Tubal Ectopic Pregnancy: Effect of ß-hCG Change in Treatment

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Abstract: *Objective*: To evaluate the effect of β-hCG of treating prediction in tubal ectopic pregnancies (TEP).

Materials and Methods: 758 patients receiving only one dose of methotrexate (mtx) treatment protocol for CAP were included in the study between January 2009 and December 2017. Patients' age, gravity, parity, ultrasonography findings, β-hCG values, and factors that may affect treatming process were recorded.

Results: It was determined that medical treatment success was predicted with 77%, 81% sensitivity and 61% and 68% specificity when the initial β-hCG value was 1435 mIU / mL and the β-hCG level on the 4th day was 1539 mIU / mL cut off value. In our study, when β-hCG values decreased by 7% between 0-4 days were taken as cut off value, medical treatment with 84% sensitivity and 77% specificity was shown to be successful. The mean β-hCG levels on the 4th and 7th days were significantly lower in the medical treatment group than in the unsuccessful group.

Conclusion: We found that patients with lower β-hCG values at baseline and day 4 had higher chances of success, and when cut off values were taken as 1435 mIU / mL and 1539 mIU / mL, success rate was significantly decreased. According to β-hCG level on day 0, day 4, and β-hCG change level between 0-4 days, we think ectopic pregnancy approach will decrease the unnecessary hospital stay.

Keywords: Tubal ectopic pregnancies, β-hCG, methotrexate.

INTRODUCTION

Ectopic pregnancy (EP) is the implantation of blastocyst away from the endometrial cavity [1]. It is one of the most important causes of mortality and morbidity in the first trimester [2]. The frequency of all pregnancies varies between 0.5% and 2% [1]. The incidence of EP increases with age, and the risk between 35-44 years of age is 3-4 times more than women aged 15-24. Black race in all age groups is 1.4 times more common than white race [3]. Several risk factors have been reported in the etiology.

As previously accepted, pelvic inflammatory disease, intrauterine device use, history of tubal surgery, use of contraceptive methods including progesterone, previous laparotomies, previous history of EP, endometriosis, infertility treatment are considered as responsible factors for the spread of surgical methods [4]. The most common site of EP is Fallot tube (FT) and it is represented in 98% of EP cases. The fallopian tube (FT) is where the ovum and sperm combine to form the zygote. TEP is caused by the inability of the embryo to move from the fallopian tube to the uterine cavity. Several factors (paracrine factors released by the embrio, proteins required for embryo receptivity, adhesion and trophoblast invasion) promote the development of the embryo's preimplantation and allow the embryo to be transported to the uterus for implantation. The problem with any of the above-mentioned factors can cause TEP [5,6]. Symptoms occur according to the location of the EP. EP is usually asymptomatic at the early stage of implantation. The most common symptoms of EP are introduced as delayed menstruation, vaginal bleeding and abdominal pain [7]. Due to the fact that ß-hCG values are routinely reviewed and transvaginal ultrasonography is widespread, TEP can be diagnosed and treated earlier [8]. Doppler USG increases the sensitivity of transvaginal ultrasonography. The fact that the ring-of-fire pattern showing the placental perfusion is outside the uterine cavity is the diagnostic finding for the diagnosis of TEP [9]. Although Ca 125, progesterone, inflammatory markers and cytokines were recommended in TEP diagnosis, treatment and follow-up, none of them were as effective as ß-hCG and ultrasonography. TEP treatment methods; follow-up treatment, medical treatment as well as surgical treatment are discussed in three groups. Patients can benefit from medical treatment if they can be diagnosed hemodynamically without rupture [10]. Medical treatment has many advantages over surgical treatment; these include less tubal damage, lower cost, protection of fertility, and reduction of morbidity and potential complications of anesthesia and surgery [11].

