

CAN INITIAL β HCG VALUES PREDICT THE NEED FOR SECOND DOSE OF METHOTREXATE IN MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY?

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ABSTRACT

INTRODUCTION

Prediction of requirement of second dose of methotrexate in patients treated with single dose would help in guiding treatment and counseling. The aim of this study is to determine whether pretreatment beta HCG values can predict the need for second dose of methotrexate in medically managed ectopic pregnancy.

MATERIALS AND METHODS

46 women with ectopic pregnancies who were managed medically were included. The median of beta HCG titres on day 1, day 4 and day 7 was assessed in patients who responded to single dose methotrexate and those who required a second dose.

RESULTS

Out of the 46 patients studied, 41 responded to medical treatment (success 91%). 14 out of 41 required second dose of methotrexate (34%). Two patients required third dose of methotrexate. Five patients required surgery.

DISCUSSION

The median of day 1 and day 4 beta HCG values were not statistically different between those who responded to single dose methotrexate and those who required a second dose. Only day 7 values were found to be different.

CONCLUSION

The beta-hCG titre on day 1 and day 4 is not a predictor of requirement of second dose of methotrexate.

KEYWORDS

Ectopic Pregnancy, Chorionic Gonadotropin, Methotrexate, Treatment Outcome, Second Dose.

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INTRODUCTION: The incidence of ectopic pregnancies is estimated to be approximately 2% of all pregnancies. Improvement in transvaginal sonography and beta-hCG assays allows early diagnosis of extrauterine pregnancy resulting in a significant decline in maternal mortality.⁽¹⁾

Medical treatment of an unruptured ectopic pregnancy is a popular, cost-effective practice.⁽²⁾ The single-dose methotrexate protocol is the most frequently used protocol with a reported success rate of 65% to 94% as is associated with minimal toxic side effects, few complications and better compliance of patients.^(3,4,5) The term "single-dose" is actually misleading, because patients receive an additional dose in case of suboptimal response, which is required in approximately 15% of patients.⁽⁶⁾ Followup of patients treated with the single-dose protocol includes assessment of β HCG levels on days 1, 4 and 7. A 15% decrease in β HCG level from day 4 to day 7 is expected and was shown to predict successful treatment in 93% of patients.⁽⁷⁾

Initial β HCG level was shown to be the single most important predictor of treatment success in cases of ectopic pregnancies.⁽⁸⁾

The aim of our study was to investigate the correlation between beta-hCG levels on days 1, 4 and 7 as a predictor of second-dose requirement.

MATERIALS AND METHODS:

Patients: We enrolled 46 patients with ectopic, non-ruptured pregnancy in a retrospective, hospital-based analysis. All of the women were treated at the Institute of Maternal and Child Health between January 2015 and June 2016. The ectopic pregnancy diagnosis was made using a popular algorithm.⁽⁸⁾ Our department uses single-dose methotrexate protocols.⁽⁷⁾ We administered 50 mg/m² of methotrexate every 7 days and a drop beta-HCG concentration of less than 15% (between days 4 and 7) was a crucial indicator for the administration of the next dose of methotrexate. Surgical intervention took place in cases of tubal rupture and in patients who did not respond to methotrexate treatment. Tubal rupture was diagnosed on the basis of haemodynamic and clinical signs such as rapid blood pressure drop, increased abdominal pain and the presence of blood in the abdomen cavity confirmed by ultrasound. The biochemical nonresponse criteria included a plateau or over 50% serum beta-hCG level increase after

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each dose of methotrexate. To exclude spontaneously regressed ectopic pregnancy, the beta-HCG concentration was observed for 2 consecutive days and only patients with a rising serum beta-HCG level and ultrasound-confirmed ectopic pregnancy qualified for medical treatment.

The beta-hCG level was measured at the hospital laboratory by Enzyme Immunoassay.

The results are given in mIU/mL.

Out of the 46 patients studied, 41 responded to medical treatment (success 91%). 14 out of 41 required second dose of methotrexate (34%). Two patients required third dose of methotrexate. 5 patients required surgery due to evidence of rupture or failure to respond to medical treatment. Evaluation of the possible correspondence between the initial HCG concentration and the number of methotrexate single doses was done. The medical data was collected from the patients' medical histories. Data on the women's mean age, week of gestation, gestation sac diameter, pregnancy loss history, etc. Each patient gave formal consent for initial methotrexate therapy.

STATISTICAL ANALYSIS: Statistical analysis was done using SPSS 16.0 for Windows. Quantitative data was expressed as mean and standard deviation or median and range and categorical data as frequency and percentages. Quantitative data was analysed by Student's 't' test if data was normally distributed or by Mann-Whitney test and Wilcoxon test when data was not normally distributed. Categorical data was analysed by chi-square test or Fisher's exact test. A p value <0.05 was considered to indicate statistical significance.

RESULTS: We treated 41 women successfully with methotrexate. Out of 5 patients who required surgical management, only two manifested the haemodynamic symptoms of tubal rupture.

The analysed epidemiological factors age, gestational age, h/o ectopic pregnancy and h/o pregnancy loss were comparable between the two groups. (Table 1).

