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Is it possible to predict the success of single dose methotrexate in the treatment of tubal ectopic pregnancies?

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ABSTRACT

Objectives: In this study, the aim was to determine whether the use of endometrial thickness or neutrophil/lymphocyte and platelet/lymphocyte ratio would be useful in predicting the success of methotrexate in the treatment of ectopic pregnancies located in the fallopian tubes.

Materal and methods: This study was carried out by retrospectively examining 68 study group cases with an ultrasonographically detectable gestational sac in the fallopian tubes and 189 control group cases with an unruptured ectopic pregnancy diagnosis at any location. The cut-off value of endometrial thickness was calculated as a new marker between the cases in which single-dose methotrexate treatment was successful and the cases with treatment failure. Treatment success was evaluated with different models including endometrial thickness, fetal cardiac activity status, measurable crown-rump length, and β-hCG.

Result: The cut-off value of β-hCG for treatment success was determined as 2960.5 ng/mL, and the cut-off value for endometrial thickness was determined as 10.5 mm. Although NLR seems to be a marker with a cut-off value of 2.49, it does not provide an extra benefit in combined use as it is not a specific predictor. The highest success in predicting treatment success was achieved in the modeling in which crown-rump length + fetal cardiac activity + β-hCG + endometrial thickness were used together.

Conclusions: The use of endometrial thickness as a marker seems to be quite reliable in predicting treatment success. And we think it would be beneficial to thin the endometrium before using methotrexate.

Key words: ectopic pregnancy; endometrial thickness; prognostic endometrial knownledge; human chorionic gonadotropin- β; single-dose methotrexate; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio

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INTRODUCTION

Ectopic pregnancy may constitute two percent of all pregnancies, and is often located in the fallopian tubes [1]. The management of ectopic pregnancies includes expectant management, pharmacological treatment with methotrexate, or surgery. However, methotrexate is relatively contraindicated in patients with initial human chorionic gonadotropin-β (β-hCG) levels of > 5000 mIU/mL, a gestational sac size of > 4 cm, presence of fetal cardiac activity and hemoperitoneum, which indicate a high treatment failure rate. Nevertheless, the use of methotrexate in the treatment of ectopic pregnancies is still the most commonly preferred treatment method in unruptured ectopic pregnancies [2]. The two most common methods of using methotrexate in ectopic pregnancy are; it is a single dose administration of calculated by the equation 50 mg/m^2 based on body surface area (without need for leucovorin rescue), or multiple dose regimen of 1 mg/kg (alternating with 0.1 mg/kg leucovorin rescue) [3]. Any ectopic and/or existing embryo with a pretreatment mass greater than 3.5 cm and a human chorionic gonadotropin level greater than 5000 mIU/mL is more likely to fail medical therapy and may be more suc-

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cessfully treated surgically [4]. But, these human chorionic gonadotropin-β levels and gestational sac sizes are admirably high, and they carry a risk of rupture. When a pregnant sac becomes larger in the tube and the tubal lumen cannot accommodate, tubal rupture may occur. Some previous studies have suggested that higher human chorionic β-hCG levels and gestational age seem to be significant risk factors for developing a ruptured ectopic pregnancy [5, 6]. So, paying special attention to pregnancies at risk of failure with a single dose of methotrexate [4].

Methotrexate is a folinic acid antagonist (folic acid analogue) that shows its effectiveness by inhibiting dihydrofolate reductase. By binding to dihydrofolate reductase, it reduces thymidylate, purine synthesis and cell proliferation. As can be seen, it is a pharmaceutical agent that interferes with almost all cellular activities such as nucleic acid synthesis, DNA-RNA repair, cellular replication [7]. Therefore, besides malignant cells or tissues; normal cells with rapid cellular turnover, such as trophoblast, bone marrow, endometrium, keratinocytes, and reproductive cells, are also highly sensitive to these effects of methotrexate [8]. Erdil et al. [8], in their study with methotrexate in ectopic pregnant and non-pregnant uterus, showed that the expression of some superficial receptors was also significantly affected at the endometrium level. This result suggests that the endometrium is also a factor in the success of methotrexate, which we use in the treatment of ectopic pregnancy [8]. However, in another study, Tas et al. [9] reported that the endometrial thickness did not affect the results in their study evaluating the success of single--dose methotrexate administration.

