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Early Prediction for the Requirement of Second or Third Dose Methotrexate in Women with Ectopic Pregnancy Treated with Single Dose Regimen

Dr. Sumood Abdulla Ahmed

M.B.Ch.B. \ F.I.B.O.G. \ (Obstetrics and Gynecology), Iraqi Ministry of Health, Salah Aldin Health Directorate, Salah Al-Din General Hospital, Salah Aldin, Iraq

Abstract: Background: Ectopic pregnancies are a life-threatening emergency since they can invade maternal blood vessels, causing catastrophic hemorrhage and it is the leading cause of maternal mortality in the first trimester, and it accounts for 3 % of all pregnancy-related deaths even in developed countries. **Objectives:** To investigate the predictive factors for the requirement of additional doses of methotrexate in women with ectopic pregnancy treated with a single dose methotrexate regimen. **Study design & settings:** A prospective study was conducted on the gynecological and obstetrics department in Salah Aldin teaching hospital for the one-year duration from the 1st of Feb. 2020 to the end of Nov. 2020. Whereas 125 patients were included in this study divided into two groups [one group A (75) was treated with a single dose of methotrexate and group B (50) with multiple doses]. **Results**: The mean age group was between 20-29 years; the patient with a success treatment rate with a single dose was 73.3%, while for those who were treated with multiple doses with 64% success rate. Highly significant reduction in serum ß-hCG for ectopic pregnant women treated with a single methotrexate dose after four days and seven days of treatment. The resolution time was 31±SD days for those who were treated with a single dose, while it was 56±SD days for the multiple doses. **Conclusion:** The single dose of the methotrexate therapy could be positively offered to most stable patients experiencing medical management of an ectopic pregnancy, and a decline in the serum level of β-hCG between days 1 and 4 is related with a high treatment success rate. The change in the serum level of β-hCG between days 1 and 4 appears to be an early predictive factor of an additional dose of methotrexate.

Keywords: Early prediction, Third dose methotrexate, Ectopic pregnancy.

INTRODUCTION

Ectopic pregnancy occurs when a fertilized ovum implants outside the endometrial cavity. The name ‘ectopic’ is derived from the Greek word ‘ektopos,’ meaning ‘out of place.’ Complicating 1–2% of all pregnancies, ectopic pregnancies are a life-threatening emergency since they can invade maternal blood vessels, causing catastrophic hemorrhage [Tong, S. *et al*., 2014]. Ectopic pregnancy is the leading cause of maternal mortality in the first trimester, and it accounts for 3 % of all pregnancy-related deaths even in developed countries. Most of the women with ectopic pregnancy undergo urgent surgery either with laparoscopy or laparotomy with a suspect of tubal rupture and intra-abdominal bleeding [Bottin, P. *et al*., 2014].

The ectopic pregnancy is estimated to occur in one of fifty pregnancies worldwide, and the incidence is increasing. The mortality rate from ectopic pregnancy, on the contrary, has declined 10-fold during the past 35 years because of improved diagnostic techniques and early surgical interventions. During the same period, nonwhite women had an overall risk of death 3.4 times higher than white women. Even though the survival rate is increasing, ectopic pregnancy remains the leading cause of pregnancy-related death in the first trimester of pregnancy due to tubal rupture.

The fallopian tube is a carefully controlled environment to facilitate oocyte transport, fertilization, and migration of the early embryo to the uterus for implantation [(5)]. Most data suggest tubal EP stems from both abnormal embryo transport and an alteration in the tubal environment, which enables abnormal implantation to occur [Shaw, J.L.V. *et al*., 2010].