Evaluation of the possible correspondence between the initial HCG concentration and the number of methotrexate single doses followed. Twenty seven (65.9%) were cured with a single dose of methotrexate, but it was necessary to repeat the injection in 12 women (29.2%). Only 2 patients (4.9%) required three single doses of methotrexate. The median HCG values on day 1 was 3,541 (range 448-13,000) and that on day 4 3,430 (range 201-13,510) in those patients who responded to single dose methotrexate. On day 7, the median HCG value was 1,314 (range 111-9,774).

The median HCG values on day 1 was 3,532 (range 529-6,842) and that on day 4 3,896 (range 821-5,238) in those who required second dose of methotrexate. On day 7, the median HCG value was 4,417 (range 1,655-11,699).

The range of the beta-HCG concentration was very wide in each group of patients, but having compared the medians of beta-HCG titre on day 1 and day 4, the difference did not prove to be statistically significant. The median values on day 7 was statistically different (p value 0.009). Median

beta-HCG value on day 7 was significantly low in patients who required only single dose of methotrexate. (Table 2).

The HCG values on day 7 was three times higher in patients who required a second dose.

When the fall in HCG from day 1 to day 4 and day 7 were considered in the two groups, it was found that HCG values significantly reduced from day 1 to day 7 in the single dose group whereas the values increased significantly from day 1 to day 7 in the second dose group. (Table 3).

Variable	MTX single dose (N=27)	MTX 2/3 doses (N=14)	P value
Age*	27±5.4 yrs.	25.7±3.9 yrs.	0.434
Gestational age*	7.3±1.5 wks.	6.9±1.3 wks.	0.463
H/O ectopic pregnancy#	3 (11.1%)	4 (28.6%)	0.205
H/O pregnancy loss#	8 (29.6%)	4 (28.6%)	0.62

Table 1: Demographic Variables in the Two Groups

*Value expressed as mean±SD.

#Value expressed as frequency (%) Age, gestational age, h/o ectopic pregnancy and h/o pregnancy loss were comparable between the two groups.

Variable	MTX Single Dose (N=27)	MTX 2/3 Doses (N=14)	P value
Initial BHCG	3741.5 (445-13670)	3493.5 (75-6326)	0.243
Day 1	3541 (448-13471)	3532 (529-6842)	0.437
Day 4	3430 (201-15857)	3896 (821-9661)	0.77
Day 7	1314 (111-9774)	4417 (1655-11699)	0.009

Table 2: Comparison of Beta-HCG Values in the Two Groups

Value expressed as median (range), median BHCG value on day 7 was significantly low in patients who required only single dose of MTX.

Variable	P Value (MTX Single Dose)	P Value (MTX 2/3 Doses)
Day 1 to Day 4	0.161	0.007
Day 1 to Day 7	< 0.0001	0.006

Table 3: Fall in Beta-HCG in the Two Groups

For MTX, single-dose group beta-HCG values significantly reduced from initial value to day 7. But, for MTX, 2/3 doses group beta-HCG values significantly increased from initial value to day 7.

DISCUSSION: Medical treatment with methotrexate has become the treatment of choice in haemodynamically stable ectopic pregnancies.⁽⁹⁾

Prediction of requirement of second dose of methotrexate at treatment outset would be helpful in counseling patients regarding the need for successive doses of methotrexate and chance of failure and need for surgery. Parameters studied include parity, sac size, gestational age and findings on transvaginal USG.

The role of initial beta-HCG concentration as a predictor of treatment success with a single dose of methotrexate is well established.^(8,10,11) Levels of beta-HCG on day 4 after treatment, however, show high variability and in many cases beta-HCG levels continue to rise throughout the fourth day of treatment.⁽¹²⁾

Agostini et al⁽¹³⁾ demonstrated a positive predictive value of 97% for treatment success in cases in which beta-HCG levels decline by 20% or more between day 1 and 4. However, the predictability of second dose requirement based on day 1, day 4 and day 7 values is less studied. The purpose of this study was to clarify this issue.

Less than 22% reduction in human chorionic gonadotropin levels from day 1 to 4 was found to be a predictive factor for the requirement of an additional dose of methotrexate in single-dose regime.⁽¹⁴⁾ Gabbur et al reported that absolute levels of beta-HCG on day 4 after methotrexate treatment were not shown to be a good predictor for treatment success. Only day 7 HCG values were associated with successful single-dose therapy.⁽¹⁵⁾

In our study, also the median HCG values on day 1 and day 4 in patients who responded to a single dose and in those who required a second dose were not statistically different. The median HCG values on day 7 were significantly different in those who required a second dose. In the group treated with a single dose of methotrexate, the median beta-HCG concentration was 3048 mIU/mL with the lowest and the highest values differing by almost twenty five times. It is interesting that the lowest beta-HCG values were below 1000 mIU/mL in the groups treated with more than one dose of methotrexate.

The success of methotrexate treatment may depend on the trophoblastic activity and day 1 HCG values alone are not predictive of requirement of second dose of methotrexate.

CONCLUSION: The value of the initial level of beta-HCG was not a valid indicator of the number of methotrexate cycles essential for a successful outcome.

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