On the other hand, there are also studies in the literature reporting that hematological parameters can be an effective marker in predicting the success of methotrexate due to inflammatory processes [10, 11]. Akkaya et al. [12] reported that MPV and RDW could be used as independent markers to predict the success of treatment.

Today, research on the factors affecting the success of single dose methotrexate is still ongoing. The vast majority of them are concentrated on human chorionic β-hCG. In our study, we aimed to evaluate whether the endometrial thickness (ET), neutrophil/lymphocyte (NLR) and thrombocyte/ /lymphocyte ratios (PLR) measured at the time of diagnosis can also be used as a marker to predict the efficacy of methotrexate. Based on these results in the literature, we aimed to reveal whether there are other markers that are stronger in predicting the success of single-dose methotrexate use in ectopic pregnancies located in an unruptured fallopian tube.

Impact statement

What is already known on this subject?

Precise information that can predict the success of a single dose of methotrexate is still not available in the literature. Many modalities have been developed and proposed. Often, gestational sac size, fetal cardiac activity status, β-hCG value and similar markers are used.

What the results of this study add?

Endometrial thickness provides us with information about the success in predicting the prognosis with a very high accuracy. This finding made us think that it may be very useful in clinical management.

What the implications are of these findings for clinical practice and/or further research?

Our study concluded that endometrial thickness affects treatment success. In this case, curettage the endometrium before methotrexate administration may increase the success rate of a single dose of methotrexate. However, it also revealed that NLR and PRL are not specific markers for the medical treatment of ectopic pregnancy.

MATERIAL AND METHODS

Ethics

All ethical approvals required for the study were obtained from the Çanakkale Onsekiz Mart University Clinical Research Board. (2022-YÖNP-0013/ 06.04.2022:06-13).

Selection and creation of the sample of the study

Women who were diagnosed with ectopic pregnancy and treated in our clinic between 2011 and 2021 were retrospectively analyzed. All the data obtained were provided by scanning the hospital electronic patient record system. As a result of this preliminary research, full data of 189 cases of ectopic pregnancy whose initial treatment was methotrexate were reached. Due to the changes in the electronic patient registration system over the years, the inability to access all the data of all the cases has created a limitation. Since it was aimed to evaluate the factors that may affect the success of a single dose of methotrexate, the cases that were ruptured at the time of diagnosis and required acute abdominal surgery were not included in the study. Apart from this, cases with rheumatic, inflammatory or similar chronic diseases for any reason were not included in the sample to avoid drug interactions. None of the women included in the study were heterotopic pregnancy. After all these exclusion criteria were applied, the number of ectopic pregnancy cases with fallopian tube localization to be included in our study was determined as 68 without bias. All of these 68 cases had a gestational sac that could be observed and measured ultrasonographically in the fallopian tubes. Cases that were evaluated as ectopic pregnancy with their biochemical and sonographic findings at the start of treatment, but who did not have a gestational sac that could be visualized in the fallopian tubes ultrasonographi-

cally due to the level of serum β-hCG hormone at the time of decision were not included in this group. This elimination was necessary and important for the validity and reliability of the results of the study. Of course, an exception to this was the cases in which surgical treatment was applied as a result of treatment failure and tubal rupture was detected. These have already been reported separately as treatment failure. And, all of the cases without observable gestational sac located in the fallopian tube were considered as other locations (cervical, cesarean scar, cornual, ovarian, unknown location etc.) to avoid any bias. Therefore, in our study, we did not specify any rate about the frequency of ectopic pregnancy locations. It was confirmed that all cases included in the sample received the standardized dose of methotrexate accepted in the literature (50mg of methotrexate per square meter of body surface area).