Nowadays, MTx is the most frequently used agent for the treatment of TEP in the world. The most

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important factors in the preference of MTX are low cost, low side effect and high success rates (64-94%) [12]. Inhibits the dehydrofolate reductase enzyme that is involved in the conversion of folic acid to tetrahydrofolate and inhibits tetrahydrofolate formation, which is essential for DNA synthesis. However, it leads to a breakdown of protein synthesis. Mtx has a cytotoxic effect on cells in the synthesis phase period. Side effects such as bone marrow depression, hepatotoxic, nephrotoxic mouth and intestinal mucosa are side effects. In addition, the effects of the drug are antagonized by externally administered folinic acid [13].

The dose of mtx can be repeated and the surgery can be performed in patients who fail single-dose therapy. When the success of medical treatment is low, surgical treatment is preferred. If the patient has severe bleeding and the β-hCG level is higher than 5000 mIU / mL. Surgical treatment in CAP is curative [14]. Pregnancy rates in patients undergoing laparotomy or laparoscopy are similar . Most studies have shown that when the surgical treatment is compared with medical treatment, the reproductive result is similar [15]. In this study, we aimed to compare the success rates of the patients taking a single dose of MTX treatment in our hospital and those who failed and to determine the factors affecting the success.

MATERIAL METHOD

This study included 758 patients who were diagnosed with TEP between January 2009 and December 2017 at the Tepecik Training and Research Hospital, which is a tertiary care center addressing an even larger population with a population exceeding 4 million. The Local Ethics Committee approved the study. All steps of the current study followed the 1964 Helsinki Declaration adopted the universal principles. Detailed menstrual anamneses as well as personal data such as age, gravida of all patients with TEP diagnosis code were examined in the database of our gynecology department. The database was then used to identify patients with TEP who were treated with a single dose of Mtx. When multiple applications were detected for the TEP, the first application was recorded for analysis. The patients who were not follow-up were excluded because our primary goal was patients who were under follow-up for the first day and after the TEP. Patients with suspicious obstetric and gynecological history were followed and those who were not followed continuously were excluded from the study. Patients with chronic and systemic diseases such as Diabetes Mellitus, Hypertension, Kroner artery disease, peptic ulcer, hematological and immunological disorders, patients with inflammation and malignancy were removed from the study. Patients being hemodynamically unstable, ruptured and had intrauterine pregnancy, tubal embryonic activity positive, high liver and renal function tests and patients who did not accept mtx treatment were not included. Pregnancy weeks of all patients were confirmed by the last menstrual period. Weight and height were measured according to BMI [Body weight (kg) / height (m^2)] formula. Five milliliters of blood samples were collected at admission and venous blood samples were centrifuged at a rate of 4000 rpm for 10 minutes. Then, serum samples were separated and β-hCG levels were studied using chemiluminescence technique (Advia Centaur, Siemens Ltd). CAP was diagnosed in the case that the serum β-hCG value was> 1500 mIU / mL and the intrauterine pregnancy pouch could not be shown on transvaginal ultrasonography.

The ectopic pregnancy focus was stated when β-hCG value was <1500 mIU / mL, β-hCG increased by less than 60% in 48 hours or there was no chorion villus in pathological examination as a result of dilatation curettage (D / C) and / or β- hCG values are determined by not falling. According to our protocol, cases diagnosed with CAP were hospitalized and treated. Patients were operated within 24 hours of admission and later by a transvaginal ultrasonography specialist gynecologist and radiologist. Serial β-hCG follow-up was performed and the diagnosis was confirmed by diagnostic curettage and / or operative from all cases. Cases with a decrease of> 15% in the β-hCG measurements, clinically stable in our follow-up, were considered in follow-up only although TEP was absorbed. Endometrial abortion was performed. In patients with inadequate increase in series β-hCG measurements or <15% decrease. Daily series β-hCG measurements were continued after endometrial abortion. In our follow-up, a single dose method was used as a medical treatment for treatment of patients, who had given previous approval, with β-hCG level plateau with daily decreased <15% or β-hCG level plateau with increased level, hemodynamically stable, unrebated, asymptomatic. According to our clinical experience, systemic mtx treatment and monitoring with serial β-hCG measurements reduced the need for surgery, thus; it was contributed morbidity and mortality positively. Those who wanted elective surgery were treated with a laparoscopic or open surgery. Mtx treatment was altered considering the single dose protocol (50 mg / m2) and was applied as an

