

## The Decline in $\beta$ -hCG Levels as a Predictive Factor for the Success of Ectopic Pregnancy Treatment with a Single-Dose Methotrexate Regimen

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### Abstract

**Introduction and Objectives:** Ectopic pregnancies account for 1.5 - 2% of all pregnancies in the first trimester in the United States. Methotrexate is considered the first-line medication for treating ectopic pregnancy. The effectiveness of treating ectopic pregnancy with a single dose of Methotrexate in clinical practice is based on a decrease in  $\beta$ -hCG levels by  $\geq 15\%$  between day 4 and day 7. This decrease in  $\beta$ -hCG during these days after a single dose of methotrexate has a positive predictive value (PPV) of 93%. The objective of our study is to evaluate the decline in  $\beta$ -hCG levels as a predictive factor for the success of ectopic pregnancy treatment with a single-dose methotrexate regimen.

**Materials and Methods:** This study included patients diagnosed with ectopic pregnancy who were admitted to the Gynaecology Department at University Hospital of Obstetrics and Gynecology "Queen Geraldine" Tirana, during the specified period from 2018 to 2021 and treated with a single-dose methotrexate regimen. Two tests were conducted. The first test analyzed changes in  $\beta$ -hCG levels between day 1 and day 4, while the second test analyzed changes in  $\beta$ -hCG levels between day 4 and day 7. The data obtained from both tests were analyzed using MedCalc software. To determine the statistical difference between the predictive values of the two tests, the Chi-squared test was used. The p-value was considered significant at  $< 0.05$ .

**Results:** The success rate of treatment with a single dose methotrexate regimen, without the need for additional doses of methotrexate or surgical intervention, was 70.7%. In the first test, the Positive Predictive Value (PPV) was calculated to be **85%**, predicting treatment success with a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 1 and day 4. The sensitivity and specificity were **64%** and **73%**, respectively. In the second test, the Positive Predictive Value (PPV) was calculated to be **89%** for predicting treatment success with a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 4 and day 7. The sensitivity and specificity were **82%** and **75%**, respectively. The p-value of 0.28 indicates that there is not statistically significant difference between the two tests. Therefore, the decline in  $\beta$ -hCG levels between day 1 and day 4 has approximately the same prognostic value as the decline in  $\beta$ -hCG levels between day 4 and day 7.

**Discussion:** From our study, it was found that a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 1 and day 4 after treatment with a single dose of methotrexate regimen predicts treatment success in 85% of cases, without the need for additional interventions (medical or surgical). The fact that a decrease  $\geq 15\%$  in  $\beta$ -hCG levels can accurately predict the success of methotrexate treatment in less than 4 days makes it a valuable early indicator for predicting the success of ectopic pregnancy treatment.

**Conclusion:** According to our study, the success of a single-dose methotrexate regimen can be predicted three days earlier compared to the standard protocol prediction (Single-Dose Regimen). By predicting the success of treatment sooner, the treatment protocol can be adjusted more promptly. This allows for the administration of a second dose of methotrexate three days earlier if needed, potentially improving the outcome of ectopic pregnancy treatment.

**Keywords:** Ectopic Pregnancy; Human Chorionic Gonadotropin ( $\beta$ -hCG); Medical Management; Methotrexate; Positive Predictive Value (PPV)

### Introduction

Ectopic implantation refers to implantation outside the endometrial cavity. Ectopic pregnancies account for 1.5-2% of all pregnancies in the first trimester in the United States [1,2]. They are also responsible for 2.7% of all pregnancy-related maternal deaths [3]. According to demographic distribution, the highest incidence of ectopic pregnancies is among women aged 35 - 44 years (27.2 per 1,000 reported pregnancies) [5].

Approximately 95% of ectopic pregnancies are implanted in the fallopian tube. The ampulla (70%) is the most common site, followed by the isthmic portion (12%), the fimbrial portion (11%), and interstitial tubal pregnancies (2 - 3%) [4].

