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Prediction of methotrexate treatment outcome in tubal ectopic pregnancy based on days 0 and 4 and 7 Human Chorionic Gonadotrophin Levels

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Abstract

Background and objective: Methotrexate is highly effective in treating ectopic pregnancy with a single dose. Effectiveness is evaluated on days 4 and 7, successful outcome defined as a 15% decrease in beta-Human Chorionic Gonadotrophin levels. The aim of the study is the evaluation of Methotrexate's effectiveness in treating tubal ectopic pregnancy by tracking beta-Human Chorionic Gonadotrophin levels on day 0 and day 4.

Methods: A cohort study was conducted on 55 individuals diagnosed with tubal ectopic pregnancy at Sulaymaniyah Maternity Teaching Hospital Kurdistan region, Iraq from May 2022 to May 2023. Data was collected from medical files and ultrasound assessments, monitoring the participants' beta-Human Chorionic Gonadotrophin after methotrexate administration.

Results: On the first day of methotrexate treatment, ectopic mass sizes ranged from 10 × 20 to over 30, decreasing to 8 × 20 to over 20 by the seventh day. Beta-Human Chorionic Gonadotrophin levels on days 1, 4, and 7 were 1499.34, 1220.877, and 796.21, respectively, showing significant changes ($p<0.001$). Methotrexate treatment success rate was 69.8%, However, a significant correlation was found between treatment outcome and ectopic sizes on days 1 and 7 ($p=0.000$ and $p<0.000$, respectively). Treatment outcome was also significantly related to beta-Human Chorionic Gonadotrophin levels on day zero ($p=0.007$), burst not on days 4 or 7 ($p>0.05$).

Conclusion: Methotrexate is an effective treatment for tubal ectopic pregnancy, with beta-Human Chorionic Gonadotrophin levels as a reliable marker for predicting outcome.

Keywords: Beta-Human Chorionic Gonadotrophin, Early prediction, Methotrexate, Tubal ectopic, Treatment success

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Introduction

Ectopic pregnancy is a rare condition where fertilized eggs implant outside the uterus. It poses a significant threat to the mother's health. [1] Risk factors include age, previous pelvic surgery, history of ectopic pregnancy, female sterilization, use of intrauterine devices, previous pelvic inflammatory disease, smoking during pregnancy, and history of infertility.[2] Most ectopic pregnancies occur in the fallopian tubes, with the majority in the ampullary part. Only a small percentage occur in the interstitial part.[3,4] EP is characterized by symptoms such as vaginal bleeding, abdominal pain, and amenorrhea. The bleeding may be brownish or similar to a menstrual period, often occurring after a missed period. Pain follows the bleeding, varying in type, location, and intensity .[4] The pain is typically due to the enlargement of the fallopian tube, which cannot accommodate the growing embryo, leading to rupture and bleeding.[1] the timely identification and management of ectopic pregnancy can prevent rupture lesion the need for operation, and reduce morbidity and mortality risk .[5]The diagnosis of EP usually depend on the (Beta-Human Chorionic Gonadotrophin) and transvaginal ultrasound features of EP are: (1) presence of the “blob sign,” an irregular adnexal mass that extends away from and near the ovary.; (2) the visualization of a lesion with a presence of hyperechoic ring surrounding the gestational sac; and (3) the identification of a gestational sac with an embryonic pole, either in the presence or absence of a yolk sac, coexist with cardiac activity .[6]Ectopic pregnancy treatment options include conservative management, medical management using methotrexate and surgical intervention. Methotrexate is suitable for women who meet specific criteria, including absence of severe pain, hCG level below 1500 IU/L, small unruptured ectopic pregnancy, no positive cardiac activity, no intrauterine pregnancy, and ability to attend follow-up sessions. [7]Methotrexate (MTX) has been recommended as a safe and cost-effective treatment for ectopic pregnancy since 1993. The single-dose protocol, introduced by Stovall et al., has become popular due to its lower cost and convenience. Regular monitoring of β-hCG levels is essential during methotrexate administration. Common adverse effects may include nausea, vomiting, fatigue, weakness, mouth sores, hair loss, skin rash, diarrhea, constipation, dizziness, headache, and abdominal pain .[8,9] The β-hCG level has been demonstrated as a dependable indicator of treatment success. [10] In medical method of management, treatment success is described when there is a decline in β-hCG levels greater than 15% from days 4 to 7. Allowing continuous biological monitoring until the solution reaches an ideal outcome is .[11] Approximately 15-20% of cases may require another dose of methotrexate after using this protocol, also1% may need a third dose as β-hCG levels increase .[12] Clinicians and patients should allow a minimum of seven days to elapse before seeing signs of treatment success or requiring further testing based on these results. Identifying Predictors of failure of methotrexate treatment include elevated first human chorionic gonadotropin (hCG) levels greater than 5000 IU/mL, positive fetal heart activity, larger ectopic pregnancy greater than 4 mm, and observation of free fluid in the abdominal cavity by ultrasound .[13-15]This study was conducted to explore the possibilities of using human chorionic gonadotropin (hCG) levels on 0 day and 4rth day as early predictors of methotrexate treatment outcomes in tubal ectopic pregnancies.

