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METOTREKSAT TEDAVİSİ ALAN EKTOPİK GEBELİKLERDE RÜPTÜRÜ ETKİLEYEN RİSK FAKTÖRLERİ: RETROSPEKTİF BİR ÇALIŞMA

RISK FACTORS INFLUENCING RUPTURE IN METHOTREXATE-TREATED ECTOPIC PREGNANCIES: A RETROSPECTIVE STUDY

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ÖZET

AMAÇ: Bu retrospektif çalışmanın amacı, metotreksat (MTX) ile tedavi edilen ektopik gebeliklerde rüptürü öngören klinik ve biyokimyasal risk faktörlerini belirlemek ve medikal veya cerrahi tedavi kararlarını yönlendirmektir.

GEREÇ VE YÖNTEM: Çalışmaya MTX tedavisi almış toplam 284 ektopik gebelik vakası dahil edildi. Bu hastalardan 50'si rüptür nedeniyle cerrahi müdahaleye ihtiyaç duymuştur, 234'ü ise yalnızca medikal tedavi ile başarıyla izlenmiştir. Veriler IBM SPSS Statistics 22 programı ile analiz edilmiştir. İncelenen değişkenler; demografik özellikler (yaş, parite), obstetrik ve cerrahi öykü (abortus, önceki ektopik gebelik, karın ameliyatları), son adet tarihine göre gebelik haftası, kan grubu, rahim içi araç (RİA) varlığı, semptomlar, fetal kalp atımı (FKA), ektopik odak boyutu, Douglas boşluğunda sıvı varlığı, endometriyal kalınlık, beta-hCG düzeyleri ve patoloji sonuçlarıdır.

BULGULAR: Cerrahi müdahale gerektiren hastalarda, medikal tedavi ile başarı sağlananlara kıyasla ektopik odak boyutları ($p < 0,01$), endometriyal kalınlık ($p < 0,01$), başlangıç (1. gün) ve takip beta-hCG (4-7. günler) düzeyleri ($p < 0.001$), fetal kalp atımı (FKA) görülme oranı ($p < 0,01$) ve önceki over/tubal cerrahi öyküsü ($p < 0,05$) anlamlı olarak daha yüksek bulundu. Ayrıca bu grupta karın ağrısı şikâyeti daha sık görülürken ($p < 0,01$), vajinal kanama şikâyeti anlamlı düzeyde daha düşük olarak saptandı ($p < 0,05$).

SONUÇ: Ektopik kitle boyutu, endometriyal kalınlık, yüksek beta-hCG seviyeleri, FKA varlığı ve önceki over/tüp cerrahisi, MTX ile tedavi edilen ektopik gebeliklerde rüptür riskini öngörmede önemli göstergelerdir. Bu risk faktörleri, medikal tedavi planlanmadan önce dikkatle değerlendirilmelidir.

ANAHTAR KELİMELER: Rüptür, Ektopik Gebelik, Metotreksat Tedavisi, Tubal Cerrahi.

ABSTRACT

OBJECTIVE: This retrospective study aimed to identify clinical and biochemical factors that predict rupture in ectopic pregnancies treated with methotrexate (MTX) and to guide treatment decision-making between medical and surgical approaches.

MATERIAL AND METHODS: A total of 284 patients diagnosed with ectopic pregnancy and initially treated with MTX were included. Among them, 50 patients required subsequent surgical intervention due to rupture, while 234 patients were successfully managed with MTX alone. Data were analyzed using IBM SPSS Statistics version 22. Variables assessed included demographic characteristics (age, parity), obstetric and surgical history (abortion, previous ectopic pregnancy, prior abdominal surgeries), gestational age, blood type, presence of intrauterine device (IUD), presenting symptoms, fetal cardiac activity (FCA), size of ectopic mass, Douglas pouch fluid, endometrial thickness, serial beta-hCG levels, and pathology results.

