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Medical Management of Ectopic Pregnancy: A Comparison of Regimens

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Abstract

Medical management has become increasingly popular in the treatment of ectopic pregnancy. Given its convenience, for many it is used as a first line treatment, but this is not always the optimal choice for the patient. It is important to understand the options for medical treatment and when it is appropriate to treat a particular patient with medical management, or when one should opt for surgical management. This review outlines the different regimens for methotrexate administration and the associated risks and benefits to medical management.

Keywords

Ectopic pregnancy; methotrexate; treatment; hCG; medical treatment

Introduction

The incidence of ectopic pregnancy is 1–2% in the United States. Since the 1980's, there has been a significant decline in mortality, decreasing from 1.15 deaths per 100,000 between 1980–1984 to 0.50 deaths per 100,000 between 2003–2007. Despite this decrease, ectopic pregnancy is still a leading cause of morbidity and mortality and there remains a racial disparity, with a higher mortality rate for African American women.¹ While there are a greater percentage of women treated medically as compared to surgically, one must remain mindful of both the advantages and limitations of medical and surgical management of ectopic pregnancy and when it is appropriate to use a specific treatment. Medical management may not always be the optimal choice for a particular patient. We summarize here various options for medical management, their success rates and disadvantages.

Pharmacology of Methotrexate

Methotrexate is a folate antagonist, which acts to block DNA synthesis by inactivating the enzyme dihydrofolate reductase. Its main action is in S phase of the cell cycle, but it can affect cells at any stage of the cell cycle. Methotrexate acts on rapidly dividing cells at the implantation site, most notably trophoblast cells.²

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Indications and contraindications for methotrexate treatment

As methotrexate affects rapidly proliferating tissues, absolute contraindications include conditions that may be affected by the effects of methotrexate including chronic liver disease, pre-existing blood dyscrasias, pulmonary disease, peptic ulcer disease and immunodeficiency. Additionally, patients who have sensitivity to methotrexate, have an intrauterine pregnancy, or are breastfeeding are not candidates for methotrexate therapy.

Relative contraindications include an unruptured mass, >3.5 cm, fetal cardiac activity and a quantitative hCG level which exceeds 6,000–15,000 mIU/ml.³ These contraindications have been developed to limit treatment to early gestations and those without evidence of early or impending rupture. Of note, the contraindication of a large mass is likely due to the presence of hemorrhage within the fallopian tube. The contraindication is not the size of the gestational sac (as erroneously labeled in the table in the ACOG practice bulletin).³ In these situations, a clinician must make the best decision for the patient, keeping in mind that methotrexate success rates decrease when these circumstances exist. This decreased success rate must be clearly disclosed to the patient.

Medical treatment protocols

The use of methotrexate to treat ectopic pregnancy was first cited in 1982.⁴ Several studies followed this one and demonstrated successful treatment of ectopic pregnancy using alternating doses of methotrexate and leucovorin.^{5–7} This protocol, known as the multiple dose protocol, was modified from the treatment of choriocarcinoma. The multiple dose regimen consists of an intramuscular injection of 1 mg/kg of methotrexate with 0.1 mg/kg leucovorin factor rescue 24 hours later. Leucovorin is folinic acid, which is the active form of folic acid. It is used to protect cells from effects of methotrexate and decrease its side effects. This regimen is continued on alternating days until the hCG level drops by 15% over two days. Up to 4 doses may be given to one patient, but not all four doses have to be given. In a study by Stovall et al,⁷ 96 of 100 patients were successfully treated and none required more than four doses. The overall success rate of multi-dose treatment in a meta-analysis by Barnhart et al is reported as 92.7% (241 of 260 patients) with a 95% CI 89–96%.⁸

In 1991, a one-dose protocol was proposed, but this protocol is a misnomer as often more than one dose is often needed. Their protocol consisted of 50 mg/m² of methotrexate administered on day 0. Serial hCG values are drawn and compared between days 4 and 7 post treatment. Treatment is considered successful if a 15% drop in hCG level is noted between days 4–7. However, a second dose is administered on day 7 if a 15% drop is not observed and the patient remains an appropriate candidate for medical management. Thirty patients were enrolled in this study and 29/30, or 96.7%, patients were successfully treated. The quantitative hCG range for these patients was 30–16,700 mIU/ml. Five out of 6 patients who had ectopic pregnancies with cardiac activity were also successfully treated.⁹