The transport of an oocyte and embryo through the tube relies on both smooth muscle contraction and ciliary beating, which are affected by several local factors—toxic, infectious, immunologic, and hormonal. Smoking and infection have been shown to decrease cilia density, while ciliary beat frequency has been shown to be responsive to the changing hormonal milieu of the menstrual cycle [Van Mello, N.M. *et al*., 2012; Shetty, V.H. *et al*., 2014]. Samples of fallopian tube epithelium incubated in estradiol (E2) and nitric oxide (NO) have been found to demonstrate increased ciliary motility, which may cause aberrant tubal transport[Stulberg, D.B. *et al*., 2014; Orozco, E.M. *et al*., 2015; Cohen, A. *et al*., 2014]. Nitric Oxide also affects smooth muscle contractility in the fallopian tube; expression of NO has been found to vary during the menstrual cycle, with possible implications for normal and ectopic implantations[Cohen, A. *et al*., 2014]. Finally, E2-mediated effects via estrogen receptors on gene regulation and expression—including pathways

*Corresponding Author: Dr. Sumood Abdulla Ahmed

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implicated in implantation and apoptosis—may be involved in the aberrant tubal function and ectopic pregnancy, though more research is needed to clarify these pathways [Ranji, G.G. *et al*., 2018; Jurkovic, D. *et al*., 2017].

Inflammation in the fallopian tubes is also implicated in the establishment of EP by inducing tubal dysfunction or damage that may lead to retention of an oocyte or embryo and by promoting embryo implantation in the fallopian tube via inflammatory cytokines.

Following tubal damage by smoking or infection, upregulation of pro-inflammatory cytokines has been noted, promoting embryo receptivity, invasion, and angiogenesis in the tube. For instance, interleukin 1 (IL-1), produced by tubal epithelial cells following Chlamydia trachomatis infection, is a vital signal for embryo implantation in the endometrium; IL-1 also recruits neutrophils downstream, leading to further tubal damage. [Bottin, P. *et al*., 2014; Panelli, D.M. *et al*., 2015; Yildirim, A. *et al*., 2015] Macrophages and intraepithelial lymphocytes are also increased in women with ectopic pregnancy, potentially affecting tubal function and predisposing them to tubal ectopic pregnancy.

MATERIAL AND METHOD

Patients

Sample Size

125 women with ectopic pregnancy treated with a single dose methotrexate regimen. The patients were divided into two groups (case and control), the cases group-B (n=50) included the patients who need for a second or third dose of the methotrexate, while the control group-A (n=75) included those who were treated only with a single dose of the drug (methotrexate).

Study Design and Setting

A prospective study was conducted on the gynecological and obstetrics department in Salah Aldin teaching hospital for the one-year duration from the 1st of Feb. 2020 to the end of Nov. 2020
Inclusion criteria:

Patients with confirmed ectopic pregnancy treated with a single dose methotrexate regimen and agreed to participate were included in this study.

Hemodynamically stable.
Unruptured tubal or other ectopic pregnancy.
Persistent trophoblast after salpingotomy.
Serum quantitative βHCG < 5000 IU/L
Size of ectopic mass < 3.5cm
Normal LFTs, U & E's, and FBC

Data Collection

Data was collected entirely by a designed questionnaire form and depending on hospital-based medical records for patients with tubal ectopic pregnancy who were treated by methotrexate with the only a single-dose regimen. The collected data included the demographic characteristics, gynecological history, BMI, and smoking history of the patients. Ultrasound was done to the patients by a hospital ultrasound scanner to measure the endometrial thickness, ectopic mass, and free peritoneal fluid. The maternal serum β-hCG concentration level was measured on day 1st,4th, and 7th day of the treatment at an outside laboratory. The treatment outcome of a single-dose regimen and the time for resolution of ectopic pregnancy (β-hCG become less than five mIU/L).

Treatment Protocol

Regarding to the single-dose protocol of the management with methotrexate, intramuscular methotrexate injection in a dose of 50 mg/m2 was given to the ectopic pregnant women. The body surface area was measured by the help of charts (these charts that used nomograms of the patient's body weight and height).

$$\text{BSA } (m^2) = \sqrt{\frac{\text{ht (cm)} \times \text{wt (kg)}}{3600}}$$

Serum b-hCG of the patients was measured on the 1st, 4th, and 7th day after injection of the methotrexate. If the B-hCG serum level had a decline of at least of 15 % between the days 4 and 7, serial measurements were repeated until five mIU/L.

If the β-hCG maternal serum decline between days 1 and 4 is less than 15 %, a second dose of methotrexate injection was required. Similarly, after the second dose, the minimum level of 15 % decline on maternal serum β-hCG concentrations between days 4 and 7 were needed to define the success of the methotrexate single-dose regimen. If this was not the happened, a last-third dose of

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methotrexate injection was required. If β-hCG serum levels were not decreased sufficiently as formerly defined after the third dose of methotrexate, patients with ectopic pregnancy must be treated by surgery.