RESULTS: Patients who required surgical intervention had significantly larger ectopic mass sizes ($p < 0.01$), increased endometrial thickness ($p < 0.01$), higher initial (day 1) and follow-up (days 4-7) beta-hCG levels ($p < 0.001$), more frequent presence of fetal cardiac activity ($p < 0.01$), and a greater history of prior ovarian or tubal surgery ($p < 0.05$) compared to those successfully treated medically. Additionally, abdominal pain was more common in the surgical group ($p < 0.01$), while vaginal bleeding was less frequent ($p < 0.05$).

CONCLUSIONS: Ectopic mass size, endometrial thickness, elevated beta-hCG levels, presence of fetal cardiac activity, and prior tubal or ovarian surgery are significant predictors of rupture in ectopic pregnancies treated with MTX. These risk factors should be carefully evaluated before initiating medical management to reduce the risk of treatment failure and adverse outcomes.

KEYWORDS: Rupture, Ectopic Pregnancy, Methotrexate Treatment, Tubal Surgery.

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INTRODUCTION

An ectopic pregnancy is defined as the implantation of a fertilized ovum outside the endometrial cavity. In approximately 97% of cases, this occurs in various segments of the fallopian tubes, such as the ampullary, fimbrial, isthmic, or interstitial regions. Less commonly, implantation may occur in the cervix, ovary, previous cesarean scar, or peritoneal cavity (1). Ectopic pregnancy is a leading cause of maternal morbidity and mortality during the first trimester, and its prevalence is increasing worldwide. However, determining accurate incidence rates is challenging due to a decline in inpatient management and an increase in multiple hospital admissions per cases (2).

The primary etiology of ectopic pregnancy involves disruption of normal tubal anatomy, often due to tubal surgery or infection, which impairs the ciliary function necessary for ovum transport (3). A combination of clinical history, physical examination, transvaginal ultrasonography (TVUS), and serial measurement of serum β-hCG levels is recommended to facilitate early and accurate diagnosis (4). In cases where the diagnosis is unclear or complex, additional diagnostic tools may be employed, including Doppler imaging, magnetic resonance imaging (MRI), culdocentesis, and diagnostic laparoscopy (5).

The treatment approach for ectopic pregnancy is determined by various factors, including the patient's clinical condition, serum β-hCG levels, ultrasonographic findings (such as size and location of the ectopic gestational sac), hemodynamic stability, rupture status, and future fertility or contraceptive preferences (6). Management strategies are typically categorized into three approaches: expectant management, medical therapy (e.g., methotrexate), or surgical intervention (e.g., salpingectomy or salpingostomy). The selection of the most appropriate strategy depends on patient suitability and personal preferences (4).

Effective management of ectopic pregnancy remains a critical clinical challenge. The present retrospective study evaluated demographic, clinical, biochemical, and radiological parameters in patients with ectopic pregnancy treated with methotrexate. Parameters analyzed included maternal age, gravidity, parity, abortion history, prior ectopic pregnancy, previous abdominal surgery, gestational age by last menstrual period, blood group, clinical presentation, and ultrasonographic findings such as fetal cardiac activity, ectopic mass size, Douglas pouch fluid presence, and endometrial thickness. Serial serum β-hCG levels, histopathological results from dilatation and curettage, and definitive postoperative pathology reports were assessed for their predictive value regarding treatment success. The study also examined whether specific clinical and biochemical parameters could reliably indicate tubal rupture, thereby informing the choice between medical and surgical management.