intramuscular (IM) after calculation of the body surface area. The day of administration was considered as Day 0 and serum β-hCG levels were determined on Day 4 and Day 7. Patients with a β-hCG level of> 15% between days 4 and 7 were considered to respond to medical treatment and the β-hCG measurement at day 11 was repeated. Subsequently, weekly β-hCG follow-up was monitored and β-hCG values were controlled by weekly β-hCG follow-up until reaching to negative values (<5 mIU / mL). In some patients, the follow-up period could be 2 months. Patients with an increase in β-hCG levels of> 15% between days 4 and 7 and with a plateau or an increase in their levels were administered IM as an additional mtx (50 mg / m2).

The patients who are in the study were separated into two groups; success and failure and the description of unsuccessful medical treatment: patients with elevated serum β-hCG levels in spite of two doses of mtx (poor response to mtx) and surgery at any stage of the treatment and these patients were identified as cases requiring surgery.

Statistical Analysis

SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) was used to analyze the data collected. Descriptive statistics were presented as the mean ± standard deviation for normal distributed numerical data, median (min-max) for non-specific distributed numerical data number and percentage for categorical data.The conformity of the numerical variables to the normal distribution was evaluated with the Kolmogorov-Simirnov and Shapiro-Wilk tests. It was determined that the numerical variables other than β-hCG change variables between ages and days 4 and 6 were not suitable for normal distribution. In the comparison of the numerical variables, MT-t test was used for normal distributed variables. In non-parametric tests, Mann-Whitney U test was used for independent variables. Diagnostic characteristics of β-hCG on day 0, day 4, and day 7 were evaluated by curve analysis using the Receiver Operating Characteristics (ROC) in predicting the success of Mtx in patients with CAP. Sensitivity and specificity of these limits were calculated in the presence of significant limit values. Type-1 error level below 5% of the diagnostic worth of the test was paraphrased as statistically important

RESULTS

A total of 758 patients diagnosed with CAP underwent a single dose mtx treatment protocol and were diagnosed histologically between January 2009 and December 2017. In the current study, all patients who were considered eligible for Mtx treatment were followed until β-hCG levels returned to normal; this group was accepted as a success group. The left behind 131 patients were operated for intense abdominal pain, acute abdomen or hematological instability and were seen as unsuccessful (Figure **1**) group. Although a number of 627 (82.7%) out of all enrolled patients showed successful Mtx treatment, 131 (17.2%) patients (all had tubal rupture) were not treated with medical treatment. While 517 (82.4%) of the 627 patients who were successful in medical treatment had a single dose, 110 (17.5%) had an additional dose of mtx (Figure **1**).

The groups were similar in terms of age, BMI, gestational age, gravida, parity, TEP size (p = 0.584, p = 0.343, p = 0.238, p = 0.704, p = 0.387, P = 0.139).