Advances in transvaginal sonography technology and improvements in immunohistochemical techniques for assessing Human Chorionic Gonadotropin ( $\beta$ -hCG) have enabled earlier diagnosis of ectopic pregnancies. As a result, their treatment is much faster, preventing complications. This has reduced the rates of maternal morbidity and mortality [6].

In a normal pregnancy, the  $\beta$ -HCG level doubles every 48 - 72 hours until it reaches 10,000 - 20,000 mIU/mL [7,8]. In ectopic pregnancies,  $\beta$ -HCG levels usually increase less. It was determined that for a normal intrauterine pregnancy, the limit for the increase in  $\beta$ -hCG after 48 hours should be  $\geq 35\%$  [9]. Based on the results of these recent studies, the 66% "cut-off" is no longer useful for diagnosing ectopic pregnancy [10].

No single serum  $\beta$ -HCG level is diagnostic of an ectopic pregnancy. Serial serum  $\beta$ -HCG levels are necessary to differentiate between normal and abnormal pregnancies and to monitor resolution of ectopic pregnancy once therapy has been initiated [9,10].

The discriminatory zone of  $\beta$ -HCG (the level above which an imaging scan should reliably visualize a gestational sac within the uterus in a normal intrauterine pregnancy) is as follows:

- 1500 - 1800 mIU/mL with transvaginal ultrasonography, but up to 2300 mIU/mL with multiple gestates [11-13].
- 6000 - 6500 mIU/mL with abdominal ultrasonography [13,14].

Ectopic pregnancy can be treated through surgical, medical, or expectant management. Surgical treatment can be done via laparotomy or laparoscopy, depending on the situation and the patient's condition. Medical treatment typically involves the use of methotrexate, a medication that helps to dissolve the ectopic tissue [15]. This approach is generally considered for patients who are stable and whose ectopic pregnancy is detected early. Expectant management is an option for selected cases where the ectopic pregnancy is not causing symptoms and the  $\beta$ -HCG levels are low or decreasing [16]. This approach involves closely monitoring the patient to see if the pregnancy resolves on its own.

Methotrexate is considered the first-line medication for treating ectopic pregnancy. Approximately 35% of patients are candidates for starting methotrexate therapy [17]. The effectiveness of methotrexate therapy varies from 78% to 96% [18]. In two studies conducted by Nguyen and Skubisz in 2010, it was observed that a decrease in  $\beta$ -hCG levels  $\geq 15\%$  between day 1 and day 4 after a single-dose methotrexate treatment provides earlier prognostic information compared to the prognostic information available between day 4 and day 7. In these studies, the positive predictive value (PPV) for predicting treatment success was 100% and 88%, respectively [19,20].

Multiple studies have shown that the failure rate of methotrexate therapy is 14.3% when the initial  $\beta$ -hCG level is above 5,000 mIU/mL, compared to 3.7% when the initial  $\beta$ -hCG level is below 5,000 mIU/mL [21]. About 4 - 5% of women with ectopic pregnancy experience unsuccessful treatment with methotrexate and, as a result, may require surgical intervention [18].

## Methods

A retrospective cohort design study of the decline in  $\beta$ -hCG levels as a predictive factor for the success of ectopic pregnancy treatment with a single-dose methotrexate regimen. This study included patients diagnosed with ectopic pregnancy who were admitted to the Gynaecology Department at University Hospital of Obstetrics and Gynaecology “Queen Geraldine” Tirana, during the specified period from 2018 to 2021 and treated with a single-dose methotrexate regimen.

Out of 260 patients diagnosed with ectopic pregnancy:

- 126 patients underwent surgical intervention,
- 123 patients were initially treated with methotrexate, single dose regimen,
- 11 patients were managed expectantly.

Our study focused exclusively on the group of patients who were initially treated with methotrexate.

Data were collected from medical records and charts through a thorough desk review. The collected data include: the dates when treatment with methotrexate was initiated; serial  $\beta$ -hCG measurements before the start of treatment and on days 1, 4, and 7 after methotrexate treatment; the outcome of the single-dose methotrexate regimen.

