

GENERAL GYNECOLOGY

An alternative monitoring protocol for single-dose methotrexate therapy in ectopic pregnancy

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OBJECTIVE: We sought to determine the sensitivity and specificity of alternative monitoring regimens in predicting the need for a second methotrexate (MTX) dose in women undergoing medical therapy for ectopic pregnancy.

STUDY DESIGN: We reviewed 187 women who received MTX for ectopic pregnancy.

RESULTS: We defined MTX treatment success as a clinically stable patient whose day-7 beta human chorionic gonadotropin (β -hCG) level decreased by $\geq 50\%$, compared with the day-of-treatment (DOT)

β -hCG. In comparison to the standard MTX monitoring protocol, this model was 100% sensitive and 57.4% specific in predicting the need for a second MTX dose in women whose DOT β -hCG was < 2000 mIU/mL and was 100% sensitive and 37.9% specific in women whose DOT β -hCG was ≥ 2000 mIU/mL.

CONCLUSION: This model is an alternative to the traditional MTX monitoring regimen.

Key words: ectopic pregnancy, methotrexate, therapy monitoring

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The original protocol for monitoring women treated for an ectopic pregnancy with single-dose methotrexate (MTX) was to measure their beta human chorionic gonadotropin (β -hCG) levels on the day of treatment (DOT) (also referred to as day 1 [D1]), D4 and D7.¹⁻³ Therapy was considered successful if the patient was clinically stable and her β -hCG level decreased by $\geq 15\%$ between D4–D7 and then decreased to 0 in

the next several weeks.¹⁻³ If the patient was clinically stable, but there was $< 15\%$ decrease in the D4 and D7 β -hCG levels, a repeat MTX dose on D7 was recommended.¹⁻³ In a metaanalysis of 1067 women with ectopic pregnancies treated with single-dose MTX, 14.5% received > 1 MTX dose using these criteria.⁴ Often, the D4 β -hCG will increase above the DOT β -hCG, and the patient may have vaginal bleeding or lower abdominal pain.^{2,5,6} The clinical dilemma at this point is whether an increase in the D4 β -hCG is normal or reflects an impending treatment failure.

It would be more convenient for the patient and simplify medical decision making if MTX treatment were monitored by clinical symptoms and less blood draws. The goal of this study was to review patients who were treated with single-dose MTX for the diagnosis of ectopic pregnancy to determine the sensitivity and specificity of various comparisons of DOT and D7 β -hCG in predicting the need for a repeat dose of MTX. We also calculated the unadjusted and adjusted odds ratios of MTX success, using the absolute β -hCG levels on each day of monitoring. Finally, we calculated the attributable risk of receiving a repeat MTX dose using various alternative monitoring strategies and the number of

women needed to treat with MTX to avoid the D4 clinical evaluation.

MATERIALS AND METHODS

This study was approved by the institutional review boards at the University of Texas Health Sciences Center San Antonio (UTHSCSA) and the Medical University of South Carolina (MUSC). The electronic medical records of patients who were treated with single-dose MTX therapy for the diagnosis of ectopic pregnancy from Jan. 1, 2004–Dec. 30, 2008, at UTHSCSA and from Jan. 1, 1997–Dec. 30, 2008, at MUSC were abstracted for the following variables: age, ethnicity (Hispanic, non-Hispanic white, non-Hispanic black), DOT, D4 and D7 β -hCG, number of MTX doses, and need for surgical therapy. No patient was contacted to confirm additional information. We chose this time frame because a research-quality gynecology database was present at MUSC for this period, and electronic medical records were present at UTHSCSA during this time frame, facilitating data collection.

The diagnosis of ectopic pregnancy was made by members of the resident and faculty staff at the 2 institutions. Since there are various ways in which the diagnosis of an ectopic pregnancy may be made, several of these diagnostic reg-

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imens were used.¹⁻³ In general, a woman presenting with a β -hCG of >2000 mIU/mL or abnormally plateauing β -hCGs and no ultrasonographic or surgical specimen evidence of an intrauterine pregnancy was diagnosed with an ectopic pregnancy. Patients who were clinically stable, were able to follow up for β -hCG monitoring, and had no contraindications to receiving MTX therapy, such as abnormal platelet counts or liver function test results, were eligible for MTX therapy. Patients with fetal cardiac activity in the adnexa were not excluded for MTX therapy, nor was there a defined upper limit of β -hCG level above which patients were excluded for MTX therapy. The need for surgical treatment of ectopic pregnancy was made based on the patient's clinical symptoms, not trends in their β -hCG levels.

