Articles

Methotrexate Therapy
Nonsurgical Management of Ectopic Pregnancy

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Ectopic pregnancy has become a surgical epidemic over the past two decades. To minimize the morbidity, mortality, and financial burden created by this rapidly growing health problem, nonsurgical alternatives have been investigated, including treatment with methotrexate. We reviewed current literature to evaluate the safety, efficacy, and costs associated with methotrexate treatment of tubal pregnancy. To date, 17 studies have reported on 400 patients with tubal pregnancies treated with parenteral methotrexate; the overall success rate was 92% (95% confidence interval, 89% to 95%). Single-dose parenteral methotrexate has been shown to be safe, effective, and associated with minimal costs when used in carefully selected patients. A prospective, randomized clinical trial comparing medical and surgical management of ectopic pregnancy is needed to assess the risks, benefits, and costs of these two approaches.

(Slaughter JL, Grimes DA: Methotrexate therapy—Nonsurgical management of ectopic pregnancy. West J Med 1995; 162:225-228)

The incidence of ectopic pregnancy has reached epidemic proportions in the United States. In 1989, a total of 88,400 cases of ectopic pregnancy were reported, accounting for 1.6% of all pregnancies.[1]

The increasing frequency of this disorder is of particular concern because of associated morbidity and mortality: ectopic pregnancy causes 13% of all pregnancy-related deaths and is the leading cause of maternal death in African-American women.[1] Implications for future fertility are similarly grim: the conception rate overall is 60% after ectopic pregnancy, with rates of 20% for recurrent ectopic pregnancy, 30% for spontaneous abortion, and only 30% for subsequent live birth.[2] In addition, the financial burden of ectopic pregnancy in the United States is substantial, with an estimated cost of $1.1 billion in 1990 alone.[3] This figure includes only hospital charges and lost wages, with no account of the cost of subsequent morbidity.

In the past, ectopic pregnancy has been treated surgically. Cases of ectopic pregnancy were diagnosed late, often after rupture. Laparotomy with salpingectomy was the treatment of choice. Currently, salpingectomy is required only in women with tubal rupture, anatomic distortion, or overt hemorrhage[4] because ectopic pregnancies can be diagnosed much earlier through the use of sensitive β-human chorionic gonadotropin (β-hCG) assays and transvaginal ultrasonograms. Cases diagnosed at an earlier stage are amenable to more conservative methods of treatment, such as laparoscopic salpingotomy or salpingostomy. These procedures can be done safely and efficiently for patients with unruptured ectopic pregnancies of less than 5 cm in greatest diameter.[4] Of conservative operations, however, 3% to 20% result in persistent viable trophoblastic tissue requiring additional surgical or medical treatment.[5]

The most widely studied nonsurgical therapy to date is management with methotrexate. This folinic acid antagonist inhibits dihydrofolate reductase activity, preventing synthesis of amino acids, RNA, and DNA. Methotrexate targets rapidly dividing cells, including fetus and trophoblast, bone marrow, buccal and intestinal mucosa, and malignant cells. Methotrexate has been used since 1956 for gestational trophoblastic disease.[6] Its repeated use is limited by dose- and duration-dependent side effects: severe leukopenia, bone marrow aplasia, thrombocytopenia, ulcerative stomatitis, diarrhea, liver cell necrosis, hemorrhagic enteritis, and even death from intestinal perforation.[7] Severe side effects can be prevented by following a lethal dose of methotrexate with reduced folate (leucovorin calcium [citrovorum factor]) to rescue surviving cells. In contrast, single-dose administration has few side effects.[8]

Methods

We reviewed the English-language literature on methotrexate therapy for ectopic pregnancy by conducting a MEDLINE search using key words "ectopic pregnancy" and "methotrexate" and found 113 articles.

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Adding the key word "fertility" narrowed the list to 17 articles. A search including the key word "cost" yielded no more citations. Our search was supplemented by reference lists from original research, review articles, and textbooks. We also consulted authorities in the field of ectopic pregnancy and health care policy. We used tables of binomial distribution[9] and computer software to calculate 95% confidence intervals for series reports of parenteral methotrexate therapy for tubal ectopic pregnancy and overall success rates.

Results

Beginning in 1963, methotrexate was used to treat ectopic pregnancies in patients with high surgical risk such as those with abdominal pregnancy with a bulky placenta attached to omentum and bowel[10] and interstitial[11] and cervical[12] pregnancies, with varying success rates.

