

## PREDICTORS OF SUCCESS OF METHOTREXATE TREATMENT IN WOMEN WITH TUBAL ECTOPIC PREGNANCIES

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### ABSTRACT

**Background** The use of methotrexate for the treatment of women with tubal ectopic pregnancies is now common practice. However, the clinical and hormonal determinants of the success of this treatment are not known.

**Methods** We studied 350 women with tubal ectopic pregnancies who were treated with methotrexate intramuscularly according to a single-dose protocol. Pretreatment serum concentrations of human chorionic gonadotropin and progesterone, the size and volume of the gestational mass, fetal cardiac activity, and the presence of fluid (presumably blood) in the peritoneal cavity were correlated with the efficacy of therapy, as defined by resolution of the ectopic pregnancy without the need for surgical intervention.

**Results** There was no relation between the women's age or parity, the size or volume of the conceptus, or the presence of fluid in the peritoneal cavity and the efficacy of treatment. Among the 320 women in whom treatment was successful (91 percent), the mean ( $\pm$ SD) serum chorionic gonadotropin and progesterone concentrations were  $4019 \pm 6362$  mIU per milliliter and  $6.9 \pm 6.7$  ng per milliliter ( $21.9 \pm 21.3$  nmol per liter), respectively, as compared with  $13,420 \pm 16,590$  mIU per milliliter and  $10.2 \pm 5.5$  ng per milliliter ( $32.4 \pm 17.5$  nmol per liter) ( $P < 0.001$  and  $P = 0.02$ ) in the 30 women in whom treatment was not successful. Fetal cardiac activity was present in 12 percent of the successfully treated cases and 30 percent of those in which treatment was not successful ( $P = 0.01$ ). Regression analysis revealed the pretreatment serum chorionic gonadotropin concentration to be the only factor that contributed to the failure rate.

**Conclusions** Among women with tubal ectopic pregnancies, a high serum chorionic gonadotropin concentration is the most important factor associated with failure of treatment with a single-dose methotrexate protocol. (N Engl J Med 1999;341:1974-8.)

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**M**ANY women with ectopic pregnancies are now treated with methotrexate instead of surgery. Although the exact mechanism of action is unknown, methotrexate is believed to cause either resorption or tubal abortion of the conceptus. Among the treatment protocols available, a protocol in which a single intramuscular dose of methotrexate is given, with subsequent single doses if needed, appears to be the most popular in the United States.<sup>1</sup> Women most likely to respond to methotrexate therapy are thought to be those with small gestational masses, lower serum con-

centrations of human chorionic gonadotropin and progesterone, and the absence of blood in the peritoneal cavity, but it has been difficult to determine the true effect of these characteristics on success rates, because of the small size of previous studies.<sup>2-7</sup>

The purpose of this study was to investigate the influence of pretreatment serum chorionic gonadotropin and progesterone concentrations, the size and volume of the conceptus, the presence of blood in the peritoneal cavity, and fetal cardiac activity on the outcome after intramuscular methotrexate treatment according to a single-dose protocol in 350 women with tubal ectopic pregnancies who were treated at a single institution.

### METHODS

#### Subjects

We conducted a retrospective review of 360 consecutive women with singleton tubal ectopic pregnancies who had been treated with intramuscular methotrexate by members of the Division of Gynecology at the University of Tennessee, Memphis, to identify predictors of successful therapy. All women with ectopic pregnancies who met the eligibility requirements were offered methotrexate therapy. The methotrexate protocol was approved by the institutional review committee of the University of Tennessee, and all women gave written consent before treatment. Two women with cervical pregnancies and 8 women who elected to have surgery rather than receive a second dose of methotrexate were excluded from the analysis, leaving 350 women.