The follow-up protocol for ectopic pregnancy patients was the measurement of the serum level of b-hCG at least every week. The success of the only single-dose regimen was defined as the accomplishment of b-hCG serum levels come up to 15 mIU/L with this single dose of methotrexate injection (50 mg/m2) without needed for an additional dose of methotrexate or surgery.

Ethical Consideration

The study was approved by the local thesis to the Iraqi Board for Medical Specializations and Salah aldeen teaching hospital. The purpose and procedures explain to all participants, and they were given the right to participate or not; verbal consent was taken with reassurance that interprets gained will be kept confidentially and not to be used for other research object.

Statistical Analysis

All patients' data were entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 21 was used. Descriptive statistics are presented as (mean ± standard deviation) and frequencies as percentages. Kolmogorov Smirnov analysis verified the normality of the data set. Multiple contingency tables were conducted, and appropriate statistical tests were performed; the Chi-square test was used for categorical variables, and the t-test was used to compare between two means. One-way ANOVA analysis was used to compare between more than two means. Multiple logistic regression analysis (Binary) was used to assess the predicting variables. ROC curve was used to clarify validity tests. In all statistical analysis, the level of significance (p-value) is set at ≤ 0.05, and the result is presented as tables and/or graphs. Statistical analysis of the study was done by the community medicine specialist. The endometrial thickness, ectopic mass size, and biochemical variable were statistically analyzed by using Chi-square and student t-test. Multiple logistic regression analysis was used to conclude independent predictors of the additional dose requisite.

A total of 125 women with ectopic pregnancy were included in the present study. Seventy-five women who were treated with a single dose of methotrexate were with a mean age of 27.4±8.1 years, and fifty ectopic pregnant women who were treated with more than one dose (multiple) of methotrexate were with a mean age of 25.9±6.9. No significant difference in age was observed between single and multiple ectopic pregnant women groups (p=0.4). No significant difference in obstetrical history (gravidity, parity & abortion) was observed between single and multiple doses of methotrexate. All these findings were shown in table 1 and Figures 1 and 2.

Table 1: Distribution of age and obstetrical history according to methotrexate doses of ectopic pregnant women groups

Variable	Single dose		2nd & 3rd doses		P
	No.	%	No.	%	
Age					0.4*
<20 years	13	17.5	11	22.5	
20-29 years	30	40.0	24	47.5	
30-39 years	28	37.5	14	27.5	
≥40 years	4	5.0	1	2.5	
Mean±SD	27.4±8.1		25.9±6.9		0.2**
Gravidity					0.4*
Nulliparuos	16	21.4	13	26.0	
1-3	28	37.3	22	44.0	
>3	31	41.3	15	30.0	
Mean±SD	2±2		2±1		0.99**
Parity					0.5*
No	20	26.0	17	34.0	
1-3	30	40.0	20	40.0	
>3	25	33.4	13	26.0	

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Mean±SD	3±1		2.8±1		0.2**
Abortion					0.5*
Yes	4	5.3	4	8.0	
No	71	94.7	46	92.0	

