

## CME Comparison of success rates in the medical management of ectopic pregnancy with single-dose and multiple-dose administration of methotrexate: a prospective, randomized clinical trial

Ashraf Alleyassin, M.D., Afsaneh Khademi, M.D., Marzieh Aghahosseini, M.D.,  
Leili Safdarian, M.D., Bita Badenoosh, M.D., and Ehsan Akbari Hamed, M.D.

Infertility Ward, Department of Obstetrics and Gynecology, Vali-e-asr Reproductive Health Research Center, Dr. Shariati Hospital, Tehran University of Medical Science, Tehran, Iran

**Objective:** To assess whether success rate differs in single-dose versus multiple-dose administration of methotrexate (MTX) in medical management of unruptured ectopic pregnancies.

**Design:** Prospective randomized clinical trial.

**Setting:** Tertiary university hospital.

**Patient(s):** The study population included 108 patients presenting with unruptured ectopic pregnancies who fulfilled the criteria for medical management.

**Intervention(s):** A single dose (study group) or multiple doses (control group) of MTX were administered IM.

**Main Outcome Measure(s):** Success rate of medical management in each group.

**Result(s):** Of the 54 patients on the single-dose protocol, treatment was considered successful in 48 patients (88.9%). Of the 54 patients on the multiple-dose protocol, 50 participants responded to the treatment (92.6%). The difference between success rates in the two groups was not statistically significant ( $P=.7$ ; odds ratio 0.64; 95% confidence interval 0.17–2.4). In the single-dose and multiple-dose groups, 15 (27.8%) and 20 (37%) patients, respectively, had complications ( $P=.3$ ).

**Conclusion(s):** The results of our study showed that single-dose treatment with MTX could be as successful as multiple doses. The incidence of complications did not differ between the two groups. It appears that single-dose treatment could be the first line of treatment in selected patients. (Fertil Steril® 2006;85:1661–6. ©2006 by American Society for Reproductive Medicine.)

**Key Words:** Ectopic pregnancy,  $\beta$ -hCG, methotrexate, pregnancy, success rate

The incidence of ectopic pregnancy (EP) in the United States increased from 4.5 per 1,000 reported pregnancies in 1970 to 20 per 1,000 pregnancies in 1992. Based on aggregated data from the Centers for Disease Control's National Hospital Discharge Survey and National Hospital Ambulatory Medical Care Survey, the estimated total number of EPs in 1992 was 108,800 (95% confidence interval (CI) 83,600–134,000) (19.7 per 1,000 reported pregnancies) (1). Although many reports from other countries since then indicated a trend in the decline in that incidence (2–3), EP remained the leading cause of early pregnancy fatality (1).

The use of sensitive quantitative hCG assays and high-resolution transvaginal ultrasound has resulted in earlier diagnosis of EP and more conservative treatment options

(4–6). Although operative laparoscopy replaced surgery via laparotomy, nonsurgical medical treatments such as local or systemic injection of methotrexate (MTX), a folic acid antagonist, have emerged as an alternative management protocol for women with EP (7–10). Medical management of an unruptured EP with IM MTX is common and cost effective (11). In 1997, the first randomized clinical trial on MTX versus laparoscopic salpingostomy was published. That study, by Hajenius et al. (12), showed no difference between MTX treatment and laparoscopic salpingostomy with respect to primary treatment success, tubal reservation, homolateral tubal patency on follow-up hysterosalpingography, or fertility outcome 18 months after completion of treatment.

Systemic MTX has been administered in single- and multiple-dose regimens, and the former regimen has been advocated by some to improve patient compliance and reduce side effects of treatment (13). On the other hand, a meta-analysis showed that the multidose MTX was significantly

Received August 6, 2005; revised and accepted November 16, 2005.  
Reprint requests: Afsaneh Khademi, M.D., Tehran University of Medical Science, Dr. Shariati Hospital, North Kargar Ave, 14114, Tehran, Iran (FAX: +982188029396; E-mail: afkhademi@sina.tums.ac.ir).

superior (11). Recently Lipscomb et al. (14) published an article comparing single and multiple doses of MTX in a review of the records of 677 patients. The results showed that there were no significant difference in failure rates between single- and multiple-dose protocols. To our knowledge, there is no randomized prospective study comparing the two medical regimens (11, 14).