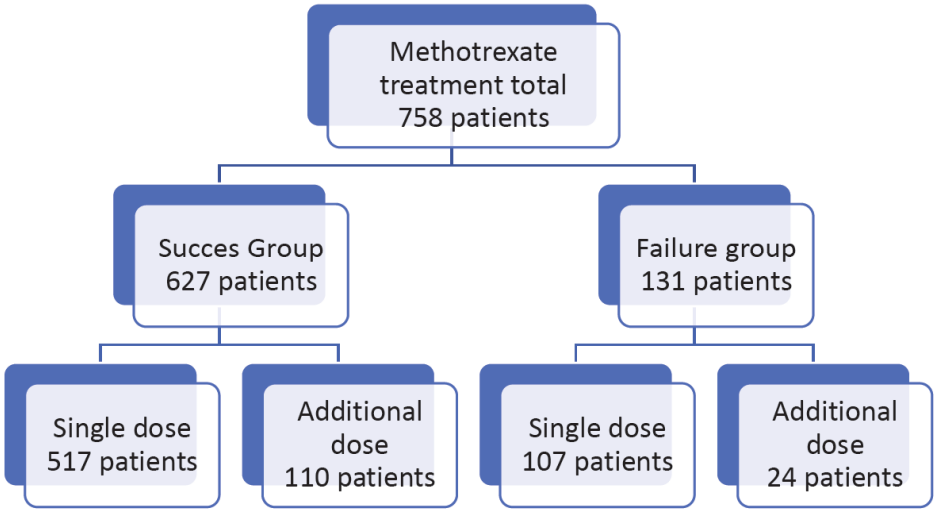

Figure 1: Flow diagram of patients included in the study.

Table 1: Comparison of Baseline Demographics and Clinical Characteristics of Patients with Tubal Ectopic Pregnancies, and b-hCG Trends of Patients (n = 758)

VARIABLES(SD)	Success Group 627(%82,7)	Failure Group 131(%17,2)	p-value
Age (years)	30,53+5,76	30,09+5,21	0,383
BMI(kg/m2)	25.47 ± 2.44	25.64 ± 2.53	0,813
Gestational age (weeks)	5,4 ± 1.8	5.2 ± 1.9	0,238
Gravida	2,75+1,44	2,80+1,46	0,704
Parity	1,12+098	1,23+1,1	0,387
TEP size (mm)	21,5+11,9	23,5+12,8	0,139
Day0 β-hCG mIU/mL	2397,19±7153,8	4263,1±3972,8	<0,001
Day4 β-hCG mIU/mL	2278,6±6416,1	5462,02±5337,5	<0,001
Day7 β-hCG mIU/mL	1699,2±4090,2	4324,1±5322,7	<0,001
Day11 β-hCG mIU/mL	2582,15±4416,63	2507,76±2633,74	0,438
(4/0) change in β-hCG	-2,46±71,9	29,4±41,4	<0,001
(7/4)change in β-hCG	-33,3±25,02	-15,1±26,4	<0,001
(7/0)change in β-hCG	-31,6±45,8**	11,4±51,4**	<0,001
(11/7)change in β-hCG	-36,4±22,8**	-35,06±21,3**	0,563

Data are presented as mean T standard deviation, median (interquartile range), and n(%), where indicated, based on two-tailed Students' t-test, Mann–Whitney U test, and Pearson's χ2. A P value of <0.05 was considered as statistically significant.
Abbreviation: SD, standard deviation; BMI,body mass index; TEP, tubal ectopic pregnancies; hCG, human chorionic gonadotropin.

Table **1** shows the comparison of demographic, clinical characteristics and serum marker levels of single-dose Mtx-treated groups with and without successful treatment.

ROC analysis of β-hCG levels at day 0 showed that the optimum cut-off point for the β-hCG level was 1435 mIU / mL (AUC: 0.734, 95% CI: 0.698-0.780, p <0.001). A cut-off value of sp-1435 mIU / mL β-hCG at day 0 may be considered as a good seer of accomplished medical treatment with Mtx (sensitivity 77% and specificity of 61%) for clinical practice. ROC analysis of β-hCG levels on day 4 showed that β-hCG below 1539 mIU / mL had a diagnostic value in predicting mtx success in patients with CAP (AUC: 0.781, 95% CI: 0.736-0.826, p <0.001) (sensitivity 81% and specificity 68%) (Figure **2**, Table **2**). As a result of the ROC analysis O-4.day, 4-7. day and 0-7.gün β-hCG changes were found to be diagnostic in predicting mtx success in patients with CAP (Figure **3**, Table **2**). 7% reduction in β-hCG values between 0-4 days was found to be successful with 84.1% sensitivity and 77.5% specificity. When the cut-off value of 23% of β-hCG between 4-7 days is taken as cut-off value, the probability of being successful with 79% sensitivity and 63% specificity is shown. When 11% decrease in β-hCG values between 0-7 days is taken as cut off value. 74 sensitivity, 65% specificity was shown to be successful (Figure **3**, Table **2**). As a result of the evaluation with ROC analysis in days 0-4, 4-7 and 0-7, β-hCG changes were found to be diagnostic in predicting mtx success in patients with CAP (Figure **3**, Table **2**). A percentage of 7% reduction in β-hCG values between 0-4 days was found to be successful with 84.1% sensitivity and 77.5% specificity. When the cut-off value of 23% of β-hCG between 4-7 days was taken as cut-off value, the probability of being successful with 79% sensitivity and 63% specificity was observed. When β-hCG values decreased from 0 to 7 days were considered as cut off values, 74% sensitivity and 65% specificity were found to be successful (Figure **3**, Table **2**). Serum β-hcg values on day 0, 4, 7 were significantly higher in mtx-less than mtx-successful group (p <0.001), whereas there was no statistically significant difference between β-hCG values in day 11 (p <0.001). = 438) (Table **1**). The average β-hCG between days 0-4 in the Mtx successful group was decreased by 2.46% while the mtx increased by 29.4% in the unsuccessful group. The difference of β-hCG change between the two groups was statistically significant (p <0.001). The mean β-hCG between days 4-7 was decreased by 33.3% in the MT group and 15% in the MTx unsuccessful group. The mean β-hCG value difference between the two groups in days 4-7 was statistically significant (p <0.001). The average β-hCG between days 0-7 in the