Single dose methotrexate regimen	
1	Administer methotrexate at a dose of 1 mg/kg intramuscularly (i.m.) on day 1.
2	Measure $\beta$ -hCG levels on day 4 and day 7.
3	If $\beta$ -hCG decreases by $\geq 15\%$ between day 4 and day 7: Continue monitoring $\beta$ -hCG levels every 7 days until the value drops to $\leq 15$ mIU/mL (similar to that of a non-pregnant woman).
4	If $\beta$ -hCG does not decrease by $\geq 15\%$ between day 4 and day 7: Repeat the methotrexate dose on day 7. Measure $\beta$ -hCG levels on day 11 and day 14.

**Table 1:** Single dose methotrexate regimen.

Before administering methotrexate, the patient must complete the following tests and examinations: complete blood count (CBC), liver function tests, renal function tests, electrolytes, and chest X-ray.

### Inclusion criteria

Patients who received the single-dose methotrexate regimen (1 mg/kg):

- Hemodynamically stable.
- Compliant with post-treatment follow-up.
- Had an initial  $\beta$ -hCG level  $< 5000$  mIU/mL.
- Had an adnexal gestational sac with a diameter of less than 40 mm on sonography.
- Minimal or no free intra-pelvic fluid on sonography.

### Exclusion criteria:

- Intrauterine pregnancy
- Hemodynamically unstable

- Ruptured ectopic pregnancy
- Breastfeeding
- Immunodeficiency
- Anemia, leukopenia, or thrombocytopenia (moderate or severe)
- Hypersensitivity to methotrexate
- Active pulmonary disease
- Active peptic ulcer
- Significant hepatic or renal dysfunction.

### Data analysis

Two tests were conducted:

1. In the first test, participants were classified into two cohort groups:
  - a.  $\beta$ -hCG decrease group: Patients who experienced a  $\beta$ -hCG decrease of  $\geq 15\%$  between day 1 and day 4 after treatment with a single dose of methotrexate.
  - b.  $\beta$ -hCG increase group: Patients who did not experience a  $\beta$ -hCG decrease of  $\geq 15\%$  between day 1 and day 4 after treatment with a single dose of methotrexate.
2. In the second test, participants were again classified into two cohort groups:
  - a.  $\beta$ -hCG decrease group: Patients who experienced a  $\beta$ -hCG decrease of  $\geq 15\%$  between day 4 and day 7 after treatment with a single dose of methotrexate.
  - b.  $\beta$ -hCG increase group: Patients who did not experience a  $\beta$ -hCG decrease of  $\geq 15\%$  between day 4 and day 7 after treatment with a single dose of methotrexate.

To calculate the number of patients who had a decrease in  $\beta$ -hCG levels  $\geq 15\%$  between day 1 and day 4 after treatment, the following steps were taken:

The percentage change in  $\beta$ -hCG levels on day 4 compared to day 1 was determined. The formula used for this calculation was:

The results from the formula that showed a decrease of  $\geq 15\%$  were counted individually to determine the number of patients in that category. The same method was used to calculate the number of patients who experienced a decrease in  $\beta$ -hCG levels  $\geq 15\%$  between day 4 and day 7 after treatment. Then, for each of the two cohort groups, the following was calculated: (a) The number of patients in whom the treatment was successful. (b) The number of patients in whom the treatment was not successful.

The data obtained from both tests were analyzed using MedCalc software. The following were calculated: (a) Positive Predictive Value (PPV), (b) Negative Predictive Value (NPV), (c) Sensitivity, (d) Specificity, (e) Confidence Interval 95%.