In this study, we compared the outcome of medical management of unruptured EPs using single-dose versus multiple-dose administration of MTX injection.

## MATERIALS AND METHODS

The study was performed during 18 months period from September 23, 2003, to March 21, 2005, at Dr. Shariati Hospital, Tehran. The hospital is a tertiary regional and teaching hospital. The investigation was a prospective randomized clinical trial. It was conducted to assess the success rates of a single dose and multiple doses of IM MTX treatment of EP.

The study was approved by the Committee for Ethics of Tehran University of Medical Sciences. Institutional Review Board approval was obtained before commencing the trial as well. All patients and their husbands provided their written informed consent.

### Patient Selection

To diagnose EP, patients with positive  $\beta$ -hCG were followed until an intrauterine pregnancy was documented. Serum  $\beta$ -hCG concentrations were measured at the Central Chemical Laboratory of our hospital. The assay was calibrated using the World Health Organization (WHO) Third International Standard (code 75/537) (formerly designated the WHO First International Reference Preparation). In patients who had the records of  $\beta$ -hCG level from other laboratories, the level was measured at the beginning of treatment in the laboratory of our hospital once again and these new records were used for analyses.

An EP was diagnosed if  $\beta$ -hCG levels were  $\geq 1800$  mIU/mL and no viable intrauterine pregnancy was evident. Suspected EP with  $\beta$ -hCG levels  $< 1,800$  mIU/mL was followed according to the algorithm of Stovall and Ling (13):

1. A  $\geq 50\%$  increase in  $\beta$ -hCG over 48 hours was considered a normal intrauterine pregnancy.
2. Declining  $\beta$ -hCG levels over 48 hours were followed by additional serial  $\beta$ -hCG samples and clinical status. These cases were considered spontaneous abortions or EP in resorption. Cases judged by the treating clinician to be an EP in resorption were not suitable to enter the study.
3. Plateauing levels or  $< 50\%$  increase in  $\beta$ -hCG over 48 hours were diagnosed as ectopic pregnancies.

These criteria were used only if the  $\beta$ -hCG level was  $< 1,800$  mIU/mL.

Criteria for patient selection for medical treatment were stable hemodynamic state, tubal mass (estimated as the biggest diameter of entire tube with gestation seen by vaginal ultrasonography) less than 3.5 cm in diameter, absence of fetal heart beat,  $\beta$ -hCG less than 15,000 mIU/mL, and fear of patient of future infertility (15, 16).

### Randomization

We used the method of block randomization, which was computer generated, using sealed envelopes (17). Therefore, according to a computerized random table, the patients were assigned to be treated with either a single dose or multiple doses of MTX (Methotrexat; Ebewe, Unterach, Austria) by IM injection. The numbers were kept in sealed envelopes and only opened once the decision to progress to treatment was made. The envelopes were stored and opened by an independent coordinator in an office away from the treatment center.

### Protocol of Treatment

The two methods used for MTX administration for EP are shown in Table 1 (18–21).

### Outcome Measures

The main outcome was comparison of success rates between single-dose and multiple-dose protocols. Success rate was defined as percentile of patients with positive response to the therapy to the total. In the single-dose group, positive response was defined as confirmation of 15% drop in serum hCG level after 1 week of treatment (Table 1), then serum hCG less than 15 mIU/mL after 6 weeks of treatment. In the multiple-dose treatment group, positive response was defined as an hCG level decrease of 15% in 48 hours, or, after four doses methotrexate were given, serum hCG less than 15 mIU/mL after 6 weeks of treatment (22–23).

### Statistical Analysis

Results are presented as mean  $\pm$  SD or percentile. Statistical analysis was conducted using Fisher exact test, Student *t* test, and chi-squared as appropriate. Odds ratio (OR) of main outcome was calculated with 95% CI. The significance level was set at .05. Data analysis was carried out using Statistical Package for Social Science 11.0 (SPSS, Chicago, IL).

Sample size calculations were based on the biggest difference between estimated success rates of single dose and multiple doses of IM injection of MTX. The success rates were chosen from research that had a total sample size of more than 30 participants (24). The lowest success rate for single-dose treatment and the highest success rate for multiple-dose treatment were 75% and 96%, respectively. To find a 21% difference in the success rate of single-dose and multiple-dose treatments, a sample size of 49 patients in each group was found to be adequate. The sample size has been estimated with  $\alpha < 0.05$ , and  $\beta = 0.2$  (25).