#### Diagnosis

The diagnosis of tubal ectopic pregnancy was made with use of a previously published algorithm.<sup>8</sup> Briefly, women with potential ectopic pregnancies were screened through the measurement of serum chorionic gonadotropin and progesterone. Women with a serum chorionic gonadotropin concentration of less than 50,000 mIU per milliliter or a serum progesterone concentration of less than 25 ng per milliliter (79.5 nmol per liter) were evaluated further. Transvaginal ultrasonography was performed initially in women with serum chorionic gonadotropin concentrations of 2000 mIU per milliliter or more; all others were followed with serial measurements of serum chorionic gonadotropin. Women with initial serum chorionic gonadotropin concentrations below 2000 mIU per milliliter and inappropriately increasing concentrations (less than a 50 percent rise in 48 hours) underwent dilation and curettage. Ectopic pregnancy was diagnosed if the serum chorionic gonadotropin concentration failed to decline by at least 15 percent within 12 to 24 hours after the procedure and if no placental villi were present in the curettage specimen. In women with rising serum chorionic gonadotropin concentrations, transvaginal ultrasonography was performed when the concentration reached 2000 mIU per milliliter. Ectopic pregnancy was diagnosed in these

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women if an intrauterine gestational sac was not seen and the serum chorionic gonadotropin concentrations continued to rise.

**Study Protocol**

The single-dose methotrexate protocol has been described in detail elsewhere.<sup>1</sup> Briefly, women with ectopic pregnancies were considered candidates for methotrexate treatment if they were hemodynamically stable; did not have free fluid (presumably blood) outside the pelvic cavity on transvaginal ultrasonography; did not desire surgical therapy; agreed to weekly follow-up until their serum chorionic gonadotropin concentrations decreased to 15 mIU per milliliter or lower; and did not have hepatic, hematologic, or renal disease, as evidenced by serum aminotransferase concentrations greater than twice the upper limit of normal, a white-cell count of less than 1500 per cubic millimeter, a platelet count of less than 100,000 per cubic milliliter, or a serum creatinine concentration greater than 1.5 mg per deciliter (133 μmol per liter). For the first 200 women enrolled in the study, the size of the gestational mass, as determined by transvaginal ultrasonography, had to be 3.5 cm or less. For the remaining 150 women, the cutoff point was raised to 4 cm if fetal cardiac activity was not present. If the ectopic gestational mass could be identified separately from a surrounding hematoma, only the size of the mass was used to determine eligibility for methotrexate treatment.

The women received intramuscular methotrexate at a dose of 50 mg per square meter of body-surface area, which was calculated with a nomogram that used height and actual body weight. The day on which a woman received methotrexate was considered day 1. Serum chorionic gonadotropin was measured on days 4 and 7. If the concentration did not decline by at least 15 percent between days 4 and 7, a second dose of methotrexate was administered. If the serum chorionic gonadotropin concentration declined by at least 15 percent, the measurement was repeated weekly until the concentration reached 15 mIU per milliliter. Failure of the serum chorionic gonadotropin concentration to fall by at least 15 percent during any successive week also resulted in repeated administration of methotrexate. If a repeated dose of methotrexate was given, the day of administration was considered a new day 1. A repeated dose of methotrexate was also given if fetal cardiac activity was still present on day 7 after the first or subsequent doses of methotrexate.

After three doses of methotrexate, if serum concentrations of chorionic gonadotropin had not decreased (according to the above criteria) or if cardiac activity was still present, then the ectopic pregnancy was treated surgically. However, an exception was made in the case of one woman who was allowed four doses. Surgical intervention was also performed for presumed tubal rupture indicated by a falling hematocrit, hemodynamic instability, or the presence of peritoneal fluid extending into the flanks. Treatment success was defined as the achievement of a serum chorionic gonadotropin concentration of 15 mIU per milliliter or less without the need for surgical intervention.