Patients and methods

This study is designed as a cohort study conducted at Maternity Teaching Hospital of Sulaymaniyah, Kurdistan Region, Iraq from May 2022 to May 2023.

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The Scientific Committee approved the study protocol at the Kurdistan Higher Council for Medical Specialties (KHCMS), Sulaimaniyah, Iraq at 8th.september 2021. Participants' verbal informed consent was gained before starting the study. The study included all patients diagnosed with tubal ectopic pregnancy who received methotrexate treatment and have the criteria for receiving the drug., including a serum hCG level lower than 1500 IU/L and up to 5000IU/L, an unruptured ectopic pregnancy size measuring below 35 mm in the absence of observable positive heart activity, and no intrauterine pregnancy on ultrasound examination and accept to participate in the research. The exclusion criteria were any case with tubal ectopic pregnancy who were unstable clinically, with an adnexal mass of more than 35 mm and a β-hCG level of over 5000 IU/L, with positive fetal heart activity, and also moderate to severe pelvic free fluid by ultrasound. All cases with ectopic pregnancy were included within one year duration. Direct interview and questionnaire are used to collect patients' data. BHCG and ultrasound will be performed for everyone on the day of treatment. A dosage of 50 mg/kg is administered, and subsequent monitoring is conducted by assessing BHCG levels and performing ultrasounds on the fourth and seventh day following the intake of methotrexate. These assessments are carried out either at the maternity hospital or at external clinics. In certain cases, alternative treatment dosages are required by giving more doses of the drug and a few individuals experience a deterioration in their condition and subsequently undergo a laparotomy. The collected data was analyzed using the Statistical Package for Social Sciences (SPSS, version 24.0). To achieve this, descriptive and inferential statistical tests were employed.

Results

The study comprised 63 patients, with 10 individuals being lost to follow-up during the course of the research. Regarding table (1) shows that 27 patients were 20 to 29 years old (50.9%), and 26 were 30 to 39 years (49.1%). Regarding the patients' parity, 15 women (28.3%) were primiparous, while 38 (71.7%) were multiparous. The results also revealed that 12 women (22.6%) had no past records of previous ectopic pregnancy, while 41 cases (77.4%) had previous ectopic pregnancy.

Table (1): The age of the patients, parity, and previous ectopic pregnancy

	Frequency (N)	Percentage (%)
Age group		
20 – 29	27	50.9
30 – 39	26	49.1
Total	53	100.0
Parity		
Primiparous	15	28.3
Multiparous	38	71.7
Total	53	100.0
The previous ectopic pregnancy		
No	12	22.6
Yes	41	77.4
Total	53	100.0

Table (2) shows that the β-hCG level on day 0 of methotrexate intake had a significant association with the final outcome of treatment (p-value = 0.007). However, β-hCG levels on days 4 and 7 have no notifiable association with the final treatment outcome (p-value > 0.05).