Methotrexate treatment of ectopic pregnancy is successful in 67% to 100% of selected patients (Table 1).[11,13-29] In 1986, an eight-day regimen of intravenous methotrexate, alternating daily with intramuscular leucovorin calcium, was used in six patients with tubal ectopic pregnancy, and five of six (83%) pregnancies resolved.[17] These results were confirmed in subsequent studies.[18,20,21] During this time, medical management of ectopic pregnancy was conducted in the context of diagnosis by laparoscopy. In 1990 a prospective, randomized trial of an algorithm without laparoscopy was used that proved to be 100% accurate in diagnosing tubal pregnancies.[30] This made possible completely nonsurgical management of tubal pregnancy. In 1991, in the first of two studies, an expanded group of 100 patients received a standard methotrexate and leucovorin regimen, with a 96% success rate.[25] Of these patients, 64 subsequently conceived, with 89 intrauterine and 11 recurrent ectopic pregnancies. Of the 100 patients, 5 had methotrexate-related side effects.

In the second study, 30 patients were given a single dose of 50 mg per m^2 of methotrexate intramuscularly, without leucovorin calcium rescue.[8] Of the 30 patients, 29 (97%) were successfully treated; no methotrexate side effects were reported. Of the 30 patients, 6 (20%) had increased lower abdominal pain on days 5 to 10 after treatment, however.[8] This complication of methotrexate treatment would be disturbing in an outpatient with an ectopic pregnancy who must be closely monitored for possible rupture.

In 1993 a series of 120 patients were given methotrexate intramuscularly, with 113 (94%) being successfully treated[29]; no side effects occurred. The mean time to resolution of the ectopic pregnancy was 35.5 ± 11.8 days, with a range of 8 to 76 days until the β-hCG titer was less than 12 IU per liter (12 mIU per ml). After methotrexate therapy, 80% of patients conceived within a mean interval of 3.2 ± 1.1 months. Of these conceptions, 87% were intrauterine, and 13% were ectopic.[29]

To date, 17 studies have reported on 400 patients with tubal pregnancies treated with parenteral methotrexate; the overall success rate was 92% (95% confidence interval, 89% to 95%). Strict criteria are required for methotrexate treatment (Table 2). The most important selection criteria for medical management are the absence of pain and the prediction that the pregnancy will not rupture before its resolution.[31] Fetal cardiac activity was considered to be a relative contraindication because the failure rate in the presence of cardiac activity (2 of 14, 14%) was higher than the failure rate in the absence of cardiac activity (5 of 106, 5%; $P < .05$) (Table 3).[29] Two cases were reported of failed methotrexate therapy (local and parenteral administration) in women with tubal pregnancy in which there was fetal heart rate activity, however.[32]

TABLE 1.—*Case Series of Parenteral Methotrexate Therapy in Tubal Pregnancy*

Study	Treatment*	Patients, No. (n = 400)	Success Rate, %	95% CI, %
Tanaka et al, 1986[11]	A1	1	100	2-100
Miyazaki et al, 1983[13]	A2	8	88	47-100
Chotiner, 1985[14]	A3	1	100	2-100
Brandes et al, 1986[15]	A4, C	1	100	2-100
Goldstein, 1986[16]	A4	7	92	64-100
	D	6		
Ory et al, 1986[17]	B1, C	6	83	36-100
Rodi et al, 1986[18]	B3, C	7	100	59-100
Haans et al, 1987[19]	B4	1	100	2-100
Ichinoe et al, 1987[20]	A6	23	96	78-100
Sauer et al, 1987[21]	B3, C	21	95	76-100
Sauer et al, 1988[22]	B3, C	4	100	40-100
Carson et al, 1989[23]	A4, C	21	90	70-99
Stovall et al, 1989[24]	A5, C	36	94	81-99
Stovall et al, 1991[25]	B3, C	100	96	90-99
Byrjalsen and Toft, 1991[26]	A6	9	67	30-93
Isaacs et al, 1992[27]	B2	8	100	63-100
Prapas et al, 1992[28]	B3, C	20	95	75-100
Stovall and Ling, 1993[29]	A7	120	94	88-98
Total			92	89-95

CI = confidence interval

*Treatment methods:
A1 = methotrexate, 30 mg given intramuscularly (IM), then 15 mg for 5 days × 3 courses.
A2 = methotrexate, 60-300 mg IM; dose based on initial urine human chorionic gonadotropin (hCG) titer.
A3 = methotrexate, 25 mg IM daily for 3 days; 20 mg IM daily for 7 days.
A4 = methotrexate, 1 mg/kg IM for 4 days.
A5 = methotrexate, 1 mg/kg IM for 5 days.
A6 = methotrexate, 0.4 mg/kg IM for 5 days every other week: 60-300 mg total dose based on initial urine hCG titer.
A7 = methotrexate, 50 mg/m^2 IM, single dose.
B1 = methotrexate, 1 mg/kg given intravenously (IV) for 4 alternating days.
B2 = methotrexate, 1 mg/kg IM for 3 alternating days.
B3 = methotrexate, 1 mg/kg IM for 4 alternating days.
B4 = methotrexate, 50 mg IM for 4 alternating days with 15 mg of folic acid taken orally.
C = leucovorin calcium (citrovorum factor), 0.1 mg/kg IM on alternate days.
D = methotrexate, 200 mg/m^2 IV.