MATERIALS AND METHODS

This retrospective study analyzed records of 284 patients hospitalized with ectopic pregnancy who received methotrexate treatment at the Gynecology and Obstetrics Department of Health Sciences University Ümraniye Training and Research Hospital between January 1, 2013, and June 30, 2018. Patients were divided into two groups: The study group comprised 50 patients who underwent MTX treatment but subsequently required surgical intervention due to rupture, while the control group included 234 patients who were successfully managed with MTX alone without requiring surgery. The inclusion criteria were women aged 17-44 years diagnosed with ectopic pregnancy, treated with methotrexate, with complete follow-up data including surgical or medical outcomes, and definitive pathology confirming the diagnosis. Exclusion criteria included patients who underwent immediate surgical intervention without receiving MTX treatment or those whose final pathology results were inconsistent with ectopic pregnancy. Data collected from patient files included demographics (age, gravidity, parity), obstetric and surgical history (abortion history, previous ectopic pregnancy, previous abdominal surgery), gestational age by last menstrual period, blood group, IUD presence, presenting complaints, ultrasonographic findings (fetal cardiac activity, ectopic mass dimensions, Douglas pouch fluid presence, endomet-

rial thickness), serial beta-hCG values, dilatation and curettage pathology results, and definitive postoperative pathology findings. Both groups received a single intramuscular dose of MTX at 50 mg/m^2 intramuscularly. A second dose of 50 mg/m^2 was administered in 32 patients (13.6%) in the control group and 15 patients (30%) in the study group based on established criteria for persistent or rising beta-hCG levels.

Ethical Committee

The Clinical Research Ethics Committee of Health Sciences University Ümraniye Training and Research Hospital approved the study on October 17, 2018 (approval number: 122).

Statistical Analysis

IBM SPSS Statistics 22 (2013) software was used to analyze the study's findings. The Shapiro-Wilks test was used to evaluate the normality of the data. Analytical methods included descriptive statistics (frequencies, standard deviations, means), Student's t-test for normally distributed parameters between groups, and the Mann-Whitney U test for non-normally distributed parameters. Fisher's Exact test, Fisher-Freeman-Halton test, and Chi-square test facilitated qualitative data comparisons. Statistical significance was established at $p<0.05$.

RESULTS

The study population comprised two groups: 50 (17.6%) patients who underwent MTX treatment and subsequently required surgical intervention due to rupture, and 234 (82.4%) patients who underwent MTX treatment but did not require surgical intervention. The mean age of the participants was 29.88 years (±5.49 years). No statistically significant differences were observed between the groups with regard to age, gestational age calculated based on the last menstrual period, gravidity, parity, number of abortions, history of vaginal deliveries, history of previous caesarean sections (C/S), history of previous ectopic pregnancies, or amount of Douglas fluid ($p>0.05$) **(Table 1)**.

Ectopic pregnancy focus dimensions were significantly larger in patients requiring post-MTX surgical intervention due to rupture compared to those successfully managed with MTX alone ($p<0.001$) Table 1. Endometrial thickness measurements were significantly greater in patients requiring post-MTX surgical intervention due to rupture compared to those not requiring surgery ($p=0.002$) Table 1.

Table 1: Evaluation of general characteristics between groups

	Surgical Intervention Required (n=50)	No Surgical Intervention (n=234)	p
	Mean ± SD	Mean ± SD	
Age, year	29.74±6.1	29.91±5.37	[1]0.839
Gestational week according to last menstrual period	6.03±1.8	5.72±2.15	[1]0.410
Gravidity	2.86±1.64	2.8±1.37	[2]0.880
Parity	1.12±1.19	1.28±1.1	[2]0.254
Abortion	0.58±1.09	0.44±0.82	[2]0.591
History of vaginal delivery	0.72±1.13	0.79±1.04	[2]0.527
History of previous cesarean section	0.4±0.73	0.49±0.79	[2]0.439
History of previous ectopic pregnancy	0.16±0.55	0.09±0.31	[2]0.778
Ectopic mass size (mm)	21.02±9.16	12.08±11.1	[1]0.000*
Amount of Douglas pouch fluid (mm)	12.66±15.78	14.94±17.45	[2]0.510
Endometrial thickness (mm)	12.04±6.48	8.77±5.2	[1]0.002*
Blood groups	n(%)	n(%)	p
A Rh positive	18 (36%)	87 (37.2%)	[3]0.881
B Rh positive	9 (18%)	36 (15.4%)	
AB Rh positive	3 (6%)	22 (9.4%)	
O Rh positive	14 (28%)	56 (24%)	
A Rh negative	4 (8%)	12 (5.1%)	
B Rh negative	0 (0%)	5 (2.1%)	
AB Rh negative	0 (0%)	1 (0.4%)	
O Rh negative	2 (4%)	15 (6.4%)	

