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## Day 4 $\beta$ HCG dynamics as an early predictor of success in medically managed ectopic pregnancies: A retrospective cohort study

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### Abstract

**Introduction:** Ectopic pregnancy occurs in 1-2% of all pregnancies and commonly affects the ampullary part of the fallopian tube. In single dose protocol, HCG levels are measured on Day 1,4 and 7 after methotrexate. A fall in levels of HCG by 15% or more between day 4 and 7 indicates success of medical management. The day 4 HCG levels may give an indication to success of this protocol need for additional doses of methotrexate, early recourse to surgery etc.

**AIM:** To analyse the trends in HCG on day 4 after medical management of ectopic pregnancy with methotrexate and analyse its predictive effect on the success of single dose protocol.

**Materials and methods:** Retrospective data of all patients with ectopic pregnancy treated medically with methotrexate from January 2017 to December 2019 was analysed. The women included had ectopic pregnancy diagnosed by transvaginal ultrasound and inappropriate HCG values. HCG. The protocol for Methotrexate administration is in accordance with the accepted guidelines (ACOG2018). HCG concentrations are measured on day 1,4 and 7.

**Results:** Statistical analysis was done in SPSS software version 18. Out of 123 patients, 74 patients responded to a single dose of methotrexate. 43 patients required additional doses of methotrexate. 6 patients required surgery. In 47.8% (56/117) of the cases there was a fall in HCG between days 1 to 4. In this sub cohort 1, 87.5% (49/56) had success with single injection of methotrexate. There was a rise in HCG values on day 4 in 52.2% (61/117). In this sub cohort 2, only 40.9% (25/61) had treatment success. Receiver Operating Characteristic curve (ROC) was plot to compare the fall in  $\beta$  HCG on day 4 and day 7. The area under the curve obtained was 0.851 ( $p < 0.001$ ) indicating good differentiating capacity for a change in  $\beta$  HCG from day 0 to 4. The optimal cut off for prediction of treatment success was a fall of 8% from day 1 to day 4.

**Conclusions:** A fall in HCG values on day 4 in can predict a high likelihood of success following medical treatment of ectopic pregnancies.

**Keywords:** Ectopic pregnancy, medical management, day 4 Human chorionic gonadotropin, methotrexate

### Introduction

Ectopic pregnancy occurs in 1-2% of all pregnancies and commonly affects the ampullary part of the fallopian tube. Long term health consequences of ectopic pregnancies include infertility and recurrent ectopic pregnancies. Early diagnosis of ectopic pregnancy before rupture is possible by highly sensitive  $\beta$ HCG assays and trans vaginal ultrasound which facilitates conservative treatment with methotrexate. Tanaka *et al.* in 1982 found methotrexate to be safe and effective in the management of ectopic pregnancy. Single dose protocol, first introduced by Stovall in 1991<sup>[1]</sup>, is widely used with success rates of 52- 96%. In this protocol HCG levels are measured on Day 1,4 and 7 after methotrexate.

A fall in levels of HCG by 15% or more between day 4 and 7 indicates success of medical management<sup>[2]</sup>. The disadvantage of the current protocol is the need to wait for 7 days to know the outcome. The day 4 HCG levels may give an indication to success of this protocol, need for additional doses of methotrexate, early recourse to surgery etc. This also helps to reduce the patient anxiety and improve patient compliance by reducing the follow up visits and early discharge of admitted patients. Early prediction of treatment success by day 4 may also help in development of new protocols. Several studies have tried to find out the early markers of treatment outcome like pretreatment and day 4 HCG concentrations.

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The aim of this study is to evaluate the role of day 4 HCG levels in early identification of treatment success.

### Aim of study

To analyse the trends in HCG on day 4 after methotrexate treatment and its possible predictive effect on the success of single dose treatment.

### Materials and methods

Retrospective data of all patients with ectopic pregnancy treated medically with methotrexate from January 2017 to December 2019 was analysed. The women included had sonographic evidence of a heterogenous adnexal mass or extrauterine sac-like structure coupled with an inappropriately increasing HCG serum concentration. Informed consent was taken.