Continuous variables were compared using the Student *t* test and categorical variables were compared using χ^2 statistic. Sensitivity, specificity, and false-negative and false-positive rates were calculated using 2×2 tables. We calculated attributable risk by comparing the percent of women who received a repeat dose of MTX using the standard monitoring protocol with the percent of women who would have received a repeat MTX dose using the various alternative monitoring protocols. The number of women receiving a repeat MTX dose to avoid 1 D4 evaluation was calculated by 1/attributable risk. We fit a series of logistic regression models to assess predictors of the need for a second MTX dose, including the absolute values of β -hCG at DOT, D4, and D7, as well as changes in β -hCG between DOT and D7. SAS software (SAS Institute, Cary, NC) was used for the analysis.

RESULTS

At UTHSCSA, 109 patients were treated for an ectopic pregnancy during the study period; 8 patients had missing data, leaving 101 patients for analysis. At MUSC, 101 patients were treated for an ectopic pregnancy during the analysis period; we excluded 14 patients with missing or mistimed β -hCG values and 1 patient with a cornual ectopic preg-

nancy, leaving 86 MUSC patients for analysis. The UTHSCSA and MUSC patients, respectively, were similar in age (mean, 28 years old; $P = .73$) and need for surgery (9.9% vs 12.8%; $P = .53$). The UTHSCSA patients had lower mean DOT β -hCG levels (2357 vs 3580; $P = .07$) and were less likely to require >1 dose of MTX (6.9% vs 16.2%; $P = .04$). At UTHSCSA, the majority of patients (76/101) were Hispanic, while at MUSC, the majority of patients (53/86) were non-Hispanic black. Since the need for surgical treatment and the DOT β -hCGs were similar among the 2 institutions, the data were combined ($n = 187$) for this analysis.

We divided the dataset into patients whose DOT β -hCG was ≤ 1999 mIU/mL vs ≥ 2000 mIU/mL, as this β -hCG level is generally accepted as the discriminatory point at which an intrauterine pregnancy may be diagnosed with transvaginal sonography.⁷⁻¹⁰

Table 1 shows the characteristics of women whose DOT β -hCG was <2000 mIU/mL vs ≥ 2000 mIU/mL. The higher the DOT β -hCG level, the more likely the patient was to require >1 MTX dose. Two MTX treatments were received by 21 of 187 (11.2%) women, and 21 of 187 (11.2%) required surgical evaluation after receiving MTX. In 76 of 187 (40.6%) women, the D4 β -hCG level increased from the DOT value.

Table 2 details the sensitivity, specificity, and false-positive and false-negative rates of various definitions of the need for a second dose of MTX, subdivided by the DOT β -hCG level. By defining the need for a repeat MTX dose as the patient's β -hCG level decreased by $\leq 50\%$ from the DOT β -hCG level, no patient requiring a repeat MTX would have been missed. Among the women with a DOT β -hCG <2000 mIU/mL, 46 extra women would have received a repeat MTX injection, using this proposed protocol. The risk of receiving a second dose of MTX increased from 5/113 to 51/113, giving an attributable risk of 40.7% (46/113); thus, 2.5 (1 of 0.407) women would receive additional MTX to avoid 1 D4 β -hCG blood draw and evaluation. Among the women with a DOT β -hCG of ≥ 2000 mIU/mL, 36 extra women

would receive an additional MTX dose, using the proposed protocol. The attributable risk of receiving a second dose of MTX went from 16/74 using the traditional monitoring protocol to 52/74 using the proposed monitoring protocol, or 48.6% (36/74); thus, 2.1 (1 of 0.486) women would receive additional MTX to avoid 1 D4 evaluation.

Although we did not base the need for surgical intervention on the β -hCG level, all 4 patients who required surgery in the DOT <2000 mIU/mL cohort had an increase in their D7 β -hCG as compared with their DOT β -hCG. Among the women whose DOT β -hCG was ≥ 2000 mIU/mL, 5 who required surgery had a D7 β -hCG that was greater than DOT, and 12 patients who required surgery had a decrease in the D7 β -hCG as compared with the DOT β -hCG, ranging from 1.39–58.18% (mean, 24.00%; median, 20.38%). All 21 patients requiring surgery had an ectopic pregnancy confirmed at the time of operation. No patient received 3 doses of MTX, and no surgeries were performed solely for patient request or to perform a tubal ligation.