**Measurement of Serum Hormone Levels and Size and Volume of the Gestational Mass**

Serum chorionic gonadotropin was measured by enzyme immunoassay and standardized to the First International Reference Preparation.<sup>9</sup> Serum progesterone was measured by radioimmunoassay. The size of the gestational mass was defined as its maximal diameter in any dimension as measured by ultrasonography. If the mass could not be differentiated from a tubal hematoma, the maximal diameter of the entire mass was used. The volume of the mass was calculated by multiplying the product of its width, length, and height in centimeters by 1.52. When the gestational mass could be distinguished from a larger mass of surrounding tissue or hematoma, the volume of the gestational mass plus the surrounding tissue or hematoma (total mass volume), as well as the volume of the gestational mass, was also calculated. If the gestational mass could not be differentiated from a surrounding hematoma, only the total mass volume was calculated. Data on women in

whom no mass was demonstrated by transvaginal ultrasonography were excluded from volume analysis but were included in all other analyses.

**Statistical Analysis**

All analyses were performed with two-sided tests. Student's t-test and Fisher's exact test were used to compare the success and failure of treatment with regard to the size and volume of the gestational mass, volume of the total mass, serum chorionic gonadotropin and progesterone concentrations, presence or absence of fluid in the peritoneal cavity, and presence or absence of fetal cardiac activity at the time of treatment. Logistic-regression analysis was then used to compare the combined effect of the statistically significant factors.

**RESULTS**

The characteristics of the 350 women with ectopic pregnancy are shown in Table 1. Among them, transvaginal ultrasonography revealed an ectopic tubal mass in 268 (77 percent), and free peritoneal fluid, presumably blood, confined to the pelvis, was found in 114 (33 percent). Three hundred twenty women (91 percent) were successfully treated with methotrexate. The women treated successfully and unsuccessfully did not differ significantly with regard to age, parity, size or volume of the ectopic gestational mass, total mass volume, or the presence or absence of free peritoneal fluid at the time of initial treatment, but the mean serum chorionic gonadotropin and progesterone concentrations and the frequency of fetal cardiac activity were lower in the successfully treated women (Table 2). Logistic-regression analysis revealed a high serum chorionic gonadotropin concentration to be the only factor significantly linked to the failure of treatment (P=0.006).

The success rates according to the initial serum chorionic gonadotropin concentrations are shown in Table 3. Among the women with initial serum chorionic gonadotropin concentrations below 10,000 mIU per milliliter, 287 (94 percent) were successfully treated, and among those with initial serum chorionic gonadotropin concentrations below 15,000 mIU per milliliter, 305 (93 percent) were successfully treated.

The relations between serum chorionic gonadotropin concentrations and fetal cardiac activity are

**TABLE 1. CHARACTERISTICS OF 350 WOMEN TREATED WITH METHOTREXATE.\***

CHARACTERISTIC	VALUE
Age — yr	26 ± 6
Gravidity — no.	3 ± 2
Parity — no.	1 ± 1
Free fluid in the peritoneal cavity — no. (%)	114 (33)
Fetal cardiac activity — no. (%)	46 (13)
Identified ectopic mass — no. (%)	268 (77)

\*Plus-minus values are means ± SD.

**TABLE 2.** ANALYSIS OF FACTORS RELATED TO THE EFFICACY OF METHOTREXATE THERAPY IN WOMEN WITH ECTOPIC PREGNANCIES.\*

FACTOR	SUCCESS	FAILURE	P VALUE
Age — yr	26±6	26±5	0.76
Parity — no.	1±1	1±1	0.15
Serum chorionic gonadotropin — mIU/ml	4019±6362	13,420±16,590	<0.001
Serum progesterone — ng/ml†	6.9±6.7	10.2±5.5	0.02
Size of mass — cm	2.0±0.8	2.1±0.8	0.89
Volume of mass — cm <sup>3</sup>	5.4±6.1	5.6±6.8	0.88
Total mass volume — cm <sup>3</sup>	9.3±16.0	6.4±6.8	0.34
Presence of free peritoneal fluid — no. (%)	102 (32)	12 (40)	0.48
Presence of fetal cardiac activity — no. (%)	37 (12)	9 (30)	0.01

\*Plus-minus values are means ±SD. Treatment was successful in 320 women and failed in 30.