HCG concentrations are measured on day 1. The protocol for Methotrexate administration is in accordance with the accepted guidelines for single dose treatment at a dose of 50mg/m<sup>2</sup>. Body surface area (ACOG 2018). HCG concentrations are measured on day 4 and 7. Treatment is defined as successful if a fall in HCG concentration of 15% or more is observed between days 4 and 7, coupled with a progressive decline in HCG to less than 0.5 mIU/ml during follow-up without the need for either further administration of MTX or surgery. Treatment failure is defined as an insufficient decrease in HCG (i.e. a decrease of less than 15% from day 4 to day 7) necessitating further doses of MTX or a need for surgical intervention because of pain or haemodynamic instability after MTX treatment

### Inclusion Criteria

1. Hemodynamically stable patient
  2. Adnexal mass less than 4 cm
  3. Patient willing for follow up
  4. No contraindications for methotrexate
- There was no well defined HCG limit that categorically precluded medical management.

### Exclusion Criteria

1. Caesarean scar ectopic or angular pregnancy
2. Presence of fetal heart on ultrasound examination
3. Hemodynamically unstable patient
4. Active pulmonary disease
5. Hepatorenal dysfunction
6. Neutropenia /Thrombocytopenia

### Study setting

The study was conducted at the Institute of Maternal and Child health, Government Medical College, Calicut.

### Study design

Retrospective cohort study

### Statistical analysis

Statistical analysis was done in SPSS software version 18.

### Results

A total of 123 patients who were treated with methotrexate were included in the study. 74 patients responded to a single dose of methotrexate (success). 43 patients required additional doses of methotrexate (failure). 6 patients required surgery and were excluded from the analysis. The overall success of single dose methotrexate was 63% (74/117). The entire cohort was split into two sub cohorts according to the rise or fall of HCG values on day 4. The frequency of rise or fall in HCG in the study cohort is given in Table 1.

**Table 1:** Frequency of rise or fall in HCG on Day 4 in the study cohort

	Frequency	%
fall	56	47.9
rise	61	52.1
Total	117	100.0

Tabulation of success or failure according to rise or fall in HCG on day 4 is given in Table 2.

**Table 2:** Tabulation of success or failure according to rise or fall in HCG on day4

		Success failure		Total
		Success	Failure	
Fall	Number	49	7	56
Rise	Number	25	36	61
Total	Number	74	43	117

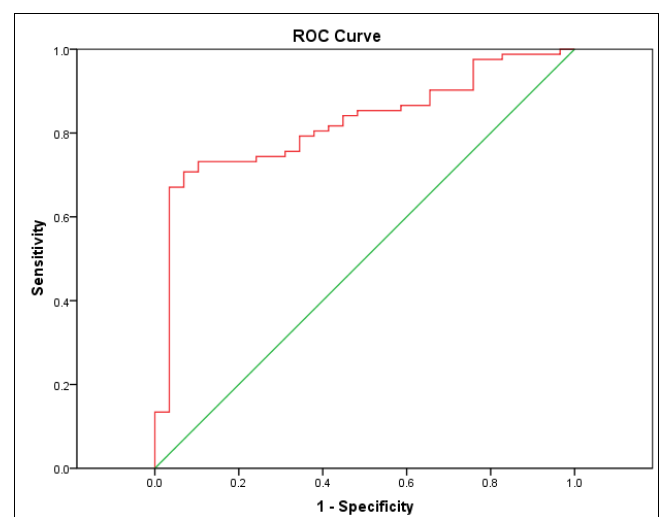
It was found that in 47.8% (56/117) of the cases there was a fall in HCG between days 1 to 4 (sub cohort 1). In sub cohort 1, 87.5% (49/56) had success with single injection of methotrexate alone.

There was a rise in HCG values on day 4 in 52.2% (61/117) (sub cohort 2).

In this sub cohort 2, only 40.9% (25/61) had treatment success.

The test performance of a fall in HCG from day 1 to day 4 was as follows, Sensitivity 66.2%, Specificity 83.7%, Positive predictive value PPV 87.5%, Negative predictive value NPV 59%. Though sensitivity is low, the fall in HCG on day 4 has got a high positive predictive value in predicting treatment success.

