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The role of HCG increment in the 48 h prior to methotrexate treatment as a predictor for treatment success

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ABSTRACT

Objective: To evaluate the role HCG change in the 48 h prior to methotrexate treatment as a predictor for treatment success.

Study design: Medical records of all women who were diagnosed with ectopic pregnancy between January 2001 and June 2013 were reviewed. Four hundred and nine patients received methotrexate due to ectopic pregnancy. The "single dose" methotrexate protocol with 50 mg/m^2 was administered to patients with progressing ectopic pregnancy. HCG levels in days 1, 4 and 7 were used to evaluate methotrexate treatment success. The percentage of HCG change in the 48 h prior to methotrexate treatment was compared between patients who were successfully treated and those who failed treatment with methotrexate.

Results: Single dose methotrexate was successful in 309 patients (75.4%, success group). The medians of HCG change in the 48 h prior to methotrexate administration were significantly higher in the "failure group" (21% vs. 4%, $p < 0.01$). In a logistic regression analysis, the of HCG percent increment prior to methotrexate administration was shown to be an independent predictor for treatment outcome. Receiver operator characteristic curve for HCG percent change was 0.751, at a cutoff value of HCG increment <12% the positive predictive value for treatment success reached 86%.

Conclusions: Percentage of HCG increment in the 48 h prior to methotrexate administration is an independent predictor for methotrexate treatment success. HCG increment <12% prior to methotrexate treatment is a good predictor for treatment success.

Introduction

The incidence of ectopic pregnancy is reported to range between 1 and 2% in the United States [1,2]. Although there is a constant decline in mortality, ectopic pregnancy it is still considered to be a major cause of maternal morbidity and mortality in the first trimester of pregnancy [3]. Early diagnosis and treatment of ectopic pregnancy is feasible with transvaginal ultrasound and serial human chorionic gonadotropin (HCG) measurements. Early treatment has the advantage of preventing tubal rupture and reduced maternal mortality. Medical treatment with methotrexate is the accepted treatment, with comparable results to surgery in appropriately selected women [4]. Although many treatment protocols have been suggested, the most widely used is the "single dose protocol" that was introduced by Stovall in 1991 [5]. Before medical treatment is contemplated, consideration must be taken regarding the risk of treatment failure. Although many factors were proven to correlate with methotrexate treatment outcome, the level of HCG was shown to be the most important predictor for treatment success [6]. The reported success rate of methotrexate treatment in the "single dose protocol" was shown to range between 65 and 96%, based on initial HCG levels [7,8]. Successive HCG level follow up prior to methotrexate treatment was shown to differentiate true progressing ectopic pregnancies from spontaneously resolving ectopic pregnancies [7,9]. Moreover, sequential HCG level follow up could detect spontaneous resolution of ectopic pregnancies in more than 60% of the women that were primarily candidates for methotrexate treatment [7,9].

As HCG change prior to methotrexate treatment may represent trophoblastic tissue activity, we wanted to investigate the role of HCG percent change prior to methotrexate treatment as a predictor for treatment outcome.

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Materials and methods

We performed this retrospective cohort study at the department of gynecology in a tertiary university-affiliated medical center. The institutional review board approved this study. Medical records of all women who were diagnosed with ectopic pregnancy between January 2001 and June 2013 were reviewed. Diagnosis of ectopic pregnancy was based on both HCG level measurement and transvaginal ultrasound confirming the presence of extra-uterine pregnancy (inhomogeneous mass adjacent to the ovary, hyperechoic ring or gestational sac with or without a fetal pole) [10]. Patients presenting with one of the following conditions were excluded from the study group and referred for immediate surgery: hemodynamic instability, HCG levels >10,000 IU, ectopic pregnancy with cardiac activity, severe abdominal pain or signs of intra-abdominal bleeding. Women who were candidates for medical treatment according to our "watchful waiting protocol" were included in our study [7]. In brief, sequential HCG level follow-ups were used to differentiate spontaneously resolving ectopic pregnancies from progressing ectopic pregnancies. Women with spontaneous daily decline of HCG of more than 15% were considered as spontaneously resolving ectopic pregnancies, and were discharged for outpatient follow up. In contrast, women with HCG level increment of more than 15% were diagnosed as having progressing ectopic pregnancy, and were treated with methotrexate. In all other cases with plateauing HCG level (daily change <15%), repeated daily HCG testing were taken for up to 5 days, after which methotrexate was administered. Criteria for methotrexate administration were according to the accepted guidelines, using the "single dose protocol" at a dose of 50 mg/m^2 [11]. Methotrexate injection day was referred as day one, and additional HCG measurements were taken on day 4 and 7 in an outpatient setting using the same laboratory. We defined treatment failure in women who returned with signs and symptoms of tubal rupture or in women in whom HCG level failed to decline >15% between day 4 and 7.