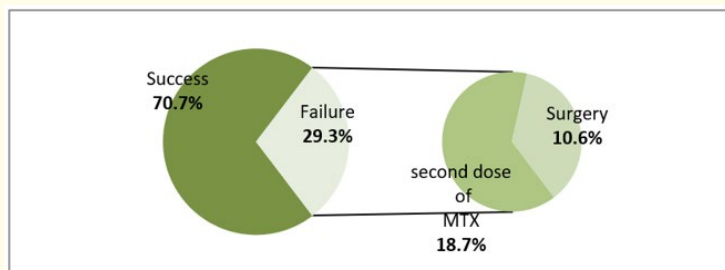
To determine the statistical difference between the predictive values of the two tests, the Chi-squared test was used. The p-value was considered significant at  $<0.05$ .

### Ethical considerations

Ethical considerations were carefully managed, with strict adherence to confidentiality and anonymity protocols for patient data, following the guidelines set by the University Hospital of Obstetrics and Gynecology “Queen Geraldine”. Every measure was taken to protect the privacy and dignity of the participants, ensuring all data were treated with the highest level of care and respect.

### Results

In our study, the success rate of treatment with a single dose of methotrexate regimen, without the need for additional doses of methotrexate or surgical intervention, was 70.7%. In 29.3% of cases, treatment failed. Of these, 18.7% required a second dose of methotrexate, while 10.6% needed surgical intervention.



**Graphic 1:** Rate of success of single dose methotrexate regimen.

### In the first test:

- 53.6% of patients showed a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 1 and day 4 after a single-dose methotrexate regimen. Of these, 56 patients (56/66) had successful treatment outcomes. Based on this, the Positive Predictive Value (PPV) was calculated to be 85%. The sensitivity and specificity for predicting treatment success with a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 1 and day 4 were 64% and 73%, respectively. The Negative Predictive Value (NPV) was 46%.
- Among the 46.3% of patients who had an increase in  $\beta$ -hCG levels between day 1 and day 4, 31 patients (31/57) still had successful treatment outcomes after a single dose methotrexate regimen.

TEST 1: Changes in $\beta$ -hCG between day 1 and day 4 after a single dose methotrexate regimen				
	Successful treatment	Unsuccessful treatment	Total	
Decrease in $\beta$ -hCG	56	10	66	PPV = 85% (95% CI = 76-91%)
Increase in $\beta$ -hCG	31	26	57	NPV = 46% (95% CI = 37-54%)
Total	87	36	123	
	Sensitivity = 64%	Specificity = 73%		

**Table 2:** TEST 1-Changes in  $\beta$ -hCG between day 1 and day 4 after a single dose methotrexate regimen.

**In the second test:**

- 65.8% of patients showed a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 4 and day 7 after a single-dose methotrexate regimen. Of these, 72 patients (72/81) had successful treatment outcomes. Based on this, the Positive Predictive Value (PPV) was calculated to be 89%. The sensitivity and specificity for predicting treatment success with a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 4 and day 7 were 82% and 75%, respectively. The Negative Predictive Value (NPV) was 64%.
- Among the 34.1% of patients who had an increase in  $\beta$ -hCG levels between day 4 and day 7, 15 patients still had successful treatment outcomes.

TEST 2: Changes in $\beta$ -hCG between day 4 and day 7 after a single dose methotrexate regimen				
	Successful treatment	Unsuccessful treatment	Total	
Decrease in $\beta$ -hCG	72	9	81	PPV = 89% (95% CI = 82-93%)
Increase in $\beta$ -hCG	15	27	42	NPV = 64% (95% CI = 52-75%)
Total	87	36	123	
	Sensitivity = 83%	Specificity = 75%		

**Table 3:** TEST 2 - Changes in  $\beta$ -hCG between day 4 and day 7 after a single dose methotrexate regimen.

**Statistical difference between the two tests**

To determine the statistical difference between the predictive values of the two tests, the Chi-squared test was used. The p-value was considered significant at  $< 0.05$ .

The p-value of 0.28 indicates that there is not statistically significant difference between the two tests. Therefore, the decline in  $\beta$ -hCG levels between day 1 and day 4 after treatment has approximately the same prognostic value as the decline in  $\beta$ -hCG levels between day 4 and day 7 after treatment.