*[1]Student t test [2]Mann whitney U test [3]Fisher freeman halton test *p<0.05*

Table 2 displays the distribution of surgical procedures performed, previous surgical history, and presents complaints among patients who received MTX therapy but subsequently required surgical intervention due to rupture. Among patients with rupture, unilateral salpingostomy was performed in 1 case (2%), and salpingectomy was performed in the remaining patients. Salpingectomy was bilateral in 4% of cases and unilateral in the remaining cases (58% right-sided, 36% left-sided). Surgical approaches included open procedures in 52% and laparoscopic approaches in 48% (Table 2).

The prevalence of previous ovarian and tubal surgery was significantly higher among patients requiring post-MTX surgical intervention for rupture (8%) compared to patients successfully managed with MTX alone (0.9%) ($p=0.025$) (Table 2). While 25% of all ectopic pregnancy patients presented without significant complaints, 74.6% reported bleeding and/or abdominal pain. Bleeding predominated in patients without rupture, whereas abdominal pain was more frequent in patients with rupture ($p=0.042$; Table 2).

Table 2: Group Comparison of Operations Performed, Previous Operations, and Complaints.

	Surgical Intervention Required	No Surgical Intervention	*Total*	p
	n (%)	n (%)	n (%)	
Operations Performed				
Right salpingectomy	15 (30%)	-	15 (30%)	-
Left salpingectomy	10 (20%)	-	10 (20%)	
Laparoscopic right salpingectomy	14 (28%)	-	14 (28%)	
Laparoscopic left salpingectomy	8 (16%)	-	8 (16%)	
Bilateral laparoscopic salpingectomy	2 (4%)	-	2 (4%)	
Left salpingostomy	1 (2%)	-	1 (2%)	
Previous operations				
None	16 (32%)	42 (17.9%)	58 (20.4%)	**[1]0.025***
Cesarean section (C/S)	12 (24%)	65 (27.8%)	77 (27.1%)	
Ovarian and tubal surgery	4 (8%)	2 (0.9%)	6 (2.1%)	
Other abdominal surgery	1 (2%)	5 (2.1%)	6 (2.1%)	
Unknown	16 (32%)	101 (43.2%)	117 (41.2%)	
Other	1 (2%)	7 (3%)	8 (2.8%)	
C/S + Ovarian and tubal surgery	0 (0%)	9 (3.8%)	9 (3.2%)	
C/S + Other abdominal surgery	0 (0%)	3 (1.3%)	3 (1.1%)	
Presenting Complaints				
None	19 (38%)	52 (22.2%)	71 (25%)	**[2]0.042***
Vaginal bleeding	12 (24%)	82 (35%)	94 (33.1%)	
Abdominal pain	16 (32%)	59 (25.2%)	75 (26.4%)	
Vaginal bleeding + Abdominal pain	3 (6%)	40 (17.1%)	43 (15.1%)	
Delayed menstruation	0 (0%)	1 (0.4%)	1 (0.4%)	

*[1]Fisher freeman halton test; [2]Ki-kare test; *p<0.05*

Table 3 presents comparisons of beta-hCG parameters between groups. Day 1, 4, and 7 beta-hCG values were significantly elevated in patients requiring post-MTX surgical intervention due to rupture compared to those successfully managed with MTX alone (p<0.001) Table 3. The mean time to a negative beta-hCG result was 33.66 days, with a maximum of 114 days Table 3. Following second-dose MTX administration, day 1, 4, and 7 beta-hCG values remained significantly higher in patients requiring surgical intervention due to rupture compared to those not requiring surgery (p=0.002) Table 3.