As mentioned previously, our intention was to investigate the role of HCG change prior to methotrexate treatment as a predictor for treatment outcome. The percentage of HCG change in the 48 h prior to methotrexate treatment was compared between patients who were successfully treated and women who failed treament with methotrexate. Calculation of HCG change was performed as follow: HCG level in methotrexate treatment day (day 1) was divided by HCG level as measured 48 h earlier (day −1). In addition, day 1 HCG level (methotrexate treatment day) was compared between the success and failure groups. A receiver-operating characteristic curve was designed to determine the optimal HCG level change for treatment success. Women with non-tubal ectopic pregnancies and incomplete data regarding HCG change prior to methotrexate treatment were excluded from our study.

Statistical methods

We used Shapiro Wilks test to evaluate the distribution of the data. Since data was not normally distributed, we used a Mann-Whitney U for comparison between continuous variables. Fisher's exact and Chi-square tests (2 by k) were used for proportional comparison. Stepwise forward regression analysis was performed to identify independent variables that were associated with methotrexate treatment outcome. Finally, a receiver-operating characteristic curve was used to assess the optimal cut-off value of HCG level change with the highest sensitivity and specificity for treatment success. P value of less than 0.05 was considered significant.

Results

During the study period 1703 women were diagnosed with an ectopic pregnancy in our department, of these, 409 patients (24%) were eligible for methotrexate treatment. Forty-six women were excluded from our study due to incomplete data regarding HCG change prior to methotrexate treatment (Fig. 1). Clinical and demographic variables of methotrexate success and failure groups are presented in Table 1. There was no difference regarding maternal age, gravidity, parity and gestational age between the two groups. Day 1 HCG levels (methotrexate treatment day) were significantly higher in the methotrexate failure group compared to the success group (2196 vs. 1437 respectively, $p < 0.001$) (Table 2).

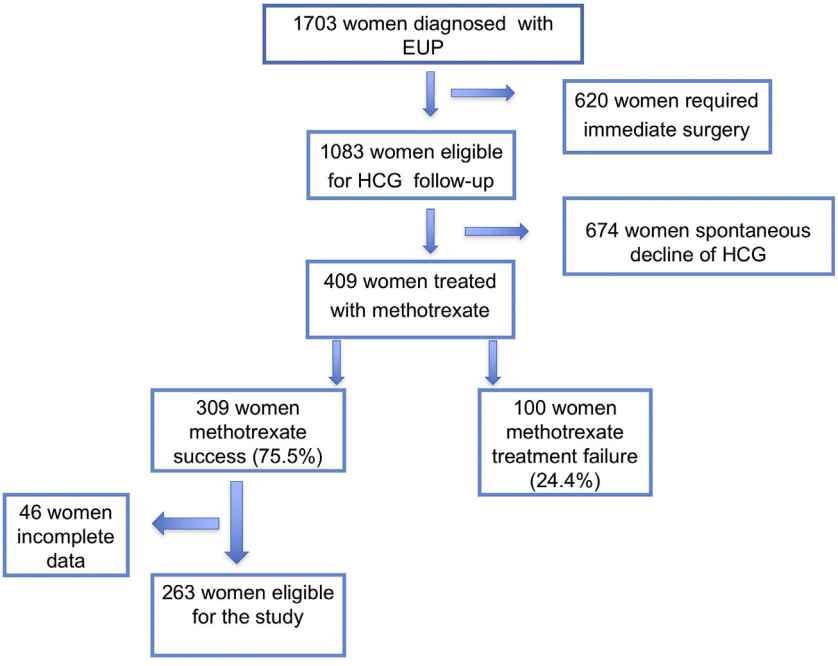

Fig. 1. Flow chart of patients admitted with ectopic pregnancy.

Table 1
Characteristics of women treated with methotrexate for ectopic pregnancies.

Characteristic	Methotrexate success group (N = 263)	Methotrexate failure group (N = 100)	*P*
Age (years)	31.3 ± 5	31.1 ± 4	0.9
Parity	0.6 ± 0.8	0.6 ± 0.6	0.4
Gravidity	2.3 ± 1.3	1.4 ± 1.2	0.2
Gestational age (weeks)	6.4 ± 1.3	6.2 ± 0.8	0.3

Data are presented as mean (±SD).