Modelling

First of all, ectopic pregnancy locations were divided into study-case group and control group. The first group consisted of only those located in the fallopian tubes (group 1), which constituted the study group, and the second group consisted of the control group with all ectopic pregnancies (group 2). The reason for creating two groups was to measure whether the results we obtained in our study, which we carried out to predict the success of single-dose methotrexate in the treatment of ectopic pregnancies localized in the fallopian tubes which was the aim of our study, to evaluate whether it was generalizable for the treatment of all ectopic pregnancies and to measure its internal consistency. This is very important for the validity and reliability of our study. First, the mean values and standard deviations of some parameters, which we think may have an effect on the success of methotrexate, were analyzed separately for both groups. And it was evaluated whether the results differed statistically. These included the following parameters; mean age (year), success rate of single dose methotrexate, presence or absence of crown-rump length (CRL), presence or absence of fetal cardiac activity (FCA), neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, endometrial thickness (mm). Neutrophil/lymphocyte ratio value was calculated by dividing the number of neutrophil by the number of lymphocyte. Similarly, the PLR value was calculated by dividing the platelet count by the lymphocyte count.

Subsequently, the median values were calculated separately in group 1 and group 2 for the success and failure of single-dose methotrexate administration by including the serum β-hCG level measured at the time of treatment to the same parameters. It was evaluated whether the medians found were statistically significant in case of ectopic pregnancy located in the fallopian tube or in the case of treatment success and failure in all ectopic pregnancies.

As a result of this statistical analysis, the cut-off values of the parameters that gave a significant value on the treatment success in any group were determined separately for both groups. And their sensitivities, specificities, positive predictive values and negarite predictive values were calculated in these cut-off values. On the other hand, no further evaluation was made at this stage for CRL and FCA, which are accepted in the literature and whose presence adversely affects the success of methotrexate.

Finally, we evaluated the effect of endometrial thickness on treatment success and failure for ectopic pregnancies with fallopian tube location, at the cut-off value that we determined for serum β-hCG, whose increase and height is also considered to have a negative effect on treatment success in the literature. We then reassessed the same analysis by adding the presence of crown-rump length to the β-hCG level and then adding the presence of fetal cardiac activity to these. Then, we also performed the same evaluation and comparison for another parameter, NLR, which we evaluated for the first time in terms of literature. This modeling is important and original in that it is the first in the literature.

Statistical evaluation

Nominal variables were expressed as frequencies and percentages (%) whereas continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) for the non-normally distributed variables. The Kolmogorov-Smirnov test was used to assess the normality assumption for the continuous variables. The significance of the difference between the tubal group and the control group was analyzed using paired samples t- test. Categorical variables were evaluated using Pearson's chi-square test or Fisher's exact test. Receiver-operating characteristic (ROC) analysis was performed to identify a threshold value for endometrial thickness, β-hCG (level at the time of treatment), NLR. ROC analysis was used to calculate the areas under the receiving operator curves (AUROC) with 95% confidence intervals for study parameters to predict methotrexate success. The DeLong test was then used for a pairwise comparison of AUROCs. All statistical analyses were conducted using SPSS for Windows (IBM Corp. Armonk, NY, USA). All p values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Our study, in which we evaluated the endometrial thickness and hematological parameters in predicting the success of methotrexate, was performed on 68 cases with an ectopic pregnancy focus located in the definitive fallopian tube, ultrasonographically or surgically detected. Initial treatment of all cases included in the study group and control group was standardized dose methotrexate.

Table 1. Shows the mean values and statistical difference of the parameters evaluated between tubal localized ectopic pregnancies and all ectopic pregnancies in the control group

Evaluated parameter	Mean ± SD		p value
	Group 1	Group 2	
Age [year]	30.47 ± 5.18	30.72 ± 5.24	0.731
Endometrial thickness [mm]	9.70 ± 3	8.95 ± 2.88	0.039
NLR	3.05 ± 2.15	2.76 ± 2.02	0.311
PLR	141.25 ± 100	122.94 ± 69.55	0.101
Measurables CRL	15 (22.1%)	24 (12.7%)	0.065
Measurables FCA	9 (13.2%)	14 (7.4%)	0.149
Success of single-dose	42 (61.8%)	138 (73.0%)	0.082
β-hCG [mIU/mL]	3862.63 ± 2428.90	2527 ± 2962.85	< 0.001