**TABLE 1****Methods of administration of IM methotrexate.**

Protocol	Evaluation
Single dose Methotrexate 50 mg/m <sup>2</sup> IM	Measurement of $\beta$ -hCG on days 4 and 7 If difference <15% repeat weekly until undetectable If difference >15% repeat and begin new day 1
Multiple doses Methotrexate 1 mg/kg IM, days 1, 3, 5, 7 Leukovorin 0.1 mg/kg IM, days 2, 4, 6, 8	Continue alternate-day injection until $\beta$ -hCG level decreases 15% in 48 hours or four doses methotrexate given, then weekly $\beta$ -hCG until undetectable

Alleyassin. Methotrexate treatment of EP. Fertil Steril 2006.

**RESULTS**

Our analysis considered 108 women diagnosed with EP whom we followed after treatment with single-dose or multiple-dose treatment with MTX.

The ages of women participating in the study ranged from 19 to 42 years (mean  $30.85 \pm 5.35$  years). In 48 patients (44.4%), the presenting pregnancy was the first pregnancy. History of EP was found in 5 patients (4.6%). Twenty-eight patients (25.9%) experienced an abortion in past, among whom curettage was done in 14 (50%) and induced abortion in 3 (10.7%). History of infertility was found in 44 patients (40.7%). In none of our patients was intrauterine device the method of contraception.

Mean gestational age was  $45.67 \pm 7.15$  days (range: 30 to 67 days) at the time of diagnosis. Pretreatment level of serum hCG varied from 185 to 9,900 mIU/mL (mean  $2,973.59 \pm 2,244.25$  mIU/mL).

The treatment was successful in 98 patients (90.74%) of the total sample.

Comparison of demographic characteristics of patients in the single-dose and multiple-dose treatment groups are presented in Table 2. Factors at the time of diagnosis that appear to predict the outcome are compared between the two groups in Tables 2 and 3 (26–29).

Of the 54 patients on the single-dose protocol, treatment was considered successful in 48 patients (88.9%). Of the 54 patients on multiple-dose protocol, 50 participants considered responding positively to the treatment (92.6%). The difference between success rates in the two groups was not statistically significant ( $P=.7$ ; OR 0.64, 95% CI 0.17–2.4).

All of the six patients in whom single-dose treatment failed responded to a second dose. Therefore, 11% of women required more than one dose of drug. Of the four women in whom multiple-dose treatment failed, two required surgical

treatment for ruptured tubal EP while receiving MTX. In the remaining two, the drop in  $\beta$ -hCG levels was not less than 15%. These two patients responded to a second dose of MTX.

Mean number of doses of MTX administration in the multiple-dose group was  $2.29 \pm 1.2$  with a range of one (38.9%) to five (3.9%) doses. The two patients in whom treatment failed needed more than four doses. In the single-dose group, the mean number of doses administered was  $1.1 \pm 0.31$  times ( $P<.000$ ). Mean duration of treatment was  $26.32 \pm 11.11$  days in the single-dose group. In the multiple-dose group, the mean duration of treatment was  $24.01 \pm 12.72$  days ( $P=.3$ ).

Complications were seen in 35 patients (32.4%). Complications were, in order of frequency, abdominal pain, diarrhea, elevated liver enzymes (greater than twice upper limits of normal), somatitis, dermatitis, and pruritus. In single-dose and multiple-dose groups, 15 (27.8%) and 20 (37%) patients, respectively, had complications ( $P=.3$ ). Eleven patients (20.4%) in the single-dose group complained of abdominal pain during treatment, which was the most frequent complaint, and 12 patients (22.2%) in the multiple-dose regimen had this complication ( $P=.8$ ). Other complications were seen in four (7.4%) and nine (16.9%) patients in the single-dose and multiple-dose regimens, respectively ( $P=.1$ ).

**DISCUSSION**

This study has evaluated treatment outcome after MTX treatment in a sample of ectopic pregnancies. Successful treatment response in the total sample was 90.7%. In a review article published in 2003, the crude overall success rate in 1,327 women was estimated as 88.8% (1,181 of 1,327) (11). Therefore, medical treatment of EP is considered a practical treatment.