**Chi-square test, ** t-test*

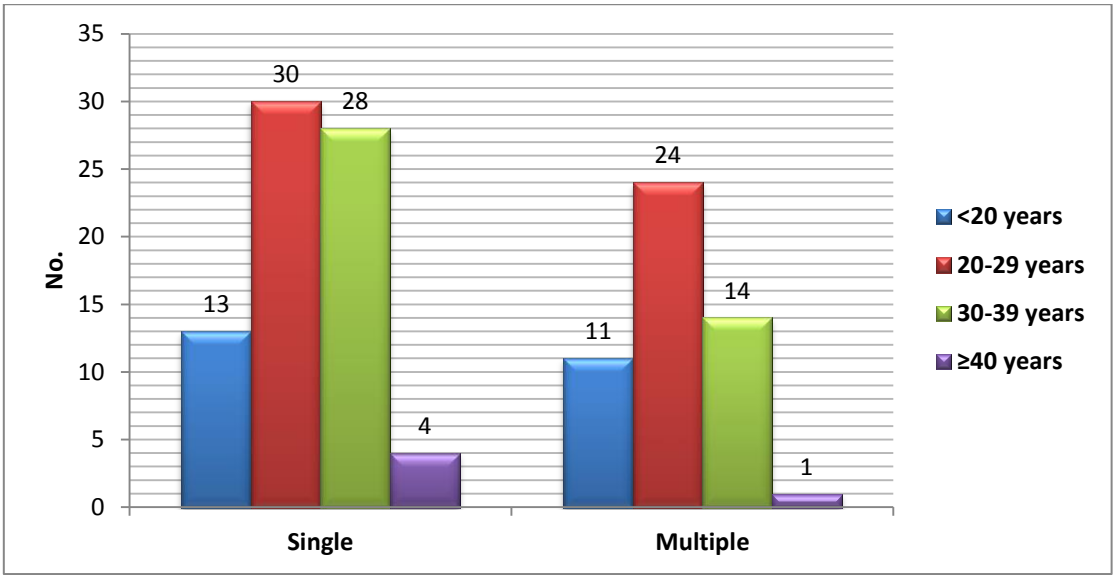

Figure 1: Distribution of age according to study groups.

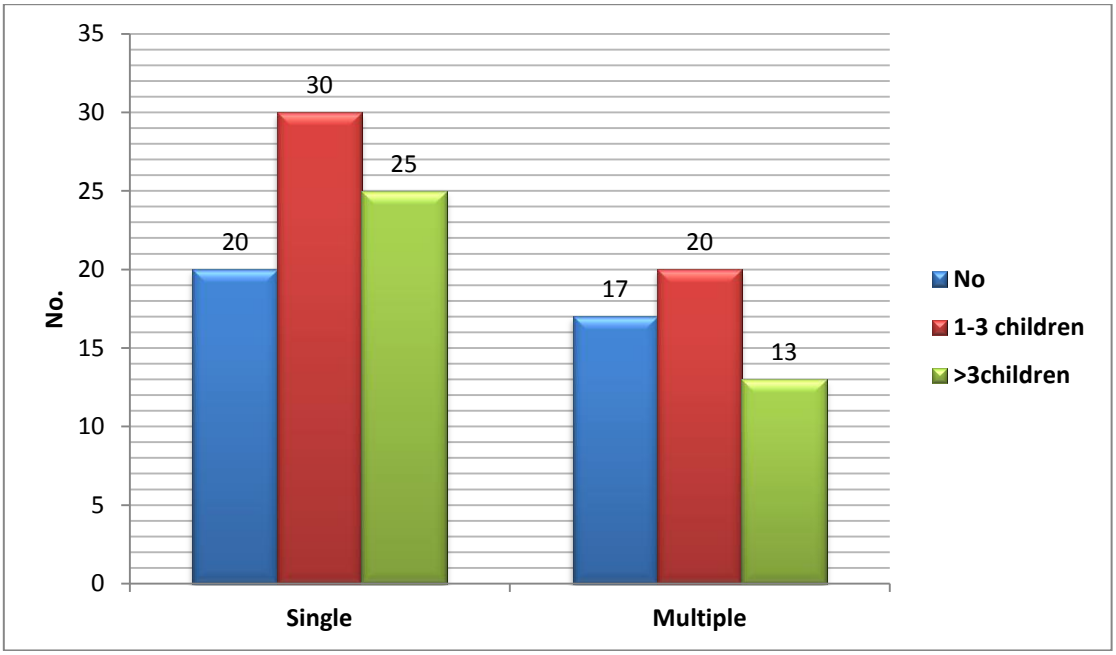

Figure 2: Distribution of parity according to study groups

As shown in table 2 and figure 3, there was no significant difference between single and multiple doses of methotrexate regarding BMI (p=0.1); the mean BMI of women with a single dose (24.9) was not significantly different from than BMI of multiple doses group (24.8). No significant difference between single and multiple doses of methotrexate regarding ectopic pregnancy risk factors.