Table 3: Evaluation of Beta-hCG Levels (mIU/mL) Between Groups.

	Surgical Intervention Required	No Surgical Intervention	p
	Mean ± SD	Mean ± SD	
Day 1	8668.84±9268.64	2611±3883.79	**0.001***
Day 4	9136.45±6196.79	2409.85±4052.06	**0.001***
Day 7	7407.73±6471.66	1930.31±4213.92	**0.001***
Week 2	-	844.11±1994.41	-
Week 3	-	246.35±555.77	-
Week 4	-	196.14±862.73	-
Week 5	-	61.04±121.34	-
Week 6	-	55.67±91.54	-
Time to beta hCG negativity. (days)	-	33.66±17.61	-
Second Dose MTX-Day 1 beta hCG (mIU/mL)	9812.58±6212.38	4807.58±7153.05	**0.002***
Second Dose MTX-Day 4 beta hCG (mIU/mL)	9412.67±4927.28	3580.61±5597.7	**0.001***
Second Dose MTX-Day 7 beta hCG (mIU/mL)	6158.6±2423.44	2146.13±3547.63	**0.002***

*Mann whitney U test; *p<0.05*

Fetal cardiac activity was detected significantly less commonly in non-ruptured ectopic pregnancies (3.4%) compared to patients with rupture (18%) (p=0.001) **(Table 4)**.

Table 4: Group Comparison of MTX Parameters, Fetal Cardiac Activity, D&C Pathology Result, and intrauterine Device (IUD) Presence.

	Ruptured Ectopic	Unruptured Ectopic	p
Day difference between first MTX dose and rupture Mean±SD	7.04±6.15	-	-
Day difference between second MTX dose and rupture Mean±SD	6.73±5.47	-	-
Fetal cardiac activity *n(%)*			
Absent	41 (82%)	226 (96.6%)	**[2]0.001***
Present	9 (18%)	8 (3.4%)	
D&C pathology result *n(%)*			
None	23 (46%)	112 (47.9%)	**[3]0.811**
Compatible with ectopic pregnancy	27 (54%)	122 (52.1%)	
Intrauterine device (IUD) *n(%)*			
No	47 (94%)	213 (91%)	**[2]0.779**
Yes	3 (6%)	21 (9%)	

*[1]Student t test; [2]Fisher's exact test; [3]Ki-kare test; *p<0.05*

ROC curve analysis identified an optimal beta-hCG cut-off value of 3524 mIU/ml for predicting rupture in patients who received MTX treatment and subsequently required surgical intervention (AUC = 0.856, 95% CI: 0.787–0.925). At this threshold, the sensitivity was 81% and the specificity was 80%, demonstrating good discriminatory power for identifying patients at high risk of rupture **(Figure 1)**.

Positive if Greater Than or Equal To[a]	Sensitivity	1 - Specificity
3524,00	,816	,198

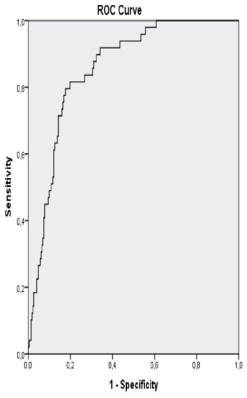

Figure 1: ROC curve and numerical equivalent ofbeta-hCG values in study

DISCUSSION

This retrospective study evaluated clinical and biochemical factors that may predict rupture in ectopic pregnancies treated with methotrexate (MTX). Patients who required surgical interven-

tion after MTX treatment exhibited increased endometrial thickness, higher beta-hCG levels, and significantly larger ectopic masses compared to those managed successfully with MTX alone. Additionally, a history of ovarian or tubal surgery and the presence of fetal cardiac activity (FCA) were more prevalent in this group. Abdominal pain was reported more frequently among patients who experienced rupture, whereas vaginal bleeding was less common. Careful assessment of these parameters is essential when considering MTX medical treatment to minimize the risk of treatment failure and rupture.

