do not decrease 15% between days 4 and 7.

Regardless which protocol is used, physicians and patients should be aware of a number of important caveats when using MTX for the treatment of ectopic pregnancy (Table 4).

Predictors of MTX Failure

The most commonly identified predictors of MTX treatment failure are listed in Table 5. Whereas the prognosis for successful medical treatment has been demonstrated repeatedly to correlate with the initial hCG level, no consensus on a threshold value that best predicts success or failure has been established (38–41). One study noted that the failure rate of single-dose treatment was 13% (6/45) for initial hCG values between 5,000 IU/L and 9,999 IU/L, 18% (4/22) for concentrations between 10,000 IU/L and 14,999 IU/L, and 32% (7/22) when hCG values exceeded 15,000 IU/L (41). Another observed a 65% (9/17) failure rate for single-dose treatment with initial hCG levels above 4,000 IU/L (38), and still others have reported failure rates of 57% and of 62% when the initial hCG concentration is over 5,000 IU/L (39, 40). Analysis after combining all published data yields an OR for failure of 5.45 (95% CI, 3.04–9.78) when the initial hCG value above 5,000 IU/L compared with that observed when hCG concentrations are below that threshold. The failure rate for single-dose MTX treatment stratified by initial hCG level is illustrated in Figure 1. Because the failure rate rises with the pretreatment hCG concentration, the single-dose MTX treatment regimen may be better reserved for patients with a relatively low initial hCG value (35, 39, 40).

Treatment

Overall, MTX is a safe and effective treatment for an unruptured ectopic pregnancy. Very rarely, life-threatening complications have been reported with MTX (42, 43). More commonly encountered treatment and side effects of MTX are listed in Table 6. Some patients develop transient pain ("separation pain") between 3 and 7 days after treatment begins (44), but such pain normally resolves within 4 to 12

FIGURE 1

Single-dose MTX treatment failure based on hCG level.

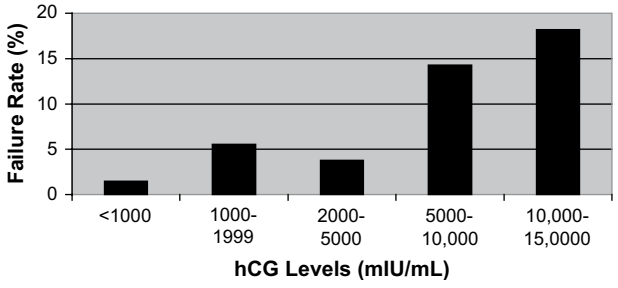

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TABLE 6

Treatment and side effects associated with MTX (25–27, 35, 42–44).

Treatment effects
Increase in abdominal girth
Increase in hCG during initial therapy
Vaginal bleeding or spotting
Abdominal pain
Drug side effects
Gastric distress, nausea, and vomiting
Stomatitis
Dizziness
Severe neutropenia (rare)
Reversible alopecia (rare)
Pneumonitis (rare)

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hours after onset. When pain is severe and persistent, it is prudent to evaluate the patient's vital signs and hematocrit, and if rupture is suspected, surgery should be performed.

Signs of treatment failure or suspected rupture are indications to abandon medical medical management and to proceed with surgical treatment. Signs suggesting treatment failure or possible rupture include hemodynamic instability; increasing abdominal pain, regardless of trends in hCG levels; and rapidly increasing hCG concentrations (>53% over 2 days) after four doses in the multi-dose regimen or after two doses in the single-dose regimen (45).

Serial ultrasonographic examinations after MTX treatment are unnecessary because ultrasonographic findings cannot demonstrate or predict treatment failure, unless evidence of recent tubal rupture is observed (46).