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Table 2: Distribution of BMI and ectopic pregnancy risk factors according to between single and multiple doses of methotrexate in ectopic pregnant women groups

Variable	Single dose		2nd & 3rd doses		P
	No.	%	No.	%	
BMI					0.1*
Normal	34	45.3	28	56.0	
Overweight	26	34.7	12	24.0	
Obese	15	20.0	6	12.0	
Mean±SD	24.9±2.3		24.8±2.2		0.7**
History of ectopic pregnancy					0.9*
Yes	6	8.0	5	10.0	
No	69	92.0	45	90.0	
History of tubal surgery					0.4*
Yes	5	6.0	6	12.0	
No	70	94.0	44	88.0	
Cigarette smoking					0.1*
Yes	14	18.6	16	32.0	
No	61	81.4	34	68.0	
Infertility treatment					0.4*
Yes	5	6.7	6	12.0	
No	70	93.3	44	88.0	
History of pelvic infection					0.5*
Yes	3	4.0	4	8.0	
No	72	96.0	46	92	

** Chi-square test, ** t-test.*

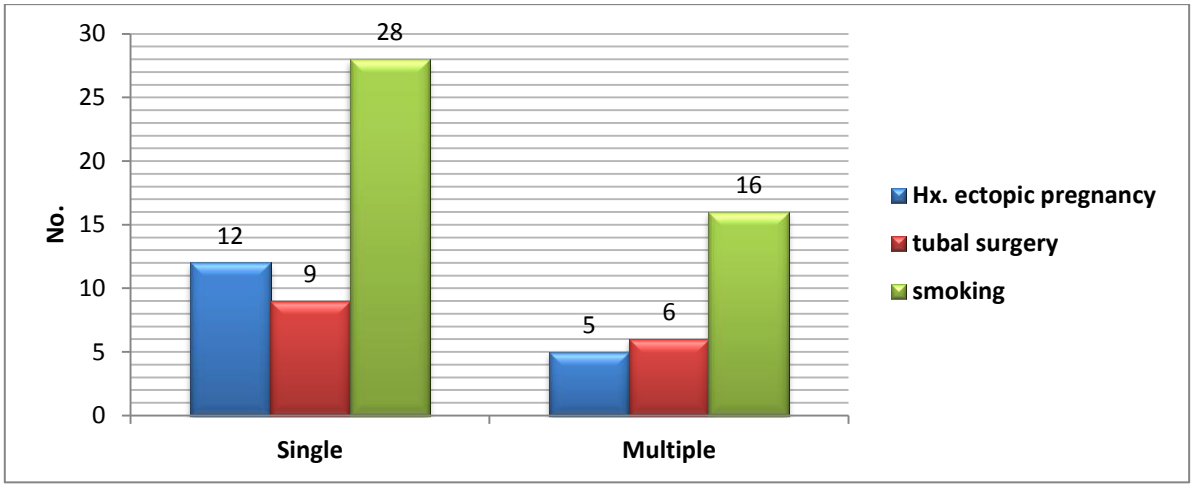

Figure 3: Distribution of some risk factors according to study groups

As shown in table 3, the treatment success rates of women treated with a single dose of methotrexate of different levels of β-hCG (<1000, 1000-1999, >2000 mIU/L) were 70%, 80%, and 80%, respectively. The treatment success rates of women treated with multiple doses of methotrexate of different levels of β-hCG (<1000, 1000-1999, >2000 mIU/L) were 69.7%, 60%, and 42.8%, respectively. The patients with success treatment in single-dose were 55/75, so the percentage of treatment success was 73.3%, while 32/50 for those who were treated with multiple doses with a 64% success rate.

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Table 3: Distribution of treatment success of different methotrexate doses according to different levels of β-hCG in ectopic pregnant women groups

Variable	Single dose		2nd & 3rd doses		P
	No.	%	No.	%	
Treatment success (<1000 mIU/L)					0.8*
Yes	35	**70.0**	23	**69.7**	
No	15	30.0	10	30.3	
Treatment success (1000-1999 mIU/L)					0.5*
Yes	12	**80.0**	6	**60.0**	
No	3	20.0	4	40.0	
Treatment success (>2000 mIU/L)					0.3**
Yes	8	**80.0**	3	**42.8**	
No	2	20.0	4	57.2	
Total treatment success					0.5*
Yes	55	73.3	32	64.0	
No	20	26.7	18	36.0	

**Chi-square test, ** Fisher's exact test.*

As shown in Table 4, there was no significant difference between single and multiple ectopic pregnant women groups regarding ultrasonography examination findings, although insignificancy, means of ectopic mass diameter and endometrial thickness were higher for women treated with multiple doses of methotrexate.