We performed a series of logistic regression models to assess our ability to predict the need for a second dose of MTX, based on the joint predictive effects of the absolute value of β -hCG at different time points, as well as specified percent decreases in β -hCGs, between DOT and D7. We found that the DOT β -hCG level was a highly significant predictor of requiring a second MTX dose ($P = .003$), with higher DOT β -hCGs, measured as a continuous variable, associated with a higher likelihood of requiring a second MTX dose. When D7 data were added to the regression model, the DOT levels were no longer significant ($P = .47$), but the D7 levels, adjusted for the DOT levels, were significant ($P = .001$) in predicting the need for a repeat MTX treatment. Finally, when D4 data were added to the logistic regression model, the D4 data were not significant ($P = .94$), nor were the DOT data ($P = .54$), but the D7 data were predictive of needing a second MTX dose ($P = .04$). Of note, maternal age and gestational age

TABLE 1
Comparison of β -hCG cohorts

Variable	DOT β -hCG <2000 mIU/mL, n/113 (%)	DOT β -hCG \geq 2000 mIU/mL, n/74 (%)	P	OR (95% CI)
Mean age, y	28 \pm 5	28 \pm 8	.77	—
Mean DOT β -hCG, mIU/mL	641 \pm 578	6400 \pm 1342	< .001	—
Hispanic	52 (46.0)	27 (36.5)	.20	1.48 (0.82–2.70)
Non-Hispanic black	32 (28.3)	25 (33.8)	.43	0.77 (0.41–1.45)
Non-Hispanic white	29 (25.7)	22 (29.7)	.54	0.82 (0.43–1.56)
Received 2 MTX doses	5 (4.4)	16 (21.6)	< .001	0.17 (0.06–0.47)
Required surgery	4 (3.5)	17 (23.0)	< .001	0.13 (0.04–0.37)
Required 2 MTX and surgery	3 (2.7)	7 (9.5)	.04	0.26 (0.07–0.96)
Prior ectopic pregnancy	6 (5.3)	5 (6.8)	.68	0.77 (0.24–2.49)
Prior live birth	53 (46.9)	33 (44.6)	.76	1.10 (0.61–1.97)
D4 β -hCG > DOT	41 (36.3)	35 (47.3)	.13	0.64 (0.35–1.15)
D7 β -hCG > DOT	16 (14.2)	19 (25.7)	.05	0.48 (0.23–1.00)
D7 β -hCG decreased by \geq 25.0% from DOT β -hCG	81 (71.7)	39 (52.7)	.01	2.27 (1.23–4.18)
D7 β -hCG decreased by \geq 30.0% from DOT β -hCG	77 (68.1)	34 (45.9)	.003	2.52 (1.38–4.60)
D7 β -hCG decreased by \geq 33.3% from DOT β -hCG	76 (67.3)	35 (47.3)	.01	2.29 (1.26–4.17)
D7 β -hCG decreased by \geq 50.0% from DOT β -hCG	62 (58.9)	22 (29.7)	< .001	2.87 (1.55–5.33)

β -hCG, beta human chorionic gonadotropin; CI, confidence interval; D, day; DOT, day of treatment; MTX, methotrexate; OR, odds ratio.

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were not significant in any of the regression models.

Table 3 illustrates the results of logistic regression analyses using various specified decreases in β -hCG to predict a second MTX dose. The unadjusted models illustrate the predictive value of each level of difference between DOT and D7. The adjusted models illustrate the predictive value of each level of difference between DOT and D7, adjusting for the absolute value of D7. These models show that we can predict the need for a second dose of MTX by comparing the DOT and D7 β -hCG levels, but the absolute value of the D7 β -hCG, measured as a continuous variable, is also significant. Adding D4 data to these models did not contribute to their predictive power, with *P* values for D4 ranging from .88–.98.

