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## HIGH HCG LEVELS AS A CUT-OFF TO GUIDE MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY: OUR EXPERIENCE

K. S. S. Madhavi, K. Avani Reddy

*Methotrexate is traditionally administered using a multi-dose regimen, but a single-dose regimen was developed for patient compliance and reduced adverse effects.*

**The aim:** To study the success of methotrexate in our hospital considering a higher cut-off level for  $\beta$ -hCG.

**Materials and methods:** A hospital-based retrospective observational study was done on 40 hemodynamically stable patients diagnosed with ectopic pregnancy from July 2017 to November 2018 at Osmania General Hospital Hyderabad. Hospital-based retrospective observational study done in 40 hemodynamically stable patients diagnosed with ectopic pregnancy for 2 years. Patients diagnosed with ectopic pregnancy by transvaginal scan and who are hemodynamically stable. The selection was made as patients diagnosed with ectopic pregnancy were admitted to the hospital. Initial serum  $\beta$ -hCG levels were measured treated with MTX + Leucovorin (i.m) and serial measurements of serum  $\beta$ -hCG levels every 48 hrs were taken. The qualitative data were presented in numbers and percentages, and the quantitative data were presented in the form of mean and standard deviation.

**Results:** 32 patients were treated with methotrexate, and 8 cases with surgically treated. 12 patients have taken one dose for successful treatment. 80 % of cases are successful with methotrexate treatment. The treatment success rate, on average, is 92 % when initial S- $\beta$ -hCG levels <5000IU/L and 68 % when initial S- $\beta$ -hCG levels > 5000 IU/L. The overall success rate is 80 % (32 out of 40).

**Conclusion:** Though the success rate is much lower with initial values >5000 (79 %) when compared to values <5000 (100 %), considering the major advantage of medical management, which is preserving the fallopian tube and thus fertility, a trial of medical management can be considered in carefully selected patients when values are >5000 with preparedness to meet any emergency

**Keywords:** Ectopic pregnancy, Human chorionic gonadotropin (hCG), methotrexate, hemodynamically stable

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### 1. Introduction

Ectopic pregnancy is a significant cause of morbidity and mortality in the first trimester of pregnancy. There are >100,000 cases reported/per year in India, but the actual number is much greater because only cases managed surgically are reported. In the past, most patients with ectopic pregnancy presented with acute symptoms and intra-abdominal haemorrhage, which meant resorting to immediate surgery, but the scenario has been much different in recent times [1]. Advances in laboratory and imaging technologies in the last few decades allow an early diagnosis of ectopic pregnancy, even before the patient develops any symptoms. Consequently, in many such patients, surgery is not always necessary. The greatest advance in the management of ectopic pregnancy has been the development of medical management, which became available in the mid-1980s [2]. Therefore, medical management is a feasible option and a priority over surgery in properly selected cases. Earlier studies show that success with methotrexate is predicted by initial S- $\beta$ -hCG values. However, there is no consensus about the upper limit of S- $\beta$ -hCG levels that can predict a successful treatment [3]. To study the success of methotrexate in our hospital considering a higher cut-off level for  $\beta$ -hCG.

### 2. Materials and methods

A hospital-based retrospective observational study was done on 40 hemodynamically stable patients diagnosed with ectopic pregnancy from July 2017 to November 2018 at Osmania General Hospital Hyderabad.

**Inclusion criteria:** patients diagnosed with ectopic pregnancy by transvaginal scan and hemodynamically stable.

**Exclusion criteria:** Hemodynamically unstable patients, Ruptured ectopic pregnancy, Fetal cardiac activity on TVS and Gestational sac size more than 4 cm.

Ethical approval and informed was obtained.(ECR/180/OMC/AP/2016/07/45 dated on 15/12 2016)

The selection was made as patients diagnosed with ectopic pregnancy were admitted to the hospital. Initial serum  $\beta$ -hCG levels were measured treated with MTX + Leucovorin (i.m) and serial measurements of serum  $\beta$ -hCG levels every 48 hrs were taken.

MTX is given in a dosage of 1 mg/kg IM on day 1,3,5,7, and leucovorin is given in a dosage of 0.1 mg/kg on day 2,4,6,8. If a decrease in S- $\beta$ -hCG of >15 % compared to the previous value was observed, then injections were stopped, and HCG was measured weekly until it was <10 IU/L.

Raw data were entered into a Microsoft Excel spreadsheet. Appropriate statistical tests were done using SPSS 17A and openepi.com to compare qualitative data and quantitative data. The qualitative data were presented in numbers and percentages, and the quantitative data were presented in the form of mean and standard deviation.

**3. Results**

Most of the patients are in the 30–35 years age group, followed by 20–25 years, and the most common gravida is G1 (Table 1).