Table 4: Distribution of ultrasonographic examination findings according to single and multiple doses of methotrexate in ectopic pregnant women groups

Variable	Single dose		Multiple doses		P
	No.	%	No.	%	
Free peritoneal fluid					0.2*
Yes	20	26.6	12	24.0	
No	55	73.4	38	76.0	
Ectopic mass diameter (mm)					0.29**
Mean±SD	12.9±2.3		13.3±2.4		
Endometrial thickness (mm)					0.4*
Mean±SD	6.2±1.1		7.3±1		

As shown in table 5 and figure 4, there was a significantly lower mean of serum ß-hCG for ectopic pregnant women treated with a single dose of methotrexate in comparison to ectopic pregnant women treated with more than one dose of methotrexate in different periods (day 1, day four and day 7) ($p<0.001$).

Table 5: Distribution of serum ß-hCG in different times according to single and multiple doses of methotrexate in ectopic pregnant women groups

Variable	Single dose	Multiple doses	t-test	P
	Mean±SD	Mean±SD		
Initial ß-hCG	331±74	676±115	24.5	**<0.001**
Four days ß-hCG	220±52	901±246	31.9	**<0.001**
Seven days ß-hCG	159±44	811±197	37.9	**<0.001**

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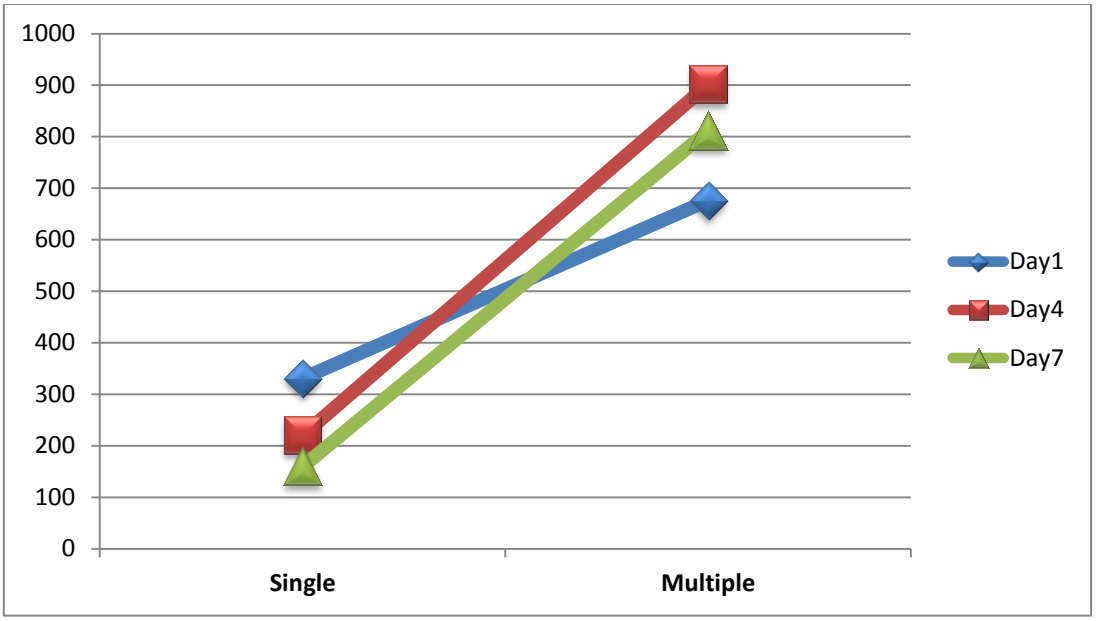

Figure 4: Distribution of serum ß-hCG in different times according to single and multiple doses of methotrexate in ectopic pregnant women groups

As shown in Table 6, there was a highly significant reduction in serum ß-hCG for ectopic pregnant women treated with a single methotrexate dose after four days and seven days of treatment ($p<0.001$), while there was no significant difference in serum ß-hCG for ectopic pregnant women treated with multiple methotrexate doses after four days and seven days of treatment ($p=0.3$).