The convenience of this method was widely appreciated and it gained popularity. In 1993, an expanded study was reported in which 120 patients were administered single dose methotrexate treatment. A total of 113 of 120 (94.2%) patients were successfully treated. Only 4 patients required a second dose of methotrexate on day 7. In this study, the mean time to pregnancy following treatment was 3.2 months (+/- 1.1).¹⁰

Many other case series of the use of single dose methotrexate have been reported in the literature, not all of which were able to replicate the success reported in these early manuscripts. Explanation regarding disparate success rates included a widening of inclusion criteria to women with more advanced gestations. Often, patients require a second “single dose.” One study quotes 14%,⁸ but both higher and lower percentages have also been

recorded, ranging from 6–78%. An additional concern was that the original success rates may have been overstated, as a uterine evacuation was not performed to rule out the possibility of treatment of a miscarriage.

A meta-analysis estimated the overall success rate of single dose protocol to be 88.1% with a 95% CI of 86% to 90%.⁸ The failure rate of single dose administration of methotrexate was estimated to be 1.96 times higher than the use of multidose treatment (CI 1.07 to 3.60, $P = 0.03$). Of note, the difference in success rates between the two protocols was confounded in that clinicians were treating women with good prognosis with single dose, and those with a higher chance of failure with multidose (i.e. those with a higher hCG value or with fetal cardiac activity). When this was corrected in a multivariable analysis, the difference in the failure rate between the two protocols was even more pronounced. The OR adjusted for hCG was 2.34 (CI 1.05 to 5.23, $P = 0.04$) and the OR was 4.74 (CI 1.77 to 12.6, $P = 0.02$) when adjusted for cardiac activity.

The advantages to the single dose protocol over multi-dose protocol are that patients require fewer visits and fewer injections. As more clinicians are using the single dose protocol, it was clear that convenience was chosen over efficacy. In an attempt to increase efficacy and maintain convenience, a novel protocol was introduced in 2007.¹¹ The two-dose protocol maximized the dose of methotrexate, without the need for leucovorin rescue. The goal of this treatment is to improve the success rate of single dose therapy, by administering two doses of methotrexate (on day 0 and day 4) while continuing the same surveillance of hCG values on days 4 and 7. Thus, no extra visits were added, maintaining convenience for patients.

In this protocol, successful treatment is considered a 15% drop in hCG between days 4–7. A second course may be given on day 7 if an appropriate drop in hCG is not observed, as long as the patient remains a candidate for methotrexate therapy. If a 15% drop is not observed between days 11–14, then the patient is referred for surgical treatment. A total of 101 patients were enrolled in the study. Of those, 88% were treated successfully with medical management. However, of those who underwent (or elected) surgical management, only 3% had a ruptured ectopic pregnancy in the course of the study. To date there have been no well-powered comparative studies between the two dose protocol and the single dose protocol, or the multidose protocol. See Table 1 for a summary of medical management protocols.

Choice of the appropriate candidate for medical management

In deciding whether a patient is a suitable candidate for medical management, it is essential to evaluate factors associated with success and failure (See Table 2). Lipscomb et al¹² studied 350 women treated with the single dose protocol. In this particular study, 91% of women were successfully treated. A high initial hCG level was the most important factor associated with failure. In patients who were successfully treated, the mean hCG level was 4019 (+/- 6362) and cardiac activity was noted in 12% of these cases. In the 30 women in whom treatment was unsuccessful, the mean hCG value was 13,420 (+/- 16,590) and cardiac activity was present in 30% of ectopics. HCG values > 5,000, an ultrasound with moderate-large free fluid, fetal cardiac activity, increase in serum hCG over a 48 hour period have all been associated with failure of medical management.¹³ A study by Mol et al¹⁴ recommends single dose methotrexate for initial hCG values <1,500 and multi-dose methotrexate for initial hCG values <3,000.

There is no established true cut-off, only a suggestion regarding a value below which methotrexate therapy will be more successful. The decision to proceed with medical or surgical management depends on the clinician's discussion with the patient. It is clear that

success rates decrease with increasing hCG. Individual situations in which methotrexate treatment is used with high initial hCG values may be appropriate, but success rates are not the same as all-comers. Consenting should be altered when choosing to use methotrexate in a woman with a high hCG value and the patient should understand the chance of failure is higher than the “typical” patient.