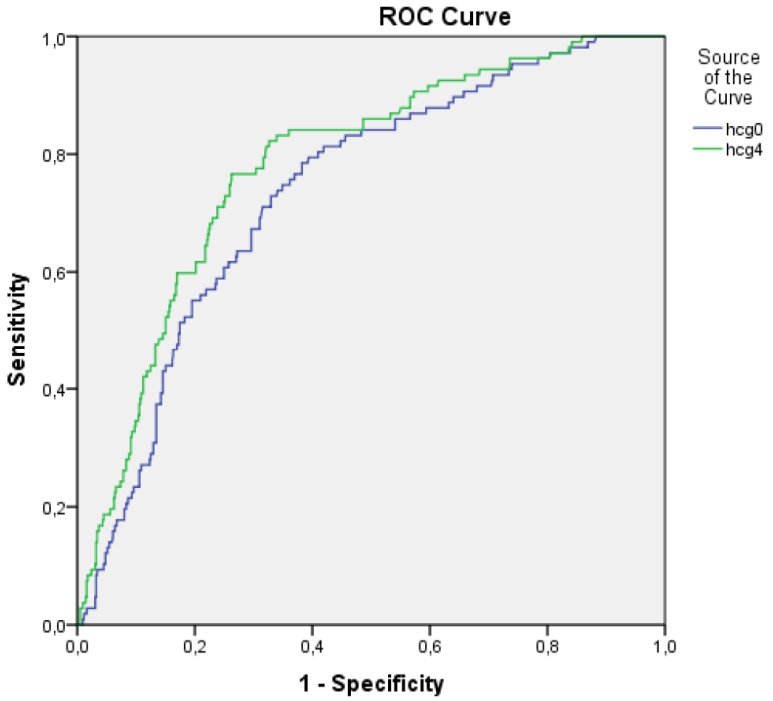

Figure 2: Receiver operating characteristic curve of hCG levels for 0 and 4 days.
Abbreviation: hCG, serum levels of total beta human chorionic gonadotropin.

Table 2: Optimum Thresholds for the Significantly Different Variables

	AUC	Optımum threshold	95%CI	Sensitivity (%)	Specificity (%)
Day0 B hCG mIU/mL	0.734	1435	0.698-0.780	77	61
Day4 B hCG mIU/mL	0.781	1539	0.736-0.82	81	68
Day (4/0)	0.79	1439	0.731-0.832	84	77
Day (7/4)	0.91	1105	0.68-0.901	78	63
Day (7/0)	0.77	1278	0.71-0.88	74	65

Abbreviation: AUC, area under the curve; CI, confidence interval; hCG, human chorionic gonadotropin.