**TABLE 2****Comparison of patient characteristics between single-dose and multiple-dose treatments with methotrexate.**

	Single-dose (n = 54)	Multiple-dose (n = 54)	P value
Age (ys)			
Mean $\pm$ SD	31.07 $\pm$ 5.19	31.62 $\pm$ 5.54	.66 <sup>a</sup>
Range	21–42	19–41	
Weight (kg)			
Mean $\pm$ SD	66.37 $\pm$ 11.74	67.18 $\pm$ 9.89	.7 <sup>a</sup>
Range	41.5–102	48–78	
Gravidity			
Mean $\pm$ SD	1.85 $\pm$ 0.9	1.94 $\pm$ 1.1	.63 <sup>a</sup>
Range	1–4	1–5	
Parity			
Mean $\pm$ SD	0.48 $\pm$ 0.63	0.66 $\pm$ 0.89	.21 <sup>a</sup>
Range	0–2	0–3	
Gestational age at the time of diagnosis (days of LMP)			
Mean $\pm$ SD	46.6 $\pm$ 7.64	44.77 $\pm$ 6.6	.2 <sup>a</sup>
Range	30–67	33–56	
Pretreatment $\beta$ -hCG level (mIU/ml)			
Mean $\pm$ SD	3146.98 $\pm$ 2389.36	2803.41 $\pm$ 2100.56	.43 <sup>a</sup>
Range	185–9900	194–8870	
Previous history of EP (%)	3 (5.6%)	2 (3.7%)	1 <sup>b</sup>
Previous history of abortion (%)	15 (27.8%)	13 (24.1%)	.6 <sup>c</sup>
Positive history of infertility (%)	29 (53.7%)	15 (23.7%)	.006 <sup>c</sup>

Note: LMP = last menstrual period; EP = ectopic pregnancy.

<sup>a</sup> P value calculated using Student *t* test for equality of means.

<sup>b</sup> P value calculated using Fisher exact test.

<sup>c</sup> P value calculated using chi-squared.

Alleyassin. Methotrexate treatment of EP. Fertil Steril 2006.

The aim of the present study was to investigate the effectiveness of two methods of MTX treatment in routine clinical practice. Barnhart et al. (11) showed that the crude overall success rate for women managed with the single-

dose therapy was 88.1% (940 of 1,067), with a 95% CI of 86% to 90%. The crude overall success rate for women managed with multiple-dose protocol was 92.7% (241 of 260), with a 95% CI of 89% to 96%. The difference between

**TABLE 3****Comparison of prognostic factors between single-dose and multiple-dose treatments with methotrexate.**

	Single-dose (n = 54)	Multiple-dose methotrexate (n = 54)	P value <sup>a</sup>
Presented with pelvic pain	50 (27%)	24 (44.4%)	NS
Vaginal bleeding	10 (18.5%)	11 (20.4%)	NS
$\beta$ -hCG level >4,000 mIU/mL	19 (35.8%)	13 (24.1%)	NS
History of ovulation induction	20 (37%)	22 (40.7%)	NS

Note: NS = not statistically significant.

<sup>a</sup> P value calculated using chi-squared.

Alleyassin. Methotrexate treatment of EP. Fertil Steril 2006.

these two success rates was statistically significant ( $P = .035$ ). Those authors emphasized that none of the trials they reviewed in their analysis was controlled or blinded. In their opinion, a randomized blinded clinical trial would be the most efficient method to reduce the potential confounders and bias in comparing the success rate of the two methods (11). Therefore, we tried to do such a study. We tried to study a group of patients who would be similar in factors which may affect the result of treatment.

Our two groups were similar in characteristics such as age, weight, gravidity, parity, gestational age at the time of diagnosis, pretreatment  $\beta$ -hCG level, and previous EP or abortion. The data about history of pelvic inflammatory disease (PID) was not included because of recall bias. Incidence of infertility was higher in the single-dose treatment group. It does not seem to play an important role in the dissimilarity of the two groups, because there was no statistically difference in mean gestational age, mean serum hCG at the time of diagnosis, and percentile of ovulation induction between the two groups (30).

We studied the two groups in relation to factors that appear to affect the result of treatment. The number of previous normal pregnancies was considered a predisposing factor for rupture of EP by Roussos et al. (27). Previous EP was cited as a risk factor for treatment failure (26). The initial serum hCG was considered to be the best prognostic indicator of treatment success in women with EP who are treated according to a single-dose MTX protocol (15). There was no statistically significant difference between single-dose and multiple-dose treatment regimens in relation to factors such as pain as a presenting symptom, vaginal bleeding,  $\beta$ -hCG level  $>4,000$  mIU/mL, history of ovulation induction, and previous EP in our study (26–29).