Finally, using the interaction terms in logistic regression models, we evaluated the possibility that the impact of a de-

crease in β -hCG (from DOT to D7) varied depending on the absolute level of β -hCG at D7. We found no support for this hypothesis: *P* values for the interaction terms were *P* = .72, .64, .66, and .34 for the models with a 50%, 33%, 30%, and 25% change, respectively.

COMMENT

Based on 187 patients previously treated for an ectopic pregnancy with single-dose MTX, we define an alternative β -hCG monitoring regimen that is highly sensitive in predicting the need for a second MTX dose. We propose that the definition of success for single-dose MTX treatment for ectopic pregnancy be defined as a clinically stable patient whose D7 β -hCG has decreased by \geq 50% from the DOT β -hCG. This protocol may be used when it is more convenient for the patient or more cost

effective for the patient and/or institution to eliminate the D4 β -hCG blood draw and clinical evaluation. Of course, any patient who is unstable or having symptoms after MTX administration warrants prompt evaluation.

Eliminating the D4 evaluation has several advantages. As long as the patient knows how to contact her health care team for questions or problems, eliminating the D4 evaluation decreases the need for a blood draw and possible clinical evaluation with physical examination and ultrasound. The D4 evaluation may also present a clinical dilemma, as several authors have found that women may have an increase in the D4 β -hCG after MTX administration.^{2,5} Reasons for this include the 36-hour half-life of β -hCG or release of β -hCG from cell death.⁵ We did not attempt to define DOT and D7 comparisons, which would necessitate surgical intervention, as this

TABLE 2
Methotrexate monitoring regimens

DOT β -hCG	Definition of need for repeat MTX dose based on β -hCG levels drawn on DOT and D7	Sensitivity	Specificity	No. of women needing repeat MTX dose MISSED with this protocol (false negative)	No. of extra women needing MTX with this protocol (false positive)	Attributable risk of receiving second MTX dose with protocol (additional women receiving extra MTX dose with alternative protocol compared with traditional protocol/total) (%)	No. of women needed to treat with repeat MTX to avoid 1 D4 evaluation (1/attributable risk)
<2000 mIU/mL (n = 113)	D7 > DOT	3/5 (60.0)	95/108 (88.0)	2/97 (2.1)	13/16 (81.3)	11/113 (9.7)	10.3
	D7 decreases by \leq 25.0% from DOT	3/5 (60.0)	78/108 (72.2)	2/81 (2.5)	30/33 (90.9)	28/113 (24.8)	4.0
	D7 decreases by \leq 30.0% from DOT	4/5 (80.0)	77/108 (71.3)	0/77 (0.0)	31/36 (86.1)	31/113 (27.4)	3.6
	D7 decreases by \leq 33.3% from DOT	5/5 (100.0)	75/108 (69.4)	1/76 (1.3)	33/37 (89.1)	32/113 (28.3)	3.5
	D7 decreases by \leq 50% from DOT	5/5 (100.0)	62/108 (57.4)	0/62 (0.0)	46/51 (90.2)	46/113 (40.7)	2.5
\geq 2000 mIU/mL (n = 74)	D7 > DOT	9/16 (56.3)	48/58 (82.8)	7/55 (12.7)	10/19 (52.6)	3/74 (4.1)	24.7
	D7 decreases by \leq 25.0% from DOT	14/16 (87.5)	38/58 (65.5)	2/41 (4.9)	20/34 (58.8)	18/74 (24.3)	4.1
	D7 decreases by \leq 30.0% from DOT	15/16 (93.8)	34/58 (58.6)	1/35 (2.9)	24/39 (61.5)	23/74 (31.1)	3.2
	D7 decreases by \leq 33.3% from DOT	15/16 (93.8)	33/58 (56.9)	1/34 (2.9)	25/40 (62.5)	24/74 (32.4)	3.1
	D7 decreases by \leq 50% from DOT	16/16 (100.0)	22/58 (37.9)	0/22 (0.0)	36/52 (69.2)	36/74 (48.6)	2.1

β -hCG, beta human chorionic gonadotropin; D, day; DOT, day of treatment; MTX, methotrexate.

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decision is primarily based on clinical symptoms.