**Discussion**

Medication treatment is considered successful if, after a single dose of methotrexate regimen (1 mg/kg), the  $\beta$ -hCG level falls below 15 mIU/mL without the need for additional medical or surgical interventions [18]. Medication treatment is deemed unsuccessful if, after the initial dose of methotrexate, additional doses of methotrexate or surgical intervention are required.

According to Stovall and colleagues, a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 4 and day 7 after treatment with a single dose of methotrexate regimen indicates that the treatment was successful [22]. Kirk and colleagues determined that a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 4 and day 7 after a single dose of methotrexate regimen had a Positive Predictive Value (PPV) of 93% for predicting treatment success [23].

In two studies conducted by Nguyen and Skubisz in 2010, it was observed that a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 1 and day 4 after a single dose of methotrexate provides earlier prognostic information compared to the information obtained between day 4 and day 7. In these studies, the Positive Predictive Value (PPV) for predicting treatment success was 100% and 88%, respectively [19,20].

In our study, it was observed that Positive Predictive Value (PPV) was 85% for predicting methotrexate treatment success with a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 1 and day 4. The sensitivity and specificity were 64% and 73%, respectively.

In our study, Positive Predictive Value (PPV) was calculated to be 89% for predicting treatment success with a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 4 and day 7. The sensitivity and specificity were 82% and 75%, respectively.

The p-value of 0.28 indicates that there is not statistically significant difference between the two tests. Therefore, the decline in  $\beta$ -hCG levels between day 1 and day 4 after treatment has approximately the same prognostic value as the decline in  $\beta$ -hCG levels between day 4 and day 7 after treatment.

From our study, it was found that a decrease  $\geq 15\%$  in  $\beta$ -hCG levels between day 1 and day 4 after treatment with a single dose of methotrexate regimen predicts treatment success in 85% of cases, without the need for additional interventions (medical or surgical).

The fact that a decrease  $\geq 15\%$  in  $\beta$ -hCG levels can accurately predict the success of methotrexate treatment in less than 4 days makes it a valuable early indicator for predicting the success of ectopic pregnancy treatment. Therefore, significantly reduces the anxiety of waiting to see if a single dose of methotrexate will be effective and increases the likelihood of promptly adjusting the treatment protocol in cases where  $\beta$ -hCG levels do not decrease by  $\geq 15\%$ . The disadvantage of our study is that the sample size is small and is taken from a single center. Findings of our study may not be applicable to the broader population due to limited representativeness.

### Conclusion

This study found that a decrease in  $\beta$ -hCG levels of  $\geq 15\%$  between day 1 and day 4 after a single dose of methotrexate predicts treatment success in 85% of cases, without the need for additional (medicinal or surgical) interventions.

Consequently, the success of a single-dose methotrexate treatment can be predicted three days earlier compared to the standard protocol prediction (see the "Single-Dose Regimen" table). By predicting the success of treatment sooner, the treatment protocol can be adjusted more promptly. This allows for the administration of a second dose of methotrexate three days earlier if needed, potentially improving the outcome of ectopic pregnancy treatment.

According to the standard protocol by Stovall, success prediction for single-dose methotrexate treatment generally occurs between day 4 and day 7 after single dose of methotrexate regimen [22].

If treatment failure is anticipated, a second dose of methotrexate is administered on day 7 following the initial dose. Our study indicates that predicting treatment success and the need for a second dose can be accomplished three days earlier, facilitating more timely adjustments to the treatment plan.

### Disclosure of Interests

The authors express that there is no conflict of interest for the publication of this article.

### Bibliography

1. Hoover RN, *et al.* "Adverse health outcomes in women exposed in utero to diethylstilbestrol". *New England Journal of Medicine* 365.14 (2011): 1304-1314.
2. Stulberg DB, *et al.* "Ectopic pregnancy rates and racial disparities in the Medicaid population, 2004-2008". *Fertility and Sterility* 102.6 (2014): 1671-1676.
3. Creanga AA, *et al.* "Pregnancy-related mortality in the United States, 2011-2013". *Obstetrics and Gynecology* 130.2 (2017): 366-373.
4. Bouyer J, *et al.* "Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases". *Human Reproduction* 17.12 (2002): 3224-3230.