The success rate was 88.9% in the single-dose and 92.6% in the multiple-dose treatment group. We failed to find a statistically significant difference between the two groups, which were matched in demographic and some prognostic characteristics (Tables 2 and 3). A difference of 2.7% was found in the success rate of the two groups. Although the sample size was estimated to find a 21% absolute difference, it seems that the difference of 2.7% in success rate is too little to be a clinically important difference.

Lipscomb et al. (14) reviewed 667 cases of EP that underwent medical treatment. In their analysis of 643 patients, the success rate for the 546 women treated with the single-dose protocol was 90%. The 97 women treated with multiple doses had a success rate of 95%. The difference in success rate was not statistically significant ( $P = .18$ ). Lipscomb et al. (14) compared patients whose data came from the same database and institution. In that research, both groups were comparable with regard to factors that are generally thought to increase failure rate.

Our results were similar to Lipscomb et al.'s results. The main difference between our patients and theirs was pres-

ence of cardiac activity in some of their patients. In Lipscomb et al.'s study, 10.3% of the single-dose group had cardiac activity of pregnancy product demonstrated on ultrasound compared with only 3.1% of the multiple-dose group (14). Therefore, it seems that the single-dose group was at higher risk for failure. We excluded patients with positive cardiac activity. The difference of success rate became smaller in our patients in comparison to Lipscomb research.

In the meta-analysis done by Barnhart et al. (11), the difference was only 4.6% (92.7% vs. 88.1%), but because of a large number of patients the difference was statistically significant. However, we need to ask if a statistically significant difference is clinically important.

We found that the incidence of side effects was not significantly different between the two groups. On the other hand, the multiple-dose protocol is more cumbersome to administer. Those issues are other additional factors that encourage us to use the single-dose treatment.

The limitation of our study was in our sample size. The power of our study was not large enough to detect small differences in success rates ( $<21\%$ ) between the two methods. Although it would be of interest to study an even larger sample size, the results of our study showed that single-dose treatment with MTX could be as successful as multiple-dose treatment. Randomized clinical trials considering long-term side effects, cost, and other aspects of MTX treatment of EP could answer the question of which protocol is best as the first step of treatment for selected EPs in practice.

*Acknowledgments:* We gratefully acknowledge the participation of the infertility ward crew of Dr. Shariati Hospital: Sedigheh Amrollahi, B.Sc., Nahid Abbassi Moaff, B.Sc., Zahra Rezaian Movahed, B.Sc., and Mehrnoosh Amini, B.Sc.

## REFERENCES

- Centers for Disease Control and Prevention. Current Trends Ectopic pregnancy— United States, 1990–1992. *MMWR Morb Mortal Wkly Rep* 1995;44:46–8.
- Coste J, Bouyer J, Germain E, Ughetto S, Pouly JL, Job S. Recent declining trend in ectopic pregnancy in France: evidence of two clinicoepidemiologic entities. *Fertil Steril* 2000; 74:881–6.
- Irvine LM, Setchell ME. Declining incidence of ectopic pregnancy in a UK city health district between 1990 and 1999. *Hum Reprod* 2001;16: 2230–4.
- Lehner R, Kucera E, Jirecek S, Egarter C, Husslein P. Ectopic pregnancy. *Arch Gynecol Obstet* 2000;263:87–92.
- Mol BW, Hajenius PJ, Engelsbel S, Ankum WM, Van der Veen F, Hemrika DJ, et al. Serum human chorionic gonadotropin measurement in the diagnosis of ectopic pregnancy when transvaginal sonography is inconclusive. *Fertil Steril* 1998;70:972–81.
- Shalev E, Yarom I, Bustan M, Weiner E, Ben-Shlomo I. Transvaginal sonography as the ultimate diagnostic tool for the management of ectopic pregnancy: experience with 840 cases. *Fertil Steril* 1998; 69:62–5.
- Fernandez H, Benifla JL, Leladier C, Baton C, Frydman R. Methotrexate treatment of ectopic pregnancy: 100 cases treated by primary transvaginal injection under sonographic control. *Fertil Steril* 1993;59:773–7.