†To convert values for progesterone to nanomoles per liter, multiply by 3.18.

**TABLE 3.** SUCCESS RATES OF METHOTREXATE TREATMENT IN WOMEN WITH ECTOPIC PREGNANCIES AS A FUNCTION OF THEIR INITIAL SERUM CHORIONIC GONADOTROPIN CONCENTRATIONS.

SERUM CHORIONIC GONADOTROPIN CONCENTRATION (mIU/ml)	SUCCESS		FAILURE	SUCCESS RATE (95% CI)*
	no.			
<1000	118	2	98	(96–100)
1000–1999	40	3	93	(85–100)
2000–4999	90	8	92	(86–97)
5000–9999	39	6	87	(79–98)
10,000–14,999	18	4	82	(65–98)
≥15,000	15	7	68	(49–88)

\*CI denotes confidence interval. Treatment was successful in 320 women and failed in 30.

shown in Table 4. Among the 22 women with initial serum chorionic gonadotropin concentrations of 15,000 mIU per milliliter or more, 11 (50 percent) had fetal cardiac activity, and all 4 of the women with serum chorionic gonadotropin concentrations of 50,000 mIU per milliliter or more had fetal cardiac activity. Two of these four women were successfully treated with methotrexate. Fetal cardiac activity was present in 12 percent of the successfully treated women and 30 percent of those for whom treatment was not successful (P=0.01).

**TABLE 4.** RELATION BETWEEN SERUM CHORIONIC GONADOTROPIN CONCENTRATIONS AND FETAL CARDIAC ACTIVITY IN WOMEN WITH ECTOPIC PREGNANCIES.

SERUM CHORIONIC GONADOTROPIN CONCENTRATION (mIU/ml)	FETAL CARDIAC ACTIVITY PRESENT* no. with cardiac activity/total no. (%)
<5000	14/261 (5)
5000–9999	12/45 (27)
10,000–14,999	9/22 (41)
≥15,000	11/22 (50)

\*The denominator is the number of patients with the given serum chorionic gonadotropin concentration.

Of the 350 women in the study, 283 (81 percent) received one dose of methotrexate, 60 (17 percent) received two doses, 6 (2 percent) received three doses, and 1 (0.3 percent) received four doses. Of the 320 successfully treated women, 261 (82 percent) received only one dose. The initial serum chorionic gonadotropin concentrations were similar in the women who received one dose and those who received more than one dose. The serum progesterone concentrations and the frequency of fetal cardiac activity were higher among the women who required more than one dose of methotrexate (P<0.001).

## DISCUSSION

All previously published protocols for systemic methotrexate treatment of women with ectopic pregnancies have restricted treatment to women with a gestational mass less than 3 to 4 cm in size. Many protocols further restrict treatment to those with a predefined initial serum chorionic gonadotropin concentration, usually less than 5000 or 10,000 mIU per milliliter. The presence of fetal cardiac activity or free peritoneal fluid is often considered a relative contraindication to methotrexate therapy. Most of these restrictions are based on limited or anecdotal evidence.

The most studied prognostic factor has been the serum chorionic gonadotropin concentration. In a review of 23 studies (all from 1990 or earlier) from which failure rates could be determined according to serum chorionic gonadotropin concentrations, treatment was unsuccessful in 9 of 265 women (3 percent) with serum chorionic gonadotropin concentrations of 10,000 mIU per milliliter or less and in 6 of 19 women (32 percent) with serum chorionic gonadotropin concentrations above 10,000 mIU per milliliter.<sup>4</sup> The authors concluded that a serum chorionic gonadotropin concentration above 10,000 mIU per milliliter was a risk factor for treatment failure.

Among 50 women with ectopic pregnancies who were treated with a single-dose methotrexate protocol in a study by Stika et al., the authors concluded that those with initial serum chorionic gonadotropin concentrations above 5000 mIU per milliliter "had a greater probability of requiring either surgical intervention or multiple doses of methotrexate," but the exact increase in risk was not given.<sup>7</sup> Interestingly, none of the 11 women in whom treatment was unsuccessful had an initial serum chorionic gonadotropin concentration above 3490 mIU per milliliter.