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Table (2): An association between treatment outcome and β-hCG on days 0, 4 and 7 of methotrexate intake

	single dose of the methotrexate Mean ± SD	2nd and 3rd doses of the methotrexate Mean ± SD	Laparotomy Mean ± SD	p-value
β-hCG of day 0 of receiving methotrexate	1238.62 ± 1170.410	1299.44 ±1642.478	3134.43 ± 2172.205	0.007
β-hCG of day 4	1119.892 ± 1053.6595	843.389 ± 490.6047	-	0.051
β-hCG of day 7	830.51 ± 766.988	938.44 ± 590.751	-	0.335

Table (3) shows the size of ectopic masses on day 0 of receiving methotrexate. As indicated, ectopic masses were 10 - 20 mm in 35 women (66%), 20 - 30 mm in 16 (30.2%), and above 30-35 mm in 2 (3.8%). Moreover, regarding their fluid on day 0 of receiving methotrexate, mild free fluid was observed in 32 women (60.4%), and 21 women (39.6%) had no free fluid. Also shows the size of ectopic masses on the 7th day after receiving methotrexate. As shown, ectopic masses were 10 to 20 mm in 34 women (64.2%) and 20 - 30 mm in 7 women (13.2%). Moreover, none of the women had free fluids on the 7th day after receiving methotrexate.

Table (4) demonstrates that size of ectopic masses on days 0 and 7 of receiving methotrexate had a significant statistically association with the final outcome of the treatment (p-value<0.001). However, no correlation was found between the final outcome of the treatments and the patients' fluid on day 0 of receiving methotrexate (p-value=0.422).

Table (3): The size of ectopic masses and fluid on day 0 of receiving methotrexate

Size in day 0 of receiving methotrexate	Frequency (N)	Percentage (%)
10 – 20	35	66.0
20 – 30	16	30.2
30-35	2	3.8
Total	53	100.0
Fluid in day 0 of receiving methotrexate		
Mild free fluid	32	60.4
No free fluid	21	39.6
Total	53	100.0
Size in the day seven after receiving methotrexate		
Not available	12	22.6
8 – 20	34	64.2
20 * 30	7	13.2
Total	53	100.0
Fluid in the day seven after receiving methotrexate		
(No free fluid	53	100.0

Table (4): An association between the final outcome of the treatment and size of ectopic masses on days 0 and 7 of receiving methotrexate

	Final outcome			Total	p-value
	Received the single dose of methotrexate	Laparotomy	2nd and 3rd doses of the methotrexate		
Size on day 0 of receiving methotrexate					

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10 – 20	31(83.8)	0(0.0)	4 (44.4)	35 (66.0)	<0.001
20 – 30	5 (13.5)	7 (100.0)	4 (44.4)	16 (30.2)	
> 30	1 (2.7)	0(0.0)	1(11.1)	2 (3.8)	
Total	37(100.0)	7(100.0)	9(100.0)	53(100.0)	
Fluid on the day of receiving the methotrexate					
Mild free fluid	20(54.1)	5(71.4)	7(77.8)	32(60.4)	0.422
No free fluid	17(45.9)	2(28.6)	2(22.2)	21(39.6)	
Total	37(100.0)	7(100.0)	9(100.0)	539100.0)	
Size in the day seven after receiving methotrexate					
Not available	6(16.2)	5(71.4)	1(11.1)	12(22.6)	<0.001
10 – 20	30 (81.1)	0(0.0)	4 (44.4)	34 (64.2)	
20 – 30	1 (2.7)	2 (28.6)	4 (44.4)	7 (13.2)	
Total	37(100.0)	7(100.0)	9(100.0)	53(100.0)	