Additional considerations in the choice of patients to receive medical therapy include life circumstances and compliance. Laparoscopic treatment of an ectopic pregnancy is safe and swift. Laparoscopy also allows assessment of the pelvis, which may provide prognostic information for the likelihood of a subsequent desired pregnancy, or the need for assisted reproductive technologies. For those who do not desire future fertility, surgical sterilization is also an alternative concomitant with treatment of the ectopic pregnancy.

The use of methotrexate necessitates multiple office visits and surveillance of hCG values for weeks. If presented with an alternative many women do not preferred multiple visits due to competing demands of their time; including employment and/or child care. A second often unrealized drawback is that women can be falsely reassured that the treatment for the ectopic pregnancy is complete at the time of the injection and do not comply with the necessary follow up.

One study assessing compliance of methotrexate therapy noted that only 45.5% of patients completed follow-up, defined as documented resolution of hCG from the serum. Only 19.7% completed “appropriate” follow-up, which was defined as returning day 4, day 7 and weekly until hCG levels declined to zero. A total of 24% of patients in this group required surgery.¹⁵ Patients who are non-compliant with visits may not be appropriate candidates for methotrexate treatment, as this may put them at greater risk for adverse events. Of note, it is completely illogical to offer a single dose therapy to a woman who may have difficulty with compliance because it is only “one dose.”

This aforementioned study was conducted in an inner city environment and may be difficulty to generalize to all populations. Others have also demonstrated a lower success rate of medical management for women of low socioeconomic status. In one study, patients with low socioeconomic status were 5 times more likely to fail methotrexate treatment.¹⁶ It is not clear if this increased failure rate is due to a later presentation in the course of the disease, lower compliance, or true biological disparity.

Risks of methotrexate treatment

When administering methotrexate therapy, it is essential to remain aware of the risks and side effects of medical management. Rupture of ectopic pregnancy during methotrexate treatment ranges from 7–14%. The rate of increase in hCG is one predictor of rupture.¹⁷ In this particular retrospective case control study, 81 women were diagnosed with ectopic pregnancy and treated with methotrexate. A total of 62 women exhibited resolution of ectopic, while 19 ruptured. The majority of ruptured ectopic pregnancy occurred when there was an increase of hCG at least 66% after 48 hours persistently rising hCG concentration despite treatment. At least 9 of 19 patients who ruptured had hCG concentrations greater than the relative contraindication hCG value for methotrexate treatment.

Side effects should not be overlooked with methotrexate treatment. Most common side effects are mild and include nausea, vomiting, stomatitis, diarrhea, and elevated liver function tests. Rare, but severe side effects include nephrotoxicity, interstitial pneumonitis and alopecia dermatitis. Side effects can be limited by dose and length of treatment.

Risk of treatment of an intrauterine pregnancy

The use of methotrexate in women with an intrauterine gestation is absolutely contraindicated. Despite this contradiction, the treatment of a pregnancy of unknown location with methotrexate is common. Many women are treated with methotrexate when an ectopic pregnancy is suspected (based on non specific ultrasound findings) when the positive predictive value is only approximately 80%.¹⁸ More problematic is that some women are treated with methotrexate simply when there is no evidence of an intrauterine gestation. It has been repeatedly demonstrated that up to 50% of women with a high hCG value and no evidence of an intrauterine pregnancy on ultrasound have an intrauterine gestation, not an ectopic pregnancy.^{19–21}

There are numerous reports that have later documented an intrauterine pregnancy after a woman was treated with methotrexate. Often treatment of an intrauterine pregnancy results in miscarriage. However, some of these instances of women treated without a definitive ectopic pregnancy diagnosed have resulted in live born infants with malformations. While it is understandable that such occurrences are not often reported in the medical literature, there are reports documenting the teratogenicity of methotrexate. In one case report, a patient who was taking oral methotrexate for psoriasis gave birth to a fetus with craniofacial, skeletal, cardiovascular and gastrointestinal anomalies. In this case there was only a short, low-dose exposure to methotrexate in the first trimester.²² Another case report cited a woman who was given methotrexate at 5 weeks gestation for suspected ectopic pregnancy. In actuality, she had an intrauterine pregnancy, which survived and resulted in multiple skeletal anomalies and ambiguous genitalia.²³ A similar case was described in which methotrexate was given to a woman at 5 weeks gestation for suspected ectopic. Later in the pregnancy, an 8-week twin intrauterine pregnancy was diagnosed and spontaneously reduced to a singleton. The surviving singleton was born with a birth weight less than the fifth percentile and with hypertelorism, facial nerve palsy, scoliosis and cardiovascular abnormalities, among others.²⁴ Wrongful treatment of a woman with methotrexate has become a common reason for medical liability.

