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Article

Predictors of Methotrexate Failure and Tubal Rupture in Patients With Tubal Ectopic Pregnancy: A Retrospective Cohort Study

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Abstract

Aims/Background: Tubal ectopic pregnancy remains a potentially life-threatening condition despite advances in early diagnosis and management. Although methotrexate (MTX) is widely used in clinically stable patients, treatment escalation and tubal rupture may still occur. This study primarily aimed to evaluate MTX treatment outcomes and identify pretreatment clinical, laboratory, and ultrasonographic factors associated with tubal rupture during MTX therapy in tubal ectopic pregnancy. **Methods:** This single-center retrospective cohort study included women with confirmed tubal ectopic pregnancy managed between October 2023 and June 2025. According to the pre-established institutional protocol, patients received either primary surgical treatment or first-line systemic methotrexate treatment. Only cases with tubal localization confirmed by follow-up transvaginal ultrasonography and/or intraoperative findings were included. MTX was administered using a single-dose regimen (50 mg/m^2), with a second dose given in clinically stable patients when indicated. Requirement for a second MTX dose was considered treatment escalation rather than treatment failure; MTX failure was defined as the need for surgical intervention. Demographic, clinical, laboratory, and ultrasonographic variables were analysed. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of baseline β-human chorionic gonadotropin (β-hCG) levels and ectopic mass size for tubal rupture during MTX therapy. **Results:** A total of 194 women were included; 54 (27.8%) underwent primary surgery and 140 (72.2%) received MTX as initial treatment. Among MTX-treated patients, single-dose MTX was successful in 94 patients (67.1%), 24 (17.1%) required a second dose, and tubal rupture requiring surgical intervention occurred in 22 (15.7%). Patients who developed rupture had significantly higher baseline, day-4, and day-7 β-hCG levels, larger ectopic mass size, and a markedly higher frequency of free intraperitoneal fluid compared with those successfully treated with MTX (all $p < 0.05$). The decline in β-hCG levels between days 4 and 7 was significantly lower in patients requiring treatment escalation or developing rupture ($p < 0.001$). Although fetal cardiac activity was numerically more frequent in the MTX-related rupture subgroup, this difference was not statistically significant after analysis with the Fisher–Freeman–Halton exact test. Gestational age at presentation was significantly greater in patients who later developed MTX-related rupture than in those who underwent primary surgery ($p = 0.009$). Receiver operating characteristic analysis demonstrated excellent discriminative performance for baseline β-hCG (area under the curve [AUC] = 0.869; 95% confidence interval [CI], 0.769–0.970; $p < 0.001$; cut-off = 1670 mIU/mL; sensitivity 95.2%, specificity 77.1%) and good discriminative performance for ectopic mass size (AUC = 0.766; 95% CI, 0.632–0.900; $p = 0.001$; cut-off = 30 mm; sensitivity 68.4%, specificity 87.7%). **Conclusion:** Baseline β-hCG level and ectopic mass size are clinically useful pretreatment predictors of tubal rupture during MTX therapy in tubal ectopic pregnancy. Incorporating these variables into pretreatment risk stratification may improve patient selection, counselling, and safety during medical management.

Keywords: ectopic pregnancy; methotrexate; risk factor; tubal rupture; ultrasonography

1. Introduction

Ectopic pregnancy (EP), which accounts for approximately 1–2% of all pregnancies, is a potentially life-threatening condition and remains a leading cause of first-trimester pregnancy-related mortality, despite advances in early diagnosis [1,2]. The fallopian tube is the most common site of implantation, and delayed diagnosis may result in tubal rupture and significant maternal morbidity [1].

Timely diagnosis of EP relies on transvaginal ultrasonography combined with serial serum β-human chorionic gonadotropin (β-hCG) measurements [3]. Recent evidence has indicated that modern transvaginal ultrasound allows highly accurate diagnosis of extrauterine ectopic pregnancy, regardless of the morphological subtype, and enables early clinical decision-making without prolonged biochemical surveillance [4]. Early diagnosis is