The main disadvantage to the proposed protocol is that approximately 2 women would receive a repeat MTX dose to eliminate 1 D4 evaluation. MTX therapy entails side effects: most commonly, nausea, vomiting, and abdominal pain.³ Many of the side effects of single-dose MTX are attributable to the destruction of the ectopic pregnancy.³ The dose of 50 mg/m² used for the treatment of ectopic pregnancy has a considerably lower side-effect profile than former multidose MTX regimens.⁴ Also, it is not known if women receiving 2 50-mg/m² MTX injections 1 week apart have significantly more side effects than women receiving 1 50-mg/m² MTX dose. The side effects entailed by additional MTX doses would need to be investigated in a prospective trial. Clinicians would also have to determine the cost effectiveness of the proposed alternative monitoring regimen based on local data. However, the cost of an MTX injection is usually lower for the patient and institution than the cost of a D4 evaluation.

We combined the MUSC and UTH-SCSA data, because the morbid outcome of the medical management of ectopic pregnancy (ie, requiring surgical intervention) was not different between the 2 groups. Although the MUSC cohort's mean DOT β -hCG was higher than that of the UTHSCSA cohort, 2 previous authors have found no difference in the DOT β -hCGs of patients who would eventually require surgical therapy compared with those who did not require surgical therapy.^{5,11}

We divided the data based on the DOT β -hCG, because this value has been shown to be inversely related to the need for a repeat MTX dose, our primary outcome.^{5,7,12,13} We chose to divide the cohort into women whose DOT β -hCG was ≥ 2000 mIU/mL vs ≤ 1999 mIU/mL, because this discriminatory level is important clinically, as it is generally agreed to be the level at which an intrauterine pregnancy may be diagnosed using transvaginal ultrasound.⁷⁻¹⁰

Like previous authors, we found that the absolute β -hCG levels, particularly

TABLE 3
Odds of requiring second methotrexate dose

Definition of need for repeat MTX dose based on β -hCG levels drawn on DOT and D7	Unadjusted OR (95% CI)	Adjusted OR, adjusted for absolute value of D7 β -hCG (95% CI)
D7 decreases by $\geq 25.0\%$ from DOT	0.10 (0.03–0.30)	0.24 (0.07–0.83)
D7 decreases by $\geq 30.0\%$ from DOT	0.08 (0.02–0.29)	0.20 (0.05–0.76)
D7 decreases by $\geq 33.3\%$ from DOT	0.10 (0.03–0.33)	0.23 (0.06–0.91)
D7 decreases by $\geq 50\%$ from DOT	0.10 (0.02–0.45)	0.26 (0.05–1.3)

β -hCG, beta human chorionic gonadotropin; CI, confidence interval; D, day; DOT, day of treatment; MTX, methotrexate; OR, odds ratio.

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those on the DOT and D7, were predictive of the need for a repeat MTX injection.^{5,7,12,13} Using logistic regression analysis, we were able to show that the D4 β -hCG data were not significant, when examined with the DOT and D7 data. In addition, although a decrease in β -hCG from DOT to D7 significantly predicts treatment success, the absolute value of β -hCG at D7 is also an independently significant predictor of treatment success.

An alternative monitoring regimen is to give a second dose of MTX if the D7 β -hCG has not decreased by $>25\%$ in comparison to the DOT β -hCG.¹⁴ This group does not report the percent of patients who will require a second dose of MTX using this criteria or the sensitivity, specificity, and false-positive and false-negative rates of this regimen.¹⁴ A previous study from Kuwait followed up 77 patients treated with single-dose MTX for ectopic pregnancy and defined the need for a repeat dose if the D7 β -hCG decreased by $\leq 30\%$ in comparison to the DOT β -hCG.¹⁵ In this cohort, 3.9% (3/77) required a repeat dose and 5.2% (4/77) required surgery.¹⁵

The main limitation of this study is that it is a retrospective, hypothesis-generating study, which must be confirmed with a prospective, randomized trial. A prospective trial would also be able to determine the number of women lost to follow-up.

In conclusion, we propose an alternative monitoring regimen for women

treated with single-dose MTX for the diagnosis of ectopic pregnancy, which eliminates the need for a D4 β -hCG blood draw and clinical evaluation. The main strength of this study is that the current monitoring regimen of comparing D4 and D7 β -hCG levels was based on local requirements for the initial trial, which may or may not be applicable to various patient populations and practice patterns of today. By defining the sensitivity, specificity, and false-negative and false-positive rates of an alternative regimen, we provide clinicians with more options to tailor the monitoring of MTX therapy in ectopic pregnancy. ■

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