ADJUNCTIVE USE OF MTX

A persistent ectopic pregnancy can develop after salpingostomy or medical management. Consequently, it is important to monitor hCG levels until they become undetectable. When hCG levels rise or plateau, persistent trophoblastic tissue can be treated successfully with a single dose of MTX (47). MTX also can be given immediately after salpingostomy as a prophylactic measure, especially in circumstances where incomplete resection is more likely (47, 48). Risk for persistent ectopic pregnancy is increased in very early gestations, those measuring less than 2 cm in diameter, and when initial hCG concentrations are relatively high (48).

UNUSUAL ECTOPIC PREGNANCIES

Extratubal ectopic pregnancies make up less than 10% of all ectopic pregnancies but are associated with greater morbidity (49). Surgery often is the most appropriate first-line treatment in such cases, but multiple-dose MTX also has been used effectively.

Heterotopic Pregnancy

Heterotopic pregnancy is defined by coexisting intrauterine and extrauterine pregnancies. Approximately 1% of pregnancies resulting from assisted reproduction are heterotopic pregnancies. Unfortunately, approximately 50% of heterotopic pregnancies present with symptoms of acute rupture. Surgery usually is required and MTX is contraindicated (50, 51).

Interstitial Pregnancy

Interstitial, or cornual, pregnancies are highly morbid, with 2.2% maternal mortality. Approximately 4.7% of ectopic pregnancies implant in the interstitial segment of the tube. Such pregnancies generally are associated with very high serum hCG levels. The estimated success rate for medical treatment of interstitial pregnancy is lower than that for treatment of ectopic pregnancies located in the tubal ampulla or isthmus (52). When the embryo exhibits cardiac activity, direct injection of potassium chloride into the embryo or fetus has been suggested as an adjunct to systemic MTX treatment that may help to prevent further growth and development. Emergency hysterectomy sometimes is required (53).

Cervical Pregnancy

Cervical pregnancies are rare. Ultrasonography is the most useful diagnostic tool. Systemic MTX and uterine artery embolization have been used successfully to treat cervical pregnancy. In the presence of cardiac activity, ectopic pregnancies have also been successfully treated with direct injection of potassium chloride or MTX (54, 55).

Ovarian and Abdominal Pregnancies

Ovarian and abdominal pregnancies are diagnosed definitively at the time of surgical exploration. Therefore, MTX is not a first- line treatment for this condition.

COST ANALYSIS

Approximately 40% of women diagnosed with an ectopic pregnancy are candidates for medical management (35), and 90% of those can be treated successfully without surgery (30, 31). Whereas the costs of surgery and out-patient medical management vary widely with the treating facility and the region of the country, many cost-effectiveness analyses have favored MTX therapy. Because medical treatments can be administered in an office setting, MTX is less expensive than surgery. Primary surgical therapy is favored when the likelihood of failure or morbidity from medical treatment is high and when the time to resolution is likely to be prolonged. Such cases generally are characterized by high initial hCG levels and/or the presence of embryonic cardiac activity (56, 57).

SUMMARY AND RECOMMENDATIONS

- Ectopic pregnancies can be diagnosed at early stages, even before symptoms become evident.
- Both conservative surgery and medical therapy may be viewed as appropriate first-line therapy.
- Serial serum hCG determinations, TVU examinations, and uterine curettage provide the means for early diagnosis.
- Success rates and fertility after treatment are comparable for medical therapy and conservative surgical treatment.
- Medical therapy appears more cost-effective than surgery except when the initial hCG level is high and/or embryonic cardiac activity is observed.
- Multiple-dose MTX treatment has a lower failure rate than single-dose MTX. Single-dose MTX is sufficient to treat persistent trophoblastic tissue after salpingostomy and ectopic pregnancies associated with low initial hCG values.
- Postoperative, prophylactic, single-dose systemic MTX may reduce the incidence of persistent ectopic pregnancy after salpingostomy.
- MTX-induced embryopathy is a serious and avoidable complication that may arise when a viable pregnancy is misdiagnosed as an ectopic pregnancy and exposed to MTX treatment.

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