Discussion

The main objective of this investigation is to evaluate the potential of (hCG) levels on days 0 and 4. The study findings indicate a general effectiveness of methotrexate in treating ectopic pregnancies. Notably, the success group displayed significantly lower initial β-hCG levels and day 0 β-hCG values compared to the failure group. Moreover, the study highlights that it is possible to predict the outcome when there is a reduction of at least 15% in beta-hCG concentrations observed between days 4 and 7. According to a study by Khalil et al., The efficacy of methotrexate in managing ectopic pregnancy has been established through the observation of a notable reduction, exceeding 15%, in β-hCG levels. Additionally, Patients who were administered a subsequent dose of methotrexate demonstrated a greater decline in beta-human chorionic gonadotrophin levels, indicating a cumulative effect and suggesting enhanced treatment success .[16] The present study demonstrated significant variability in the sizes of ectopic masses at the initiation of methotrexate treatment, with the majority falling within the range of 14-20 mm. Mild free fluid was observed in over 60% of women. These findings suggest that methotrexate may exhibit greater effectiveness in smaller masses, given that the larger sizes were only observed in a minority of cases. These results emphasize the ability of methotrexate to reduce the sizes of ectopic pregnancies and resolve associated fluid accumulations within a week of treatment. Contrary to the results of current study, Pulatoğlu et al. conducted a study which indicated that the administration of methotrexate for tubal pregnancy initially leads to an increase of the ectopic mass size. Consequently, such enlargement should not be perceived as an indication of a heightened risk for treatment failure .[17] Notably, the initial average β-hCG level of 1499 showed a significant decrease on days 4 and 7, reaching 1220 and 796, respectively. These results emphasize the effectiveness of methotrexate in reducing β-hCG levels during the first week of treatment. The decline in β-hCG levels indicates the resolution of trophoblastic tissue, indicating a positive

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response to the treatment intervention. Therefore, it can be concluded that the β-hCG level is a reliable index indicating the success of MTX treatment among patients who has tubal ectopic pregnancy. In a comparable investigation, Mackenzie et al. (2023) documented that a decrease in serum Human chorionic gonadotropin (β-hCG) concentrations during the initial four days. Indicated an 85% probability of successful management for cases identified with tubal ectopic pregnancy (with initial β-hCG levels ranging from ≥1000 to ≤5000 IU/l) undergoing single-dose protocol of methotrexate .[18] The findings of our research suggest that methotrexate demonstrates a generally positive effectiveness in the management of ectopic pregnancies, with a considerable portion of instances achieving favorable outcomes with a solitary administration as well as other doses. Nevertheless, it is worth mentioning that over 13% of patients necessitated laparotomy, emphasizing the significance of closely monitoring β-hCG levels throughout the treatment process. Consistent with our findings, a study by Zhang et al supports the notion that methotrexate is generally effective in treating ectopic pregnancies, with a majority of cases achieving favorable outcomes following a single dose of 50 mg/m2, as evidenced by a fall of over 15% in β-hCG levels between days 4 and 7 post-administration. While this decline serves as a predictive indicator of likely success, the establishment of definitive rules for earlier determination of treatment outcomes was not significantly achieved. Nevertheless, serial monitoring of β-hCG levels remains crucial for assessing the response to treatment .[19]

Conclusion

It discovered that the initial β-hCG concentration on day 0 was significantly related to treatment outcome, highlighting its importance in predicting success. However, β-hCG levels on days 4 and 7 did not correlate significantly with treatment outcome. These findings underscore the impact of considering early β-hCG levels in determining the appropriate treatment approach for ectopic pregnancy management. More research is necessary to refine the predictive value of β-hCG monitoring in women with tubal ectopic pregnancy who undergo methotrexate treatment.

Disclosure:

The authors assert that they have no conflicts of interest.

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