SD — standard deviation; NLR — neutrophil /lymphocyte ratio; PLR — thrombocyte /lymphocyte ratios; CRL — crown-rump length; FCA — fetal cardiac activity ($p < 0.05$); β-hCG — human chorionic gonadotropin-β

As a result of our first statistical analysis, we determined that the age of the woman, the neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, presence of fetal cardiac activity and measurable crown-rump length did not difference between ectopic pregnancies located in the fallopian tube and all ectopic pregnancies. These findings are important in terms of showing us that the parameters we evaluated are distributed in a homogeneous and coincidental similarity between the fallopian tube or other ectopic locations. But, there was a statistically significant difference between tubal localized ectopic pregnancies and all ectopic pregnancies in terms of the mean endometrial thickness and serum β-hCG. This difference regarding β-hCG was due to low titer plateauing ectopic pregnancies in the control group and ectopic pregnancies of unknown location, which did not increase regularly and did not have an ultrasonographically detectable gestational sac. Comparison of fallopian tube parameters in the study group and all ectopic pregnancies in the control group are presented in Table 1.

Then, the statistical significance and differences of these parameters between treatment successful cases and treatment unsuccessful cases in ectopic pregnancies which were located in the fallopian tube were tested. Except for the endometrial thickness, there was no statistically significant difference between the treatment -successful cases and the unsuccessful cases which were located in the fallopian tube. In other words, the patient's age, serum β-hCG level, presence or absence of CRL, presence or absence of FCA and others were not meaningful on their own in determining the success of treatment, in group 1. However, in our control group (group 2), which included all ectopic pregnancies (cases that did not have any observable gestational sac in the fallopian tube; cases whose serum β-hCG level did not make it possible to visualize the gestational sac sonographically or those who did not show a steady increase by drawing a plateau; cases where the gestational sac is observed to be located outside the fallopian tube), except of PLR in all parameters were statistically significant on cases where the treatment was successful or failure. All data of this analysis are presented in detail in Table 2. In both the case and control groups, found that the mean endometrial thickness of 7 mm (6–9 mm) in cases which a single dose of methotrexate was successful; on the other hand, in cases which a single dose of methotrexate was not successful, this thickness was 13 mm (12–14 mm) on average. When the effect of endometrial thickness on the success rate was examined, we found that it was statistically significant ($p < 0.05$).

After this stage, we did not perform any further evaluation with PLR, which was neither selective nor statistically different between the two groups. And we calculated the cut-off values for β-hCG, NLR and endometrial thickness in both groups separately. These values were surprisingly similar in both groups, measuring 2960.5 mIU/mL for β-hCG, 10.5 mm for endometrial thickness, and 2.49 for NLR. The value of endometrial thickness (prognostic endometrial knownledge) in predicting the success of a single dose of methotrexate in tubal ectopic pregnancies and all other ectopic pregnancies is presented as the ROC curve in Figure 1. Sensitivity, specificity, positive predictive value and negative predictive value on treatment success in the fallopian tube and control group are presented in tables regarding these cut-off values. It was determined that the thickness of the endometrium differed from others in terms of sensitivity and specificity in predicting the success of treatment and gave stronger information in terms of prognosis. All results are presented in detail in Table 3.

Finally, we developed a model, and tested the strongest combination that could allow us to predict the success of single-dose methotrexate in the fallopian tubes

Table 2. The relationship of single dose methotrexate administration with ectopic pregnancies located in the fallopian tubes and the control group to variable parameters is shown