Summary

The treatment of an ectopic pregnancy with methotrexate is safe and effective in carefully selected cases. Although methotrexate treatment is beneficial in that it allows one to avoid surgery in a patient, there are certain disadvantages. Medical treatment requires extended follow-up of patients, which can be cumbersome and difficult for some patients. The need to follow patients clinically until the serum hCG is undetectable requires multiple visits, which takes valuable time from both patient and clinician. In comparison, surgical management is also safe, effective and often requires fewer follow-up visits. Furthermore, patients who are treated surgically have the same fertility rate as those who undergo methotrexate treatment. Some studies have even suggested that methotrexate doses used to treat ectopic pregnancy may worsen ovarian function in the short term,²⁵ while others do not show an effect.²⁶ These studies are limited and further studies are needed to evaluate the effect of low-dose methotrexate on ovarian reserve.

In conclusion, it is appropriate for clinicians to select suitable candidates for treatment of ectopic pregnancy with methotrexate. It is imperative to confirm diagnosis to avoid unnecessary administration of a chemotherapy, such as in a completed miscarriage, or early intrauterine pregnancy, that can have severe consequences for both mother and fetus.²⁷ There is usually no indication that methotrexate has to be administered at the first presentation of the patient, especially if she is clinically stable. If a woman is not stable, or is in significant pain, she is not a candidate for medical management. Follow up hCG or

ultrasound can often avoid unnecessary or contraindicated administration of methotrexate. Moreover, patients should have appropriate counseling, willingness for follow-up and no absolute contraindications to methotrexate treatment. Despite high success rates, there remains a substantial rate of failure, particularly in low socioeconomic groups. The choice between two acceptable treatments, medicine or surgery, should be an informed, not reflective decision.

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Methotrexate regimens used to treat ectopic pregnancy Modified from Barnhart et al.⁸

Table 1

Protocol	Dose MTX	Regimen	hCG measurement	Treatment success	When to administer additional dose
Multidose	1 mg/kg and 0.1 mg/kg LEU	Alternate daily doses of each	Days 0, 1, 3, 5, 7	hCG declines 15% from previous value	2 nd , 3 rd or 4 th dose given if hCG does not decline 15% from previous value. Maximum 4 doses
Single dose	50 mg/m ²	Day 0	Days 0, 4, 7	hCG declines 15% between Day 4 and 7	Second dose on Day 7 if hCG does not decline 15%
Two dose	50 mg/m ²	Day 0 and Day 4	Days 0, 4, 7	hCG declines 15% between Day 4 and 7	Second course on Day 7 if hCG does not decline 15%

MTX = Methotrexate, LEU = Leucovorin

Table 2

Selection of appropriate candidate for medical management of ectopic pregnancy.³

Contraindicated	Good Candidate	Poor Candidate
Hemodynamically unstable	Hemodynamically stable	High hCG (>5000 mIU/ml)
Suspected ruptured EP	Low hCG (< 5000 mIU/ml)	Large mass (>3.5 cm)
Sensitivity to MTX	Small mass (<3.5 cm)	Embryonic cardiac activity present
Intrauterine pregnancy	Unruptured mass	Significant abdominal pain
Breastfeeding	No embryonic cardiac activity	IUP has not been ruled out
Active pulmonary disease	Certainty that there is no IUP	Questionable ability to return for all outpatient visits
Renal disease	Willingness for follow-up	
Chronic liver disease	No known sensitivity to MTX	
Preexisting blood dyscrasia		
Immunodeficiency		
Peptic ulcer disease		
Unable to comply with visits and follow-up		

EP = ectopic pregnancy, IUP = intrauterine pregnancy, MTX = methotrexate