Mtx successful group decreased by 31.6% while the mtx increased by 11.4% in the unsuccessful group. The mean β-hCG value difference between the two groups in days 0-7 was statistically significant (p <0.001). While the mean β-hCG value in the Mtx successful group was decreased by 36.4% between days 7-11, the mean β-hCG decreased by 35,06% in the mtx-failed group. The mean β-hCG difference between the two groups in days 7-11 was not statistically significant (p = 0.563) (Table **1**). In addition, the β-hCG values in days 0-4 and 7 were significantly higher in patients who received an additional dose of Mtx (p <0.001). The difference of β-hCG change was statistically significant (p <0.001) (between days 0-4 and days 4-7) between two groups. The difference in β-hCG between days 0-7 was statistically significant (p <0.001) (Table **3**). There was no significant difference found between β-hCG values and changes between successful and unsuccessful groups after recurrent mtx dose (Table **4**).

DISCUSSION

The elevation in EP occurrence in recent years is due to progresses in early diagnosis methods, more conscious physicians and an increase in risk factors. TEP cases are still difficult to be diagnosed in the early stages due to lack of clinical symptoms in approximately one third of all cases. In addition, approximately half of the cases with a suspected EP are not diagnosed despite screening tests, β-hCG determination and resolution of ultrasonography. Series β-hCG valuation involves the participation of many clinics [16]. There are several difficulties in the separation of unsuccessful early uterine pregnancies

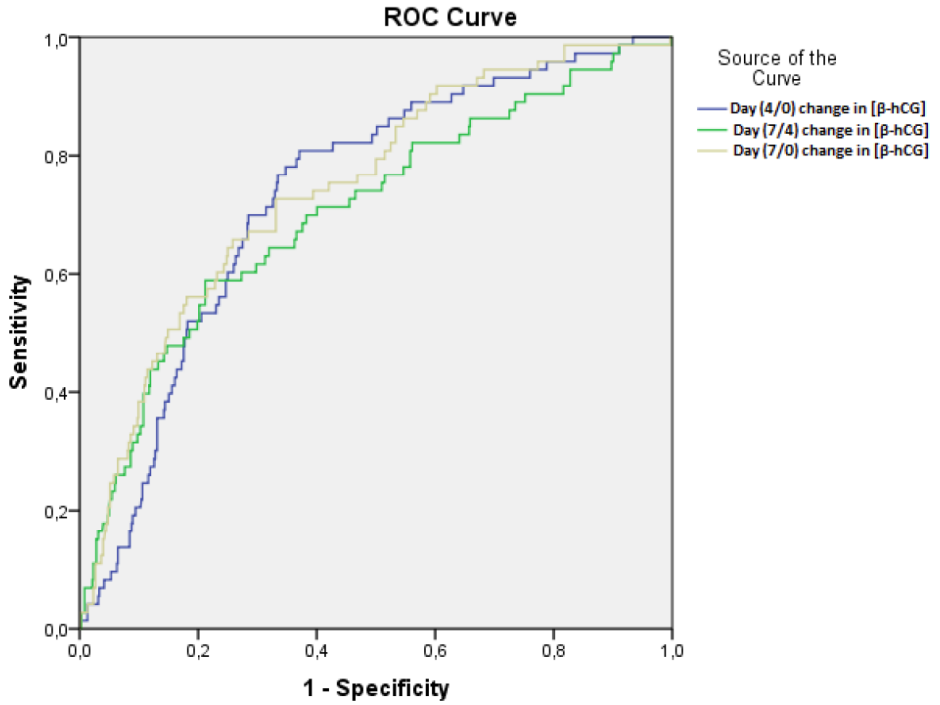

Figure 3: Receiver operating characteristic curve for changes in hCG levels between 0-4 days and 0-7 days.
Abbreviation: hCG, serum levels of total beta human chorionic gonadotropin.