Evaluated parameter		Result of treatment	Group 1		Group 2	
			Median (q1–q3)	p value	Median (q1–q3)	p value
Endometrial thickness [mm]		**Successful**	7.00 (7.00–9.00)	< 0.001	7.00 (6.00–9.00)	< 0.001
		Failure	13 (12.00–14.00)		13.00 (12.00–13.25)	
β-hCG [mIU/mL]		**Successful**	2863 (1961.50–5031.50)	0.579	1415.00 (456.25–2813.50)	< 0.001
		Failure	3364 (2035.00–6061.50)		2976.00 (826.00–6019.00)	
NLR		**Successful**	2.52 (1.69–3.23)	0.468	2.11 (1.57–2.95)	0.038
		Failure	2.65 (1.98–3.66)		2.59 (1.93–3.65)	
PLR		**Successful**	125.83 (94.61–163.1)	0.791	107.84 (88.14–142.95)	0.055
		Failure	136.00 (98.36–154.03)		125.00 (96.77–151.74)	
CRL	**Present**	**Successful**	9 (21.42%)	0.873	12 (8.4%)	0.007
	None		33 (78.57%)		126 (91.6%)	
	Present	**Failure**	6 (23.1%)		12 (23.4%)	
	None		20 (76.9%)		39 (76.6%)	
FCA	**Present**	**Successful**	5 (11.9%)	0.681	7 (5.7%)	0.044
	None		37 (88.1%)		131 (94.3%)	
	Present	**Failure**	5 (15.4%)		7 (13.7%)	
	None		22(84.6%)		44 (86.3%)	

β-hCG — human chorionic gonadotropin-β; NLR — neutrophil /lymphocyte ratio; PLR — thrombocyte /lymphocyte ratios; CRL — crown-rump length; FCA — fetal cardiac activity ($p < 0.05$)

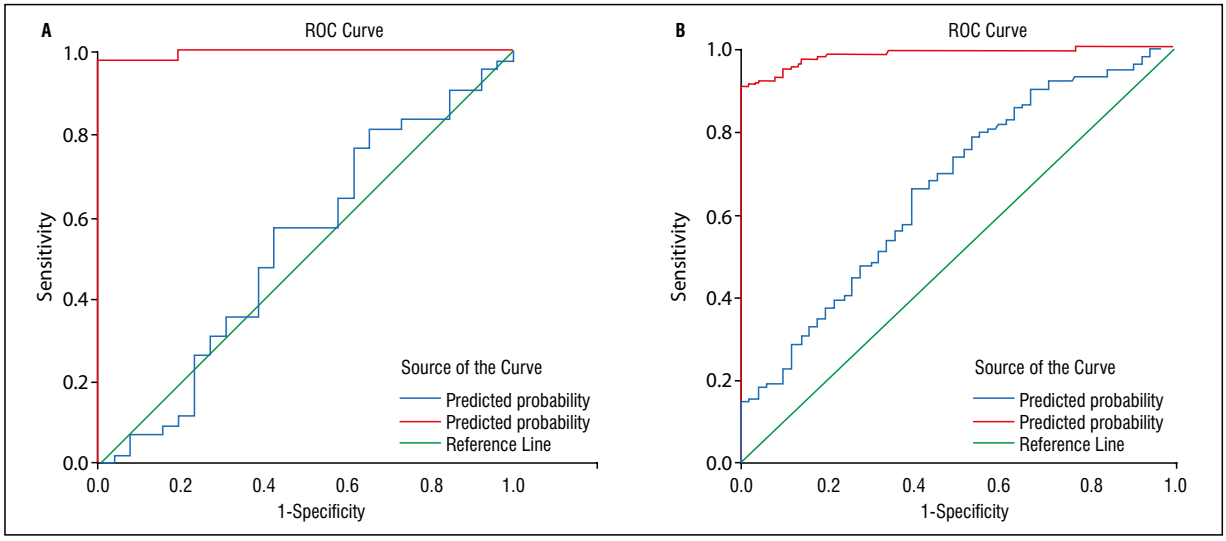

Figure 1. A. Shows the effectiveness of endometrial thickness in predicting the success of a single dose of methotrexate in tubal ectopic pregnancies, while **B** shows the effect of endometrial thickness on the success of a single dose of methotrexate in all ectopic locations; ROC — receiver operating characteristic

Table 3. Cut-off values predicting the success of single-dose methotrexate use and their confidence intervals, sensitivity, specificity, positive predictive value, and negative predictive values are presented ($p < 0.05$)