Ectopic pregnancy remains one of the leading causes of maternal mortality and morbidity in the first trimester. It occurs in 1% to 2% of all pregnancies, with an increasing incidence in populations undergoing assisted reproductive techniques (7). Current epidemiological data indicate that the prevalence of ectopic pregnancy ranges from 1% to 2% in the United States and that 2.7% of pregnancy-related deaths are caused by ruptured ectopic pregnancy (8). In developed countries, ectopic pregnancy rates are reported as approximately 19 cases per 1000 pregnancies (9). Transvaginal ultrasonography and serum beta-hCG measurement have enabled early diagnosis. They have also improved treatment outcomes by facilitating the choice between medical treatment and surgical approaches (10). It is very important to identify the clinical and biochemical determinants of rupture to minimize complications and identify patients suitable for methotrexate treatment. Previous studies have identified a history of ectopic pregnancy as a risk factor for both rupture and methotrexate treatment failure (11). In the current study, the prevalence of ectopic pregnancy history was 10% among patients who required surgical intervention after methotrexate treatment failure; however, this association was not statistically significant in predicting rupture.

Advancements in diagnostic capabilities and treatment protocols have significantly improved the medical management of ectopic pregnancy. Recent systematic reviews report medical treatment success rates ranging from 70% to 95% in appropriately selected patients (12–14). Early diagnosis through routine ultrasound and beta-hCG monitoring is supported by current evidence and has been shown to improve treatment outcomes. In this study, 82.4% of patients who began medical treatment for ectopic pregnancy were successfully managed without surgical intervention, aligning with findings in the existing literature.

The rate of ectopic pregnancy increases with advanced maternal age. A large cohort study has shown that the incidence of ectopic pregnancy is highest in women over the age of 40 (15). The role of maternal age in the risk of rupture following methotrexate (MTX) treatment remains controversial. Recent studies examining the relationship between age and rupture risk have yielded inconsistent results, indicating that further research is needed in this area. Recent studies have demonstrated that factors such as initial β-hCG levels, ectopic mass size, and the presence of free fluid are not associated with treatment outcomes, apart from age (16). In this study, however, no statistically significant difference in age was observed between the groups.

Large ectopic pregnancy sizes (≥3.5 cm) have traditionally been considered a contraindication for medical treatment, but this restriction is primarily based on older protocols that used conservative size criteria (17). Recent evidence suggests that the size of the ectopic mass is not associated with the success of methotrexate treatment, casting doubt on the exclusion criteria based on the size of the established mass. Recent studies report success rates of approximately 74% to 93% with single-dose methotrexate therapy (13,18,19). Careful patient selection is considered more important than strict size limitations. Various studies have documented success rates from 67% to 100% when strict selection criteria are applied (20). Current research indicates that initial β-hCG levels, presence of free fluid, and fetal heart activity may be more reliable predictors of treatment failure than mass size alone. Serial transvaginal ultrasound monitoring indicates that ectopic masses can be effectively managed with methotrexate. Therefore, mass size alone should not be considered an absolute contraindication to medical management in appropriately selected patients (21,22).

In this study, ectopic pregnancy focus sizes were significantly larger in patients requiring surgical intervention due to rupture after MTX compared to those successfully treated with MTX.

Our study showed that endometrial thickness was significantly greater in patients requiring surgical intervention for tubal rupture after MTX than in those successfully treated with MTX. In a study by Taşgöz and colleagues, results consistent with ours were reported. These findings showed that endometrial thickness was significantly higher in the unsuccessful treatment group (23).

Laparoscopy is currently preferred for surgical management when feasible. Recent meta-analyses have confirmed the advantages of salpingectomy over salpingostomy for subsequent pregnancies in appropriately selected patients (24). In this study, 49 of 50 patients (98%) underwent salpingectomy, with 24 procedures performed by laparoscopy (49%) and 25 by open surgery (51%). Only one patient (2%) underwent salpingostomy. These findings suggest a preference for salpingectomy over salpingostomy in cases where fertility preservation is not prioritized.