Table 2
Comparison of HCG levels between the success and failure group.

Characteristic	Methotrexate success group (N = 263)	Methotrexate failure group (N = 100)	*P*
Day 1 HCG (mIU/mL)	1437 (401–2041)	2196 (700–3037)	<0.001
% HCG change (*)	+4 (−3% + 15%)	+21 (6.5% + 41%)	<0.001
% HCG change (*) in women with HCG <1000	+5 (−1% + 17%)	+22 (13% + 43%)	<0.001
% HCG change (*) in women with HCG >2500	+8 (1% + 17%)	+22 (15% + 48%)	<0.001

Data are presented as median (range).
(*) Percent HCG change in the 48 h prior to methotrexate treatment.

In order to investigate the influence of HCG trend on treatment outcome, percentages of HCG change in the 48 h preceding methotrexate treatment were compared between the two groups. The mean HCG percent change prior to methotrexate treatment was significantly higher in the failure group compared to the success group (21% vs. 4% respectively, $p < 0.001$). Moreover, a subgroup analysis was performed in women that were considered as either "low risk" (HCG level <1000) or "high risk" (HCG level >2500) for treatment failure [7]. Similarly, mean HCG percent change was significantly higher in the failure group, independent of the absolute level of HCG. Stepwise forward regression analysis was performed including day 1 HCG level, HCG percent change prior to methotrexate treatment, age and gestational age. Both day 1 HCG level and HCG percent change prior to methotrexate treatment were shown to be independent predictors for treatment outcome (odds ratio per unit change, 1.0002; 95% confidence interval 1.00010–1.0004, P = 0.001 and odds ratio per unit change, 1.049; 95% confidence interval 1.034–1.065 P < 0.0001, respectively).

A receiver-operating characteristic curve was created in order to identify the optimal HCG percent change for methotrexate treatment outcome. The area under the curve was shown to be 0.751 (Fig. 2). At a HCG increment of 12% the sensitivity reached 73.7%, the specificity reached 71.1% and the positive predictive value for treatment success was 86.6%.

Comment

Medical management of ectopic pregnancies is considered to be an appropriate alternative for surgery. Due to its high efficacy and

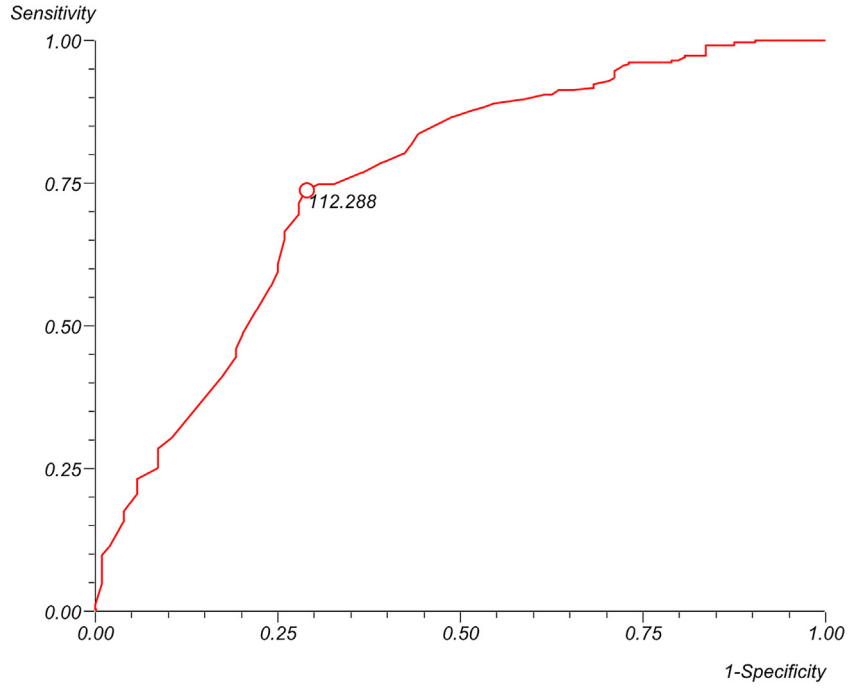

Fig. 2. Receiver operating characteristic (ROC) curve for HCG change in the 48 h prior to methotrexate treatment as a predictor for treatment success.

safety, methotrexate treatment for ectopic pregnancies has become the mainstay of therapy for hemodynamically stable patients, with a rate of 35.1% in 2007 [12]. Proper patient selection is necessary before medical treatment is contemplated, because patient compliance for HCG level follow-up is important and there is always a risk of treatment failure [13]. Successful treatment in the single dose protocol is defined by >15% decrease in HCG levels between days 4 and 7 after methotrexate treatment, with positive predictive value of 93% for treatment success [14]. Although absolute measurements of HCG on day 4 were not shown to be associated with treatment outcome, declining HCG levels between days 1 and 4 were shown to be associate with treatment success in 88–100% of the patients [15–18].