Table 3: Comparison of Descriptive Findings and β-hCG Levels According to Mtx Dose Numbers

β-hCG((mIU/mL)	Single dose (624)	Additional dose (134)	p-value
Day0	2597,9±7125,2	3288,3±4575,6	<0,001
Day4.	2389,5±6367,9	4325,4±6140,3	<0,001
Day7	1490,4±3791,8	3978,7±5567,5	<0,001
Day(4/0)	-5,07±73,1	34,6±32,7	<0,001
Day(7/4)	-37,45±24,2	-6,89±15,1	<0,001
Day(11/7)	-39,87±41,54	25,42±37,47	<0,001

A Data are presented as mean standard deviation and median (interquartile range), where indicated, based on two-tailed Students' t-test and Mann–Whitney U test. A P value of <0.05 was considered as statistically significant.

Table 4: Mtx Comparison of β-hCG levels according to Mtx success in the patients who were given additional doses

β-hCG((mIU/mL)	Success Group (110)	Failure Group (24)	p-value
Day0	3267,5±4858,8	3372,3±3029,2	0,192
Day4	4552,8±6463,3	4658,8±4461,8	0,182
Day7	3917,1±5846,3	4260,8±4142,6	0,438
(4/0) change in β-hCG	34,4±34,2	35,7±25,3	0,503
(7/4) change in β-hCG	-6,68±14,3	-7,83±18,9	0,910
(7/0) change in β-hCG	25,8±39,3	23,3±27,5	0,713
(11/7) change in β-hCG	-36,4±22,8	-35,06±21,3	0,796

Data are presented as mean standard deviation, median (interquartile range), and n(%), where indicated, based on two-tailed Students't-test and Mann–Whitney U test. A P value of <0.05 was considered as statistically significant.

(imcomplet abortus, complete abortion, missed abortion, etc.) from TEP. Therefore, diagnosis, treatment and follow-up of CAP are both psychologically discouraging and time-consuming and costly for patients who receive health care [7,8]. The methods that can accurately identify the CAP and the patient will be followed less frequently during follow-up will provide an important clinical progress in the management of the disease starting from the first admission of the patient. Ca 125, which is a marker of peritoneal irritation besides progesterone abortion, has been suggested in the diagnosis of TEP. Additionally, in increased cytokines secreted as a result of inflammation in TEP have been suggested to be important in diagnosis of this disease. A study by Soriano *et al*. showed increased levels of IL-6 and IL-8 in TEP cases [17]. A rapid affordable and inexpensive biomarker to diagnose cases in TEP-suspected cases has still not been found.

Nowadays, there has been a transition from surgical treatment to medical treatment in the treatment of the disease. In medical treatment, different kinds of administration protocols are used in clinical practice, single-, two-, and fixed-dose regimens. Single dose treatment regimens that simplify treatment and increase compliance are the most commonly used protocol [10]. The success rate of single dose Mtx treatment in asymptomatic TEP is reported between 52-94% [12] while the success rate of our single dose mtx treatment regimen was 75%. The rate of regression for TEP is similar for both single dose and multiple doses, and there are more side effects in multiple dose protocols. Patients receive less income and fewer injections. Factors that are playing a role in Mtx treatment failure are defined as existence of fetal cardiac activity in adnexes, size of the mass exceeding 4 cm, increased β-hCG level over 5000 mIU / mL, presence of free blood in the peritoneum, β-hCG concentration increasing more than 50% within 48 hours prior to mtx treatment and increased β in spite of mtx treatment -hCG concentration [18]. The most noticeable factor among these factors has been introduced to be the high level of β-hCG at the beginning of treatment. As the level of β-hCG increases, the success rates decrease. Lipscomb *et al*. found that 350 patients were successfully enrolled in a single dose of mtx treatment. A study on TEP demonstrated that serum β-hCG levels were the only and best prognostic factor affecting failure. While, the size and volume of the mass, the size of the hematoma, and the presence of free peritoneal fluid in the pelvis were not important risk factors for the failure of the treatment [19]. In the series of 503 patients published by Menon *et al*., It was found that the probability of failure of medical therapy to be started in β-hCG values higher than 5000 mIU / mL was higher than those with high baseline β-hCG values [20]. Novak-Markwitz *et al*. represented a cut off value and found a high failure rate above 1790 mIU / mL [21]. Although success rates of medical treatment with serum β-hCG values were closely related, Natale *et al*. put forward that these changes in β-hCG levels reflect differences in folic acid metabolism among individuals [22]. However, due to the fact that our series is the largest in the literature, we found that the β-hCG cut off level is a valid value. In our study, he treatment success was found to to be higher (77% sensitivity and 61% specificity) when the initial β-hCG cut-off value was below 1435. In day 4 of mtx, we found that the β-hCG value below 1539 mIU / mL could increase the success rate (81% sensitivity and 68% specificity). In our study, the β-hCG values of the days 4-7 were significantly lower in the medically treated group than in the unsuccessful group. The chances of success in treatment and the need for extra mtx doses could be estimated based on the mean β-hCG change from Day 1 to Day 4. In some studies, in addition to the initial β-hCG value, the decrease in baseline and β-hCG values on day 4 after mtx was the most important prognostic factor in predicting success. In our study, β-hCG levels between days 0-4 of the treatment decreased significantly compared to the increase in the unsuccessful group. Agostini *et al*. reported that a 20% decrease in β-hCG levels between days 0-4 predicted a successful outcome with a positive predictive value of 97% [23]. In a study by Çelik *et al*. with 93 patients with a failure of a 9.08% reduction in β-hCG values in days 0-4, treatment failure was increased up to 4.94-fold [24]. Similarly, Ustunyurt *et al*. informed a reduction in β-hCG of 22% predicting treatment success [25].