	Cut-off	AUC	SD	p value	Lower B.	Upper B.	Sens.	Spec.	PPV	NPV	Acc.
Endometrial thickness [mm]											
Group 1	10.5	0.994	0.006	< 0.001	0.982	1.000	0.929	0.990	0.990	0.897	0.956
Group 2	10.5	0.968	0.012	< 0.001	0.943	0.992	0.941	0.935	0.977	0.841	0.936
β-hCG [mIU/mL]											
Group 1	2960.5	0.540	0.074	0.579	0.394	0.686	0.542	0.656	0.718	0.471	0.588
Group 2	2960.5	0.666	0.045	< 0.001	0.578	0.754	0.511	0.775	0.811	0.456	0.704
NLR											
Group 1	2.49	0.553	0.072	0.468	0.412	0.693	0.552	0.701	0.711	0.551	0.617
Group 2	2.49	0.589	0.046	0.038	0.507	0.588	0.638	0.588	0.807	0.375	0.624

AUC — area under the curve; SD — standard deviation; B. — bounds; PPV — positive predictive value; NPV — negative predictive value; Acc. — accuracy; β-hCG — human chorionic gonadotropin-β; NLR — neutrophil /lymphocyte ratio

from this model. In this modeling, it was determined that in the presence of ectopic gestational sac located in the fallopian tubes, when added to the combination of endometrial thickness, serum β-hCG level + CRL status + FCA status, it made a very high contribution to predicting the prognosis. On the other hand, we also found that NLR did not make any prognostic significance or contribution. Simultaneously, we performed the same analyzes for the control group as a proof of modeling. And modeling has been shown to yield similar results. Table 4 contains the results for all models.

DISCUSSION

Studies on estimating the effectiveness of methotrexate used in the treatment of ectopic pregnancy are still ongoing. In the management of ectopic pregnancies, markers such as β-hCG level, presence of fetal cardiac activity, size of ectopic mass focus, presence of free fluid in douglas' dead end play a decisive role. Of course, when evaluating these markers, the status of vital signs is also taken into account [13]. As a matter of fact, these were the criteria that shaped the treatments we applied in our retrospective study as well. Patients with acute abdominal emergency surgery findings and no stabilization of vital signs were not included in the sample of our study because they were taken directly to surgical treatment. Our aim was to investigate whether endometrial thickness, NLR and PLR could be used as markers to predict treatment outcomes, apart from the criteria discussed in the literature, in the management of tubal localized ectopic pregnancies.

In our study, the cut-off value of β-hCG, which predicts the success of a single dose of methotrexate, was found to be 2960.5 mIU/mL. Recently, Sindiani et al. reported that they found this cut-off value as 3924 mIU/mL in their study with 110 patients [14]. On the other hand, Mashiach et al. reported this value as 2002.5 mIU/mL in their study on 111 patients [15]. Erdil et al. [8] calculated this value as 2678 mIU/mL in their study. Of course, this variability in hCG value can be affected by many factors. For example, the location of the ectopic pregnancy, the week of diagnosis of the ectopic pregnancy, the week of pregnancy made by the treatment decision and similar conditions will affect the measured serum β-hCG value. However, it has been reported in the literature that the success rate of methotrexate decreases and even the risk of rupture increases at when the serum β-hCG values above 5000 mIU/mL [2, 4]. But, the resistance of all tissues is unfortunately not the same. And variability can be seen between rupture times. In our study, we found the mean β-hCG value to be 3862.63 ± 2428.90 mIU/mL in cases with ultrasonographically visible ectopic pregnancy mass located in the fallopian tube. In cases where a single dose of methotrexate was successful, this mean value was 2863 mIU/mL. However, when we evaluated all ectopic pregnancies, the mean β-hCG value was measured as 2527 ± 2962.85 mIU/mL, and this value was 1415 mIU/mL in the group in which a single dose of methotrexate was successful. It is quite normal and to be expected that the results are so different. Because our most important criterion was the presence of a gestational sac that could be demonstrated ultrasonographically in the tubal location. In the control group, there were ectopic pregnancies with unknown locations, those with low β-hCG levels but drawing plateau, and others, and these constituted a very large majority. Therefore, it was necessary to determine a cut-off value at the maximum height at which effective treatment was achieved, especially in tubal localized ectopic pregnancies, and we did. We determined this cut-off value as 2960.5 mIU/mL and below in the population in which we conducted our study. This cut-off value was the most optimal result obtained both in the medical treatment of ectopic pregnancies located in the fallopian tubes and in all ectopic pregnan-