The importance of defining predictive variables for methotrexate treatment outcome is in order to increase the likelihood of treatment success while minimizing the risk of tubal rupture. Several predictors have been shown to correlate with methotrexate treatment outcome, including the presence of peritoneal fluid on ultrasound, fetal cardiac activity, size of ectopic mass and HCG level [11]. Serial HCG level measurements are crucial for the diagnosis of ectopic pregnancy and decision regarding the need for methotrexate treatment [7]. Whereas HCG curves for both viable intrauterine pregnancies and resolving pregnancies are well defined, there is no model that can adequately characterize HCG pattern in cases of ectopic pregnancies [19].

Several studies investigated the role of HCG as a marker for trophoblastic cell activity in women with ectopic pregnancy. Natale et al. and Cabar et al. examined the role of HCG concentration as a predictor for trophoblastic infiltration of the tubal wall in ectopic pregnancies. Both studies showed that higher HCG concentration was associated with deeper trophoblastic cells invasion into the tubal wall [20,21]. Kiss et al. investigated the correlation between HCG dynamics and trophoblast cells proliferative activity. A significance correlation between HCG change and trophoblast cells proliferation was shown, irrespective of HCG concentration [22]. These observations suggest that not only HCG concentration but also HCG dynamics may have a role in the prediction of methotrexate treatment outcome.

Only few studies addressed the role of HCG dynamics for predicting methotrexate treatment outcome. In his study, Dudley et al. examined those risk factors predicting tubal rupture among women who received methotrexate treatment. Both HCG incremental rates before and after methotrexate injection were shown to be independent risk factors for tubal rupture [23]. A small series by Da Costa Soares et al. examined the role of HCG increment prior to methotrexate treatment as a predictor for treatment success [24]. In this study, the mean HCG increment in the methotrexate failure group was significantly higher compared with HCG change in the methotrexate success group (36% vs. 13%, respectively). By using receiver-operating characteristic curve, the optimal cut-off value for treatment success was 11.1%.

Similarly, in our present study we have demonstrated that both HCG concentration and HCG increment in the 48 h before methotrexate treatment are independent predictors for treatment outcome. Women who failed methotrexate treatment had significantly higher HCG increments (21% vs. 4%, $p < 0.001$). In addition, by using ROC curve we have demonstrated that HCG increment of less than 12% will result in treatment success in at least 86% of the cases. The importance of the current study is not only by its large cohort of patients but also by demonstrating the importance of HCG dynamics in subgroups of women considered as either "high-risk" (HCG level <1000) or "high-risk" (HCG level >2500) for methotrexate treatment failure. The definition of "high-risk" and "low-risk" women was based on our previous report that methotrexate treatment failure in these women was 25% and 5%, respectively.

We believe that using HCG dynamics as a supplementary tool in the prediction of methotrexate treatment outcome should be considered in every woman diagnosed with ectopic pregnancy, especially in the sub-groups of patients that are considered as "low-risk" or "high-risk" for methotrexate treatment failure. Whereas low-risk women with high HCG increment should be consulted about the increased risk of treatment failure, methotrexate treatment can be offered to high-risk patients with low HCG increment that otherwise would be operated.

Our study further supports the importance of sequential HCG measurements in women with suspected ectopic pregnancy. The importance of HCG dynamics is not only in diagnosing progressing ectopic pregnancies, but also in predicting treatment outcome when methotrexate treatment is considered.

A limitation of this study is its retrospective nature. In addition, during the study period decisions regarding intervention where based on clinical judgment by different physicians.

In conclusion, HCG increment prior to methotrexate treatment is an important predictor for methotrexate treatment success and should be used as additional tool in the decision making process regarding the appropriate treatment. Women with HCG increment <12% can be reassured for treatment success irrespective of serum HCG concentration.

Conflict of interest/financial disclosure

The authors report no conflicts of interest or financial disclosure.

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