8. Glock JL, Johnson JV, Brumsted JR. Efficacy and safety of single dose systemic methotrexate in the treatment of ectopic pregnancy. *Fertil Steril* 1994;62:716–21.
9. Sadan O, Ginath S, Debby A, Rothmensch S, Golan A, Zakut H, et al. Methotrexate versus hyperosmolar glucose in the treatment of extrauterine pregnancy. *Arch Gynecol Obstet* 2001;265:82–4.
10. Vermesh M, Silva PD, Rosen GF, Stein AL, Fossum GT, Sauer MV. Management of unruptured ectopic gestation by linear salpingostomy: a prospective, randomized clinical trial of laparoscopy versus laparotomy. *Obstet Gynecol* 1989;73:400–4.
11. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing “single dose” and “multidose” regimens. *Obstet Gynecol* 2003;101:778–84.
12. Hajenius PJ, Engelsbel S, Mol BW, Van der Veen F, Ankum WM, Bossuyt PM, et al. Randomised trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy. *Lancet* 1997;350:774–9.
13. Stovall TG, Ling FW. Ectopic pregnancy. Diagnostic and therapeutic algorithms minimizing surgical intervention. *J Reprod Med* 1993;38:807–12.
14. Lipscomb GH, Givens VM, Meyer NL, Bran D. Comparison of multidose and single-dose methotrexate protocols for the treatment of ectopic pregnancy. *Am J Obstet Gynecol* 2005;192:1844–8.
15. Lipscomb GH, McCord ML, Stovall TG, Huff G, Portera SG, Ling FW. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *N Engl J Med* 1999;341:1974–8.
16. Stovall TG. Medical management should be routinely used as primary therapy for ectopic pregnancy. *Clin Obstet Gynecol* 1995;38:346–52.
17. Randomization. Available at: <http://www.randomization.com>. Accessed September 2003.
18. Lipscomb GH, Puckett KJ, Bran D, Ling FW. Management of separation pain after single-dose methotrexate therapy for ectopic pregnancy. *Obstet Gynecol* 1999;93:590–3.
19. Pisarska M. Ectopic pregnancy. *Lancet* 1998;351:1115–20.
20. Buster JE, Pisarka MD. Medical management of ectopic pregnancy. *Clin Obstet Gynecol* 1999;42:23–30.
21. Pisarska MD, Carson SA. Incidence and risk factors for ectopic pregnancy. *Clin Obstet Gynecol* 1999;42:2–8.
22. Lipscomb GH, Bran D, McCord ML, Portera JC, Ling FW. Analysis of three hundred fifteen ectopic pregnancies treated with single-dose methotrexate. *Am J Obstet Gynecol* 1998;178:1354–8.
23. Saraj AJ, Wilcox JG, Najmadi S, Stein SM, Johnson MB, Paulson RJ. Resolution of hormonal markers of ectopic gestation: a randomized trial comparing single-dose intramuscular methotrexate with salpingostomy. *Obstet Gynecol* 1998;92:989–94.
24. Lipscomb GH, Stovall TG, Ling FW. Nonsurgical treatment of ectopic pregnancy. *N Engl J Med* 2000;343:1325–9.
25. Lachin JM. Introduction to sample size determination and power analysis for clinical trials. *Controlled Clin Trials* 1981;2:93–113.
26. Lipscomb GH, Givens VA, Meyer NL, Bran D. Previous ectopic pregnancy as a predictor of failure of systemic methotrexate therapy. *Fertil Steril* 2004;81:1221–4.
27. Roussos D, Panidis D, Matalliotakis I, Mavromatidis G, Neonaki M, Mamopoulos A, et al. Factors that may predispose to rupture of tubal ectopic pregnancies. *Eur J Obstet Gynecol Rep Biol* 2000;89:15–7.
28. Tawfiq A, Agameya A, Claman P. Predictors of treatment failure for ectopic pregnancy treated with single-dose methotrexate. *Fertil Steril* 2000;74:877–80.
29. Heard K, Kendall J, Abott J. Rupture of ectopic pregnancy after medical therapy with methotrexate: a case series. *J Emerg Med* 1998;16:857–60.
30. Job-Spira N, Fernandez H, Bouyer J, Pouly JL, Germain E, Coste J. Ruptured tubal ectopic pregnancy: risk factors and reproductive outcome: results of a population-based study in France. *Am J Obstet Gynecol* 1999;180:938–44.