Among 44 women treated according to a single-dose methotrexate protocol in another study, an initial serum chorionic gonadotropin concentration of less than 15,000 mIU per milliliter or a serum progesterone concentration of less than 7 ng per milliliter (22 nmol per liter) had a positive predictive value for success of 97 percent and a negative predictive value of 69 percent.<sup>2</sup> Treatment was unsuccessful in 1 of 29 women (3 percent) with serum chorionic gonadotropin concentrations of less than 15,000 mIU per milliliter or serum progesterone concentrations of less than 7 ng per milliliter, and in 9 of 13 women (69 percent) whose serum chorionic gonadotropin and progesterone concentrations both exceeded these values.

Although the size of an ectopic gestational mass is frequently used as an exclusion criterion for methotrexate therapy, few data are available about the effect of this factor on success rates. Among 44 women in a study by Shalev et al. who were treated with intratubal injection of methotrexate, the success rates were 76 percent for those with ectopic masses 2 cm or less in diameter, as compared with 52 percent for those with masses larger than 2 cm.<sup>6</sup> Among 10 women we treated with single-dose systemic methotrexate in an earlier study, the success rate was 90 percent in those with ectopic masses between 3.5 and 4 cm, as compared with 93 percent for those with ectopic masses smaller than 3.5 cm.<sup>10</sup>

As noted above, the presence of fetal cardiac activity has also been considered a relative contraindication to methotrexate therapy. Most reports have indicated an increase in failure rates when cardiac activity was present, but success rates as high as 88 percent have also been reported when fetal cardiac activity was present.<sup>10</sup>

In addition, the presence of free peritoneal fluid, presumably blood, is considered by many to be a contraindication to methotrexate therapy, because it may indicate ongoing tubal rupture.<sup>3,6,11</sup> Historically, 70 to 83 percent of women with ectopic pregnancies had blood in the peritoneal cavity, as detected by culdocentesis, but only 50 to 62 percent of them had a ruptured fallopian tube.<sup>12-14</sup> Thus, many women with ectopic pregnancies who do not have ruptured fallopian tubes have free peritoneal blood. In the current

study, 132 of 350 women (38 percent) had evidence of free peritoneal fluid confined to the pelvis on ultrasonography, but the presence of fluid did not affect the success rate.

In this study of 350 women, higher serum chorionic gonadotropin and progesterone concentrations and the presence of fetal cardiac activity were associated with higher rates of failure of methotrexate therapy, but the size of the ectopic mass and the presence of free peritoneal blood were not. One possible explanation for the lack of correlation of failure with size of the gestational mass is that the ectopic mass could not be distinguished from a surrounding blood clot by transvaginal ultrasonography. Furthermore, size does not always predict the relative health and blood supply of the ectopic mass.

All of the factors found to affect the failure rate are related to the overall health of the ectopic conceptus. High serum chorionic gonadotropin and progesterone concentrations are associated with an ectopic conceptus that is still developing and growing. The presence of fetal cardiac activity indicates enough vascular support for the pregnancy to continue into a more advanced stage of gestation. Conversely, lower serum chorionic gonadotropin and progesterone concentrations or the absence of fetal cardiac activity may indicate either a very early or a failing ectopic pregnancy. Presumably, methotrexate is more effective with an early or failing ectopic pregnancy than with a more advanced, vigorous ectopic pregnancy.

We conclude that the initial serum chorionic gonadotropin concentration is the best prognostic indicator of treatment success in women with ectopic pregnancies who are treated according to a single-dose methotrexate protocol. The prognostic value of other proposed factors appears to be directly related to their association with the serum chorionic gonadotropin concentration. These results can be used to counsel women with ectopic pregnancies regarding the likelihood of successful treatment with single-dose systemic methotrexate.

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