Table 6: Distribution of serum ß-hCG for single and multiple doses of methotrexate in ectopic pregnant women groups at different times

Variable	Single dose	Multiple doses
	Mean±SD	Mean±SD
One day	331±74	676±115
Four days	220±52	901±246
Seven days	159±44	811±197
P-value*	**<0.001**	0.3

***ANOVA**

The acceptable cut-off points and the corresponding validity tests values for ß-hCG reduction for additional doses of methotrexate prediction in ectopic pregnancy were shown in table 8 and figure 6, cutoff ß-hCG reduction of < 22% had acceptable validity results (92.5% sensitivity, 83.5% specificity, 91.8% PPV, 83.5% NPV and accuracy 90%).

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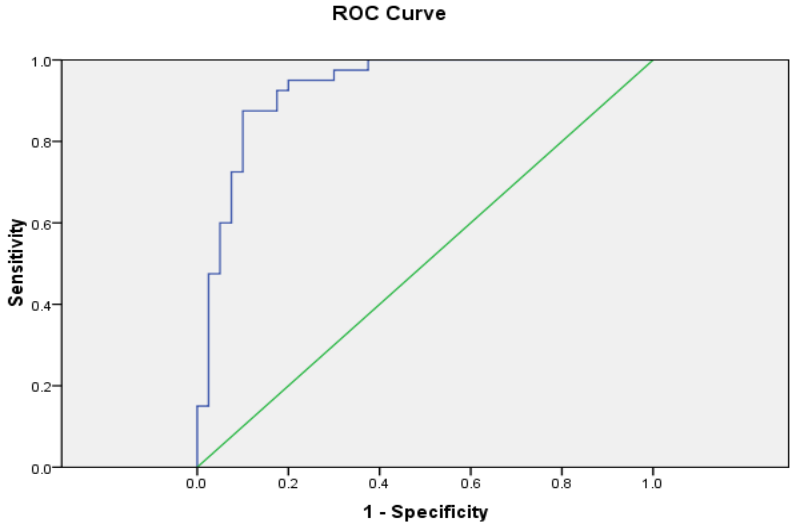

Figure 5: ROC curve of ß-hCG reduction for additional doses of methotrexate prediction in an ectopic pregnancy (AUC=0.9)

Table 7: Coordinates of the ROC Curve of ß-hCG reduction for additional doses of methotrexate in ectopic pregnancy

Cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
<22%	92.5%	83.5%	91.8%	83.5%	90%

As shown in table 8, the 22% reduction of ß-hCG cutoff value in days 1-4 was significantly a predictor for additional doses of methotrexate for women with ectopic pregnancy (p<0.001, OR=7.4).

Table 8: Multiple logistic regression analysis for a ß-hCG reduction in the prediction of additional methotrexate doses

Variable	ß	S.E.	P	OR
Constant	1.3	2.7	**<0.001**	-
ß-hCG reduction =22%	0.8	1.1	**<0.001**	7.4 CI {1.5-10.2}
ß-hCG reduction >22%	0.06	0.4	0.2	0.01 CI {0.002-0.6}

The validity results of ß-hCG reduction regarding single and multiple doses of methotrexate women groups were sensitivity (73.3%), specificity (36%), +ve predictive value (77.4%), -ve predictive value (31%), and accuracy (64%). All these findings were shown in table 9.

Table 9: Validity test results of ß-hCG reduction in comparison to study groups

Validity Test			Study Groups		
			Single	Multiple	Total
			No. (%)	No. (%)	No.
ß-hCG reduction	Positive	No. (%)	55 (73.3)	32 (64.0)	87
	Negative	No. (%)	20 (26.7)	18 (36.0)	38
	Total	No. (%)	75 (75.0)	50 (25.0)	125
Sensitivity		73.3%			
Specificity		36%			
+ve predictive value		77.4%			
-ve predictive value		31%			
Accuracy		64%			

The validity results of ß-hCG reduction cutoff values changes regarding single and multiple doses of methotrexate women groups were sensitivity (53.8%), specificity (82.6%), +ve predictive value (63%), -ve predictive value (28.5%), and accuracy (61.3%). All these findings were shown in table 10.