Table 4. Impact of the endometrial thickness and neutrophil /lymphocyte ratio score on the discrimination accuracy of MTX success

Prognostic model	AUROC (95% CI) without Endometrial thickness	AUROC (95% CI) with Endometrial thickness	DBA	SE	95% CI	Z statistic	p value
Group 1							
β-hCG	0.540 (0.394; 0.686)	0.968 (0.930; 1.000)	–0.428	0.307	–0.285; –0.570	–5.876	< 0.001
β-hCG + **CRL**	0.527 (0.375; 0.678)	0.968 (0.918; 1.000)	–0.441	0.311	–0.293; –0.590	–5.823	< 0.001
β-hCG + **CRL + FCA**	0.553 (0.408; 0.698)	0.995 (0.942; 1.000)	–0.469	0.284	–0.321; –0.616	–6.218	< 0.001
Group 2							
β-hCG	0.666 (0.578; 0.754)	0.977 (0.959; 0.994)	–0.311	0.232	–0.400; –0.222	–6.832	< 0.001
β-hCG + **CRL**	0.664 (0.576; 0.751)	0.977 (0.960; 0.994)	–0.313	0.232	–0.402; –0.224	–6.893	< 0.001
β-hCG + **CRL + FCA**	0.661 (0.573; 0.749)	0.981 (0.966; 0.996)	–0.320	0.229	–0.407; –0.232	–7.163	< 0.001
	AUROC (95% CI) without NLR	**AUROC (95% CI) with NLR**					
Group 1							
β-hCG	0.540 (0.394; 0.686)	0.596 (0.450; 0.742)	–0.056	0.378	–0.175; 0.064	–0.916	0.360
β-hCG + **CRL**	0.527 (0.375; 0.678)	0.591 (0.447; 0.734)	–0.064	0.380	0.064; 0.192	0.981	0.327
β-hCG + **CRL + FCA**	0.553 (0.408; 0.698)	0.586 (0.446; 0.727)	–0.033	0.375	–0.157; 0.091	–0.521	0.603
Group 2							
β-hCG	0.666 (0.578; 0.754)	0.667(0.576; 0.757)	–0.001	0.296	–0.045; 0.044	–0.025	0.980
β-hCG + **CRL**	0.664 (0.576; 0.751)	0.666 (0.576; 0.756)	–0.002	0.295	–0.045; 0.041	–0.098	0.922
β-hCG + **CRL + FCA**	0.661 (0.573; 0.749)	0.663 (0.573; 0.753)	–0.002	0.296	–0.046; 0.042	–0.076	0.939

AUROC — area under the receiver operating characteristic curve; CI — confidence interval; DBA — difference between areas; SE — standart error; β-hCG — human chorionic gonadotropin-β; CRL — crown-rump length; FCA — fetal cardiac activity; NLR — neutrophil /lymphocyte ratio

cies in our control group. Although different results were reported, the β-hCG cut-off value which we obtained was generally compatible with the literature.