In our study, β-hCG showed mtx success in days 0-4 up to 7% and it confirmed the fact that the number of our enrolled subjects increased the reliability of our series.

According to the configurations, in the case that there was a decrease of β-hCG less than 15% at day 7 or any increase in β-hCG concentration, the treatment protocol was repeated [20,21]. In our study, in days 4-7 and days 0-7, 23% and 36% and more decrease were successfully predicted.Cohen *et al*. set an additional dose of mtx - yen; if the cut-off value of β-hCG was

above 2234mIU / mL, it was suggested that the success rate of an additional dose of mtx was low [26]. In another study by Atkinson *et al*. 88 within the β-hCG falls from Day 4 to Day 7, were in need of an additional dose of mtx, superior to Day 1 to Day 4 [27]. In our series, 134 patients (18%) could take an additional dose of mtx. In-group analyzes of the group receiving an additional mtx dose, the first level of h-hCG levels showed a significant difference between the level of successful and unsuccessful groups. In our study, the β-hCG values at days 0, 4 and 7 taking additional dose were significantly higher than those taking single doses. On the other hand, the cost of patient treatment negatively influenced the long-term hospital follow-up outcoms.

According to significant results related to the efficacy of series, β-hCG measurements on days 0 and 4 in predicting treatment success, we did not need to evaluate β-hCG for 7 days if there was a low value when we were on day 0 and on day 0 and day 4 and 0 on day 0 and 4.According to the important results related to the efficacy of serial β-hCG measurements on days 0 and 4, if there was decreased levels of β-hCG on days 0 and 4, we did not need to evaluate β-hCG value for day 7.

Despite the high sensitivity and specificity required for the use of the percentages in our study in daily practice, these findings suggested that the adversity should be eliminated by advocating our suggestion above. Firstly, our study did not provide a retrospective design comparison in some cases. We have excluded the various obstetric and medical conditions with the potential for environmental impacts to be examined and reduced the sample size. In addition, all of the samples were analyzed during the study period and by the same tool for the entire study group. Furthermore, this study was conducted in a single institution. Our study is valuable because it is one of the largest patient series reports. The results of our assessment will be strengthened as the target of multicenter studies. We recommended that β-hCG follow-up on day 7 of series β-hCG measurements should be discontinued. In addition to co-hCG follow-ups, fertility status, clinical and laboratory findings in the room should be considered in the case of planning appropriate treatment.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

FINANCIAL DISCLOSURE

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