5. Hoover KW, et al. "Trends in the diagnosis and treatment of ectopic pregnancy in the United States". *Obstetrics and Gynecology* 115 (2010): 495-502.
6. Greene DN, et al. "Pathology consultation on human chorionic gonadotropin testing for pregnancy assessment". *American Journal of Clinical Pathology* 144.6 (2015): 830-836.
7. Cartwright PS, et al. "Serum beta-human chorionic gonadotropin levels relate poorly with the size of a tubal pregnancy". *Fertility and Sterility* 48.4 (1987): 679-680.
8. Pearlstone AC, et al. "The predictive value of a single, early human chorionic gonadotropin measurement and the influence of maternal age on pregnancy outcome in an infertile population". *Fertility and Sterility* 57.2 (1992): 302-304.
9. Morse CB, et al. "Performance of human chorionic gonadotropin curves in women at risk for ectopic pregnancy: Exceptions to the rules". *Fertility and Sterility* 97.1 (2012): 101.e2-106.e2.
10. Kadar N, et al. "A method of screening for ectopic pregnancy and its indications". *Obstetrics and Gynecology* 58.2 (1981): 162-166.
11. Branney SW, et al. "Quantitative sensitivity of ultrasound in detecting free intraperitoneal fluid". *Journal of Trauma* 39.2 (1995): 375-380.
12. Rodgerson JD, et al. "Emergency department right upper quadrant ultrasound is associated with a reduced time to diagnosis and treatment of ruptured ectopic pregnancies". *Academic Emergency Medicine* 8.4 (2001): 331-336.
13. Bernaschek G, et al. "Vaginal sonography versus serum human chorionic gonadotropin in early detection of pregnancy". *American Journal of Obstetrics and Gynecology* 158 (1988): 608-612.
14. Connolly A, et al. "Reevaluation of discriminatory and threshold levels for serum beta-hCG in early pregnancy". *Obstetrics and Gynecology* 121.1 (2013): 65-70.
15. American College of O, Gynecologists. ACOG Practice Bulletin No. 94: Medical management of ectopic pregnancy. *Obstetrics and Gynecology* 111.6 (2008): 1479-1485.
16. American College of Obstetricians and Gynecologists. Medical management of ectopic pregnancy. ACOG Practice Bulletin No. 94. *Obstetrics and Gynecology* 111 (2008): 479-485.
17. Van Den Eeden SK, et al. "Ectopic pregnancy rate and treatment utilization in a large managed care organization". *Obstetrics and Gynecology* 105.5 (2005): 1052-1057.
18. Pisarska MD, et al. "Ectopic pregnancy". *Lancet* 351.9109 (1998): 1115-1120.
19. Nguyen Q, et al. "Are early human chorionic gonadotropin levels after methotrexate therapy a predictor of response in ectopic pregnancy?" *American Journal of Obstetrics and Gynecology* 202.6 (2010): 630.e631-635.
20. Skubisz MM, et al. "Decline in beta-hCG levels between days 0 and 4 after a single dose of methotrexate for ectopic pregnancy predicts treatment success: a retrospective cohort study". *BJOG: An International Journal of Obstetrics and Gynaecology* 118.13 (2011): 1665-1668.
21. Menon S, et al. "Establishing a human chorionic gonadotropin cutoff to guide methotrexate treatment of ectopic pregnancy: A systematic review". *Fertility and Sterility* 87.3 (2007): 481-484.



22. Stovall TG., *et al.* "Outpatient chemotherapy of unruptured ectopic pregnancy". *Fertility and Sterility* 51.3 (1989): 435-438.
23. Kirk E., *et al.* "A validation of the most commonly used protocol to predict the success of single-dose methotrexate in the treatment of ectopic pregnancy". *Human Reproduction* 22.3 (2007): 858-863.

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