As a new marker, we tested, for the first time in the literature, the prognostic contribution of endometrial thickness in the medical treatment of ectopic pregnancies located in the fallopian tubes. As a result of our statistical analyzes, we determined the upper limit of the endometrial thickness as 10.5 mm, where the maximum benefit from medical treatment can be seen in the presence of an ectopic pregnancy mass located in the fallopian tubes. In addition, we tested the contribution of the cut-off value we determined for endometrial thickness in the management of all other ectopic pregnancies in our control group. The results we found were reproducible and identical. This result is very important in terms of its contribution to the literature. As a chemotherapeutic agent methotrexate affects rapidly dividing cells, which also include ovarian or endometrial cell populations [16]. Erdil et al. [8] have recently demonstrated the cytotoxic effects of methotrexate on the endometrium and its receptors. In-vitro studies of the rat uterus have demonstrated a possible effect of methotrexate on the inhibition of estrogen receptor protein synthesis [17, 18]. In one case, Kroft et al. [19] reported that secondary amenorrhea developed in a woman using methotrexate for rheumatoid arthritis. Da Costa Soares et al. [20] reported a mean value of 6.4 mm and 1,936.2 mIU/mL β-hCG for endometrial thickness in cases of success with a single dose of methotrexate. In their study,

the mean values of endometrial thickness were 11.7 mm and β-hCG was 6.831.3 mIU/mL in case of failure [20]. Takacs et al. [21] reported that the success rate of methotrexate showed significant variability at values below and above 12 mm of the endometrium. In fact, Nikolic et al. [22] reported that low-dose methotrexate can be used together with raloxifene in the treatment of endometrial hyperplasia. As a opposing view, Taş et al. [9] investigated the efficacy of a single dose of methotrexate, but reported that endometrial thickness was not a determining factor in their study. Cecchino et al. [23], in their review, reported that endometrial thickness reflects hormonal levels and that the higher the β-hCG level, the higher the endometrial thickness and the worse the prognosis of methotrexate treatment. Cecchino et al. [23] were right in their results. The rising β-hCG level increases the secretion of the hormone progesterone, which plays the most important role in the continuation of pregnancy. Increasing progesterone, on the other hand, has an anabolic effect on the endometrium, thickening and softening it, making it ready for pregnancy [24–26]. This explains the excellent agreement between β-hCG and endometrial thickness in predicting treatment success. As a note, endometrial thickness has also been tried in the evacuation of early pregnancy losses and reported to be an effective factor for the effectiveness of misoprostol [25]. The sensitivity and specificity of the cut-off value determined in our study regarding the endometrial thickness in predicting the success of methotrexate is acceptable. For this reason, we used the name 'prognostic endometrial knownledge (PEK)' for this value due to its contribution.

Akkaya et al. [12] evaluated the contribution of inflammatory markers in the prediction of ectopic pregnancy in their study, but reported that NLR and PLR did not provide any benefit. Kanmaz et al. [11], on the other hand, reported that NLR may contribute to predicting the success of a single dose of methotrexate. In our study, we found that NLR and PLR values did not make a statistical difference in the success of methotrexate in tubal ectopic pregnancies. On the other hand, NLR value showed a statistical difference in all cases diagnosed with ectopic pregnancy in our control group. The possible cause of this situation may be ectopic pregnancies of unknown location, which were treated at lower β-hCG levels in the early period. However, as a final result, NLR was far from being an accurate predictor of making any contribution to prognosis. In our study, CRL and FCA did not seem to differ statistically for single-dose methotrexate success in tubal localized ectopic pregnancies. However, the reason for this was that the cases in which only the presence of gestational sac in the fallopian tubes could be observed ultrasonographically were included in this group with great care. Because the results we obtained in our control group were statistically significant in accordance with the literature.

CONCLUSIONS

We think that endometrial thickness is a parameter that should be considered in predicting the success of methotrexate. In this case, curetting the endometrium before methotrexate administration may increase the success rate of a single dose of methotrexate. And we believe that inflammatory markers do not make any contribution to the prediction of treatment success. Although our sample is large enough to allow us to comment on this subject, the importance of the subject will increase with the presentation of other studies to the literature.

Ethics

All ethical approvals required for the study were obtained from the Çanakkale Onsekiz Mart University Clinical Research Board. (2022-YÖNP-0013/ 06.04.2022:06-13)

Authorship contributions

Concept: EP, FB; Design: EP, FB; Data Collection or Processing: EP, FB; Analysis or Interpretation: EP, DS; Literature Search: EP; Writing: EP.

Conflict of interest

The authors declared no conflict of interest.

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