Discussion

Single-dose methotrexate therapy has been shown to be as effective as the multidose regimen, but with a smaller total dose of methotrexate, no need for leuco-

TABLE 2.—*Criteria for Methotrexate Therapy*

Stovall and Ling, 1993*
Hemodynamically stable
hCG titers increased after curettage
Transvaginal ultrasonography showed an unruptured ectopic pregnancy < 3.5 cm in greatest diameter
Desire for future fertility

American College of Obstetricians and Gynecologists, 1990†
Ectopic size 3 cm or less
Desire for future fertility
Stable or rising hCG levels with peak values < 15×10^3 IU/liter (15,000 mIU/ml)‡
Tubal serosa intact
No active bleeding
Ectopic pregnancy fully visible at laparoscopy
Selected cases of cervical and cornual pregnancy

hCG = human chorionic gonadotropin

*From Stovall and Ling.[29]
†From ACOG.[4]
‡International Reference Preparation.

TABLE 3.—*Contraindications to Methotrexate Therapy*

Stovall and Ling, 1993*
Hepatic dysfunction: aspartate aminotransferase level > 2 × normal
Renal disease: serum creatinine level > 130 μmol/liter (1.5 mg/dl)
Active peptic ulcer disease
Blood dyscrasia: leukocyte count < 3.0×10^9/liter (3,000 cells/mm³) or platelet count < 100×10^9/liter (100,000/mm³)

American College of Obstetricians and Gynecologists, 1990†
Contraindications listed above, plus
Poor patient compliance
History of active hepatic or renal disease
Presence of fetal cardiac activity

*From Stovall and Ling.[29]
†From ACOG.[4]

vorin, decreased patient hospital stays, fewer side effects, and lower costs. The single-dose regimen can be given on an outpatient basis, allowing women to return to work during treatment. This compares favorably with the four- to six-week delay in return to work after laparotomy and one- to two-week delay after laparoscopy.[3] In addition, methotrexate therapy is associated with high rates of subsequent fertility: as high as 80% in one population, with most of these intrauterine.[25] The disadvantages of single-dose parenteral methotrexate include prolonged time for an ectopic pregnancy to resolve: as long as 70 to 120 days. Outpatients must be closely monitored for rupture and methotrexate side effects, making compliance an important consideration in patient selection.

Finally, the costs of different methods of managing ectopic pregnancy must be considered. In 1993, the costs of methotrexate treatment of ectopic pregnancy were compared with those of surgical methods.[3] If all eligible patients nationwide had received single-dose methotrexate therapy instead of surgical management (about 30% of all cases of ectopic pregnancy seen at San Francisco General Hospital Medical Center in 1991), an estimated 24% to 26% of hospital costs, lost wages, and costs of morbidity could have been saved. The potential annual cost savings exceeds $282 million. This estimate is based on an assumption of 28 days of disability with laparotomy, 7 days with laparoscopy, and 4 days with methotrexate therapy.[3]

Administering methotrexate appears to be a promising approach to managing ectopic pregnancies. Although it cannot be used for every patient, it offers a safe and effective nonsurgical method of treating selected patients. A randomized controlled trial comparing methotrexate treatment with surgical management is needed to define the appropriate role of methotrexate therapy for ectopic pregnancy.

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PEOPLE WHO LIVE IN GLASS HOUSES

An old man sitting up front in a hard chair, in a tattered blue robe,
with legs crossed, was asked by the psychiatry resident,
"Do you know what to kill two birds with one stone means?"

Certainly, he said. If you were walking next to me on 42nd Street
and a hoodlum ran by to steal your wallet he could put a knife in your ribs,
and twist it until the blade broke off and you could fall on me, your blood
pouring in my mouth, suffocating me, the collar of your coat stretched
across my neck, and what good would it do to yell, I've been here

before, it's not a memory lapse. I could tell you what Jimmy Walker said
when he was mayor and you'd wonder if I made it up or why they put me here
when I was twenty-five. But that was the beginning of the depression.
It was possible to stay a while, avoid the breadlines and when it was over
why go to World War II when here there was three squares and a bed,
and after that the outside seemed bleak; people never realize it
when young like you. So you sit there casually, but nervous,

stethoscope showing from a side pocket, asking me
in front of sixty students this question, hoping I give you
a concrete rather than abstract answer. There are no metaphors

here. There are the same hallways, the same room,
same robe every day. But while I think about it,
what does it mean to you, people who live
in glass houses shouldn't throw stones?

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