Receiver Operating Characteristic curve (ROC) was plot to compare the fall in  $\beta$  HCG on day 4 and day 7 (Fig.1.). The area under the curve obtained was 0.822 ( $p < 0.001$ ) indicating good differentiating capacity for a change in  $\beta$  HCG from day 0 to 4. Figure 1. Receiver operating characteristic curve of day 0–4 HCG to predict the success of methotrexate treatment for tubal ectopic pregnancy



In case of patients with fall in  $\beta$  HCG values on day 4, all the patients who had a fall of 8% and more had treatment success (NPV 100%). In patients with fall in  $\beta$  HCG on day 4 less than 8%, the chance of failure is less than 1/3rd ( PPV 32.3%).

### Discussion

The clinical significance of day 4 HCG dynamics and its prognostic value in predicting treatment success has been studied extensively. In some women who received methotrexate

therapy there is a transient rise in HCG concentrations on day 4<sup>[3]</sup>. In this study, 47.8% of the patients had a fall in HCG on day 4, and 87.5% of these patients achieved treatment success. This is comparable to other studies where 80 – 100% success could be predicted with fall in HCG values from day 1 to day 4. The test performance of a fall in HCG on day 4 in this study had a moderate sensitivity (66%) and high positive predictive value (87.5%), whereas in the study by MM Skubisz *et al.* it had a high sensitivity and positive predictive value.

Receiver operator characteristics curve plotted showed an AUC 0.85 indicating a good differentiating capacity for a fall in HCG on day 4. The optimal cut off of a fall in HCG from day 1 to day 4 was 8% and all patients who had a fall of 8% or more responded to single dose treatment. 6% to 20% fall in the HCG values on day 4 was found to be predictive of treatment success by various investigators.

Nguyen<sup>[4]</sup> *et al.* in a study of 30 participants, reported that all patients with a decline in HCG from day 0 to day 4 had treatment success (100%). They also found that rise in HCG was still associated with a 62% probability of success. In a study by Agostini<sup>[5]</sup> *et al.*, there was a 97% probability of success if the rate of decline in HCG levels was more than 20%.

In a study by MM Skubisz<sup>[6]</sup> *et al.*, of 33 patients where serum bhCG dropped between days 0 and 4 after methotrexate, the ectopic pregnancy was resolved in 88% of cases without further treatment. Of 12 women where serum bhCG rose between days 0 and 4, only 42% had treatment success.

In another study by MM Skubisz<sup>[7]</sup> *et al.*, the predictive values of three measures were compared a) Falling HCG between days 0 – 4 b) >15% fall in HCG values from day 4 to day 7 and c) >20% fall in HCG values from day 0 to day 4. In the 206 women studied, falling serum HCG between days 0 – 4 had a positive predictive value of 85% for treatment success. In women with rising HCG between days 0 – 4, 55% had treatment success. There was no significant difference in the ability of tests to accurately predict medical treatment success when comparing them individually using Fisher's exact test ( $p \geq 0.13$ ).

In a study by Girija<sup>[8]</sup> *et al.*, the HCG levels between day 0 and 4 decreased in 42.7% of cases and 80.9% of these cases had treatment success. The HCG levels increased in 57.4% of cases and 33.3% of these cases had treatment success. A 10 percent decline in day 4 HCG levels predict the treatment success with sensitivity of 77% and Specificity 81%. The area under the ROC curve was 0.82.

Levin<sup>[9]</sup> *et al.* in a study of 292 women treated with single dose methotrexate found that the optimal cut off points for prediction of treatment success were an increment of less than 17% in the 24h before treatment and decrease of more than 22% between day 1 and day 4 HCG.

In another study by Wong<sup>[10]</sup> *et al.*, in 102 patients the positive predictive value of a fall in HCG values was 91%. A 6% drop in day 0–4 serum HCG was the best predictor of treatment success.

## Conclusion

A fall in HCG on day 4 can predict treatment success with single dose protocol and a fall of 8% from day 1 to day 4 can provide an early prediction of the outcome.

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