Table 1

Demographic details in the present study

Age in years	Number of patients	Percentages
<20 yrs	12	30
20–25 yrs	8	20
25–30 yrs	4	10
30–35 yrs	16	40
Gravida		
G1	22	55
G2	10	25
G3	6	15
G4	2	5

32 patients were treated with methotrexate, and 8 cases with surgically treated (Fig. 1).

12 patients have taken one dose for successful treatment (Table 2).

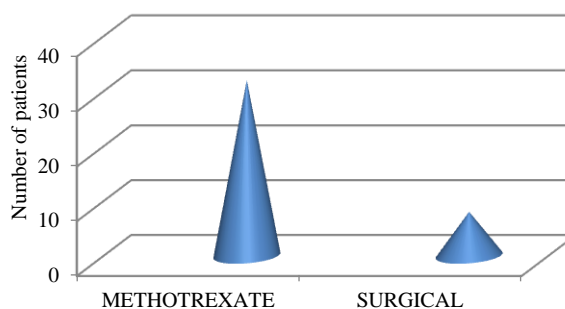


Fig. 1. Treatment given to patients with ectopic pregnancy

Table 2

Number of doses and successful methotrexate treatment

Methotrexate dose	Number of patients	Percentages
1 dose	12	30
2 doses	7	17.5
3 doses	10	25
4 doses	3	7.5
Surgical treatment		
Rising HCG	6	15
Ruptured	2	5

80 % of cases are successful with methotrexate treatment (Table 3).

Table 3

Methotrexate success rate vs initial HCG values

HCG value	Initial before treatment	After treatment with methotrexate	Success Rate
<5000 IU/L	11	11	100 % (11 out of 11)
5000–10000IU/L	24	19	79 % (19 out of 24)
>10000IU/L	5	2	40 % (2 out of 5)
Overall	40	32	80 % (32 out of 40)

The present study's overall success rate is 80 % (32 out of 40) (Fig. 2).

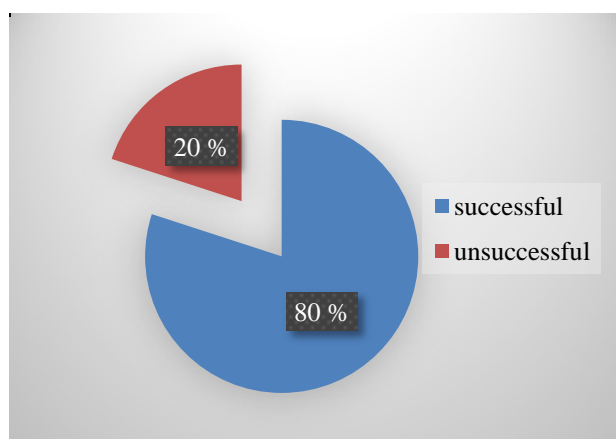


Fig. 2. Success rate with methotrexate treatment

**4. Discussion**

Ectopic pregnancies are obstetric emergencies that require immediate diagnosis and appropriate treatment. The decision has to be made between following expectant, medical, or surgical management. In this patient,

after taking the beta-HCG levels, pelvic ultrasound findings, and clinical presentation into account, we opted to start medical management with methotrexate. According to the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin 191, patients who are candidates for medical therapy should be hemodynamically stable, have an unruptured mass, and have no absolute contraindications to methotrexate [4]. According to the American Academy of Family Physicians (AAFP), expectant management can be considered when the patient is hemodynamically stable, the beta-HCG level is less than 1500 mIU/mL and fails to double in 48 hours, and the patient is reliable for follow-up. If not, medical management with methotrexate can be considered [5].

The trend between the initial  $\beta$ -hCG values and treatment outcome seems to cohere with earlier studies. In our study, the overall success rate with methotrexate treatment was 80 % (32 out of 40) which is lower compared to the study made by Lipscomb [6] in 2005, which is 90 % (578 out of 643). However, the small study population in this study makes the results uncertain. Relative contraindications for using methotrexate do not serve as absolute cut-offs but rather as indicators of potentially reduced effectiveness; one such contraindication is a high

initial hCG level. Systematic review evidence shows a failure rate of 14.3 % or higher with methotrexate when pretreatment hCG levels are >5,000 mIU/mL compared with a 3.7 % failure rate for hCG levels <5,000 mIU/ml. Studies often have excluded patients from methotrexate treatment when hCG levels are greater than 5,000 mIU/mL based on expert opinion that these levels are a relative contraindication to medical management.