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Table 10: Validity test results of ß-hCG cutoff values changes in comparison to study groups

Validity test			Study groups		
			Single	Multiple	Total
			No. (%)	No. (%)	No.
ß-hCG reduction	<22%	No. (%)	35 (53.8)	8 (17.4)	43
	>22%	No. (%)	30 (46.2)	38 (82.6)	68
	Total	No. (%)	65 (73.8)	46 (26.2)	111
Sensitivity		53.8%			
Specificity		82.6%			
+ve predictive value		63%			
-ve predictive value		28.5%			
Accuracy		61.3%			

As shown in Table 11, there was a highly significant association between higher resolution time mean and ectopic pregnant women treated with a single dose of methotrexate (p<0.001).

Table 11: Distribution of resolution time according to study groups

Variable	Single dose	Multiple doses	t-test	P
	Mean±SD	Mean±SD		
Resolution time (days)	31±12	56±4	8.6	**<0.001**

DISCUSSION

Majority of the patients with ectopic pregnancy undertake urgent surgical operations either by laparoscopy or laparotomy with suspicion of tubal rupture and intraabdominal hemorrhage. The main causes of tubal damage are the sexually transmitted diseases, smoking, and the tubal surgery. The rise in the rate of sexually infection, especially the chlamydial infections, especially in men, and replication of the use of artificial reproductive techniques over the last decade led to an increased incidence rate of extra-uterine pregnancies. Recently, most of the ectopic pregnancies women were started to be early diagnosed before the beginning of the rupture and hemodynamic instability. The current study shows that the main age group who treated with methotrexate, weather single or multiple was in the age ranged between 20-29 years old, which is not in agreement with that found by Ankum WM [(90)]. In his study when he conclude that higher maternal age was associated with increased risks for spontaneous abortion, ectopic pregnancy, and stillbirth. The ectopic pregnancy is the leading cause of death related in pregnancy in the first-trimester.

methotrexate. This is in agreement with that found by Eskandar M, While an old study by Lipscomb, *et al* ·conclude that the best prognostic indicator of MTX success is the initial level of hCG. He investigated 350 women in his study; the researcher found a 94% success rate when the initial serum hCG level was <10,000 mIU/mL and a 75% success rate when the initial serum hCG level was above 10,000 mIU/mL.

Osama, A E. *et al*., in his research to study the multiple doses against single-dose of the methotrexate protocols for treatment of some cases of ectopic pregnancy, mentioned that the receiver operator characteristic curve analysis in his study revealed that the cutoff level of 3600 mIU/ml for the serum level of b-hCG had a sensitivity and specificity of 94.5 and 92.6%, respectively, for the prediction of treatment success. And he concludes that the Methotrexate therapy is a safe and effective alternative for the management of undisturbed EP with mild side effects and with the associated advantage of avoiding invasive surgery, provided the criteria of medical management are strictly fulfilled. A multiple-dose regimen of methotrexate is more effective in the treatment of ectopic pregnancy compared with a single-dose regimen.

Gungorduk, K. *et al*., (2011), in his study (comparison of single-dose and two-dose methotrexate protocols for the treatment of unruptured ectopic pregnancy), mentioned that medical treatment with either single-dose or with two-dose systemic MTX seems to be the same therapeutic options for patients with an un-ruptured type of ectopic pregnancy. And the rate of the success between the two therapeutic regimens, the single and two-dose medication, was equal. It

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had been found that there is no statistically significant difference between the groups in factors influencing treatment with methotrexate treatment success rate. Mol, B.J. *et al*., (2002), in their meta-analysis study, mentioned that systemic methotrexate treatment is a worthy substitute in selected patients with low concentrations of serum β-hCG.

CONCLUSION

The current study concludes that single-dose of the methotrexate therapy could be positively offered to most stable patients experiencing medical management of an ectopic pregnancy, and a decline in the serum level of β-hCG between days 1 and 4 is related with a high treatment success rate. The change in the serum level of β-hCG between days 1 and 4 appears to be an early predictive factore of an additional dose of methotrexate.

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