The prevalence of previous ovarian and tubal surgery was significantly higher in patients requiring surgical intervention for rupture following methotrexate (MTX) treatment (8%) compared to those successfully treated medically (0.9%).

In a retrospective observational study, the proportion of women with abdominal pain was significantly different between the ruptured and unruptured ectopic pregnancy groups (25). In a different study, abdominal pain was identified as the most prevalent symptom among the clinical features, while vaginal bleeding was the second most common symptom in patients (26). In the present study, 25% of patients with ectopic pregnancies did not present significant symptoms, while 74.6% reported bleeding and/or abdominal pain. The occurrence of haemorrhaging was more frequent in patients without rupture, while abdominal pain was more prevalent in patients with rupture.

Recent studies have consistently demonstrated a strong association between high beta-hCG levels and the risk of ectopic pregnancy rupture. Current research indicates that the most important determinant of methotrexate treatment failure is initial beta-hCG levels, with higher levels associated with increased rupture rates (27). A large cohort study has shown that patients with a beta-hCG level of more than 5,000 mIU/mL are significantly more likely to experience treatment failure than patients with lower levels (16).

Current evidence has established beta-hCG thresholds for predicting rupture. A recent meta-analysis confirmed that serum beta-hCG levels exceeding 2,000 mIU/mL are associated with increased risk of rupture and treatment failure (28). In this study, the median baseline beta-hCG level was 5,332 mIU/mL among patients requiring post-methotrexate (MTX) surgical intervention for rupture, compared to 1,326.5 mIU/mL among those successfully managed medically. A tubal rupture threshold of 3,524 mIU/mL was identified, with 81% sensitivity and 80% specificity. Considering this threshold when selecting a treatment modality may reduce mortality and morbidity and improve treatment efficacy.

Following the administration of MTX, beta-hCG negativity usually occurs within 2–8 weeks, and most patients reach undetectable levels within 5 weeks. Recent cohort studies report a mean time to beta-hCG negativity of 22-34 days, with occasional cases of prolonged resolution extending to 12 weeks (29). In our study, the average duration of beta-hCG negativity was 33,66 days, with a maximum of 114 days, and these results are consistent with current findings.

The detection of fetal cardiac activity (FCA) remains a significant predictor of treatment failure, occurring in 30% of unsuccessful cases compared to 12% of successful treatments (11,22). Contemporary guidelines still consider FCA a relative contraindication to medical management, given its higher failure rates and increased risk of rupture (1). Our investigation found a significantly higher prevalence of FCA among patients requiring post-MTX surgical intervention for rupture (18%), compared to those who were successfully managed medically (3.4%).

In conclusion, this investigation identified a significantly higher prevalence of prior tubal surgery, elevated beta-hCG values, presence

of fetal cardiac activity, larger ectopic pregnancy dimensions, and increased endometrial thickness among patients who experienced rupture following MTX treatment. The identified rupture threshold of 3524 mIU/mL, with 81% sensitivity and 80% specificity, offers valuable clinical guidance for risk stratification and treatment planning.

This study has several limitations. Most notably, its retrospective design may introduce selection and information biases, potentially limiting the ability to establish causality. The research was also conducted at a single center, which may limit the generalizability of the results to broader populations. In addition, the relatively small number of patients who experienced rupture may have reduced the statistical power to detect subtle differences between groups.

Despite these limitations, this study adds to the literature by identifying key clinical and biochemical predictors, including ectopic mass size, endometrial thickness, beta-hCG levels, presence of fetal cardiac activity, and history of ovarian or tubal surgery, that are significantly associated with rupture risk in ectopic pregnancies treated with methotrexate. These findings may support clinicians in making evidence-based treatment decisions and selecting suitable candidates for medical management, thereby enhancing patient safety and treatment outcomes.

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