According to a study by Tenore JL, when the pretreatment beta-HCG levels are less than 5,000 mIU/ml, the failure rate is only 3.7 % compared to a failure rate of 14.3 % when the pretreatment beta-HCG levels are more than 5,000 mIU/mL [7]. Similarly, a study done by Corsan et al. found that there is a higher risk of treatment failure only when the beta-HCG levels are greater than 1,500 mIU/mL [8]. This patient had a pretreatment beta-HCG level of 454.1 mIU/mL. Unfortunately, after the second dose, the patient showed clinical features suggestive of a ruptured ectopic and was promptly taken for surgical evacuation. This raises the important question of when to avoid medical management and proceed to surgical management despite low and declining beta-HCG levels.

In a study done by Saxon et al. of 716 patients admitted with ectopic pregnancy, 29 % of those with a beta-HCG level of less than 100 mIU/mL were found to have tubal rupture during laparoscopy [9]. From this, we can conclude that the risk of tubal rupture varies across a wide range of beta-HCG levels and is, therefore, not always a reliable indicator of deferring surgical management for medical management.

Seema Menon et al. [10] included 503 women and reported successes in using single-dose methotrexate stratified by initial hCG concentration. Failure rates increase with increasing hCG levels. A substantial and statistically significant increase in failure rates is seen when comparing patients with initial hCG levels of >5,000 mIU/mL with those with initial levels of <5,000 mIU/mL (odds ratio: 5.45; 95 % confidence interval: 3.04, 9.78). The failure rate for women with an initial concentration between 5,000 and 9,999 mIU/mL was significantly higher than that for those with initial levels between 2,000 and 4,999 mIU/mL (odds ratio: 3.76; 95 % confidence interval: 1.16, 12.33). They support a substantial increase in failure of medical management with single-dose methotrexate when the initial hCG is above 5,000 mIU/mL. Methotrexate can be used cautiously in patients with ectopic pregnancy who present with hCG levels above this level.

Ewa Nowak-Markwitz et al. [11] showed a success rate of 78 % (53 of 64 women). The medians of pretreatment beta-hCG levels in the groups treated successfully and unsuccessfully (943 vs 3085 mIU/mL) and after the first dose of MTX (564 vs 4049 mIU/mL) were statistically significantly different. The decrease in beta-hCG level after one MTX dose differed statistically significantly only in successfully treated women. The receiver operating characteristic (ROC) curve cut-off value in the success group indicated an initial beta-hCG level of 1790 and 1218 mIU/mL after one MTX cycle. The median of beta-hCG titer was not statistically different in patients requiring one or more treatment cycles. Concluded that beta-hCG level of >1790 mIU/mL, the MTX

treatment of ectopic pregnancy is at risk of failure. So initial beta-hCG titer is not a predictor of the number of MTX cycles that can guarantee a successful outcome.

Though the success rate is much lower with initial values >5000 (79 %) when compared to values <5000 (100 %), considering the major advantage of medical management, which is preserving the fallopian tube and thus fertility, a trial of medical management can be considered in carefully selected patients when values are >5000 with preparedness to meet any emergency.

**Study limitations.** The retrospective nature of the study was a prominent limitation during the data collection phase due to the frequent absence of data on potential confounding factors. Additionally, this type of study can be prone to recall or misclassification bias. The small sample size is another limitation of this study, as it may make it difficult to determine the accuracy of the study findings.

**Prospects for further research.** Some studies have even suggested that methotrexate doses used to treat ectopic pregnancy may worsen ovarian function in the short term, while others do not show an effect. These studies are limited, and further studies are needed to evaluate the effect of low-dose methotrexate on ovarian reserve.

## 5. Conclusion

Ectopic pregnancy is a common and serious problem, with a significant morbidity rate and the potential for maternal death. Many patients have no documented risk factors or physical indications of ectopic pregnancy. Ultrasonography (either formal or ED-based) is the initial investigation that should be done in an ED patient with 1st-trimester bleeding or pain; indeterminate results may be clarified by measurement (single or serial) of the serum  $\beta$ -hCG and progesterone concentrations. Expert consultation with radiologists and gynaecologists is recommended whenever ectopic pregnancy is suspected.

The clinical presentation, serum  $\beta$ -hCG levels and transvaginal ultrasound findings dictate management. Methotrexate can be given to women who are hemodynamically stable and compliant and have an initial serum  $\beta$ -hCG concentration of less than 5000 IU/L and no ultrasound evidence of fetal cardiac activity. Patients who do not meet these criteria should be treated surgically. The treatment success rate, on average, is 92 % when initial S- $\beta$ -hCG levels <5000IU/L and 68 % when initial S- $\beta$ -hCG levels > 5000 IU/L. Though the success rate is much lower with initial values >5000 (79 %) when compared to values <5000 (100 %), considering the major advantage of medical management, which is preserving the fallopian tube and thus fertility, a trial of medical management can be considered in carefully selected patients when values are >5000 with preparedness to meet any emergency.

## Conflict of interest

The authors declare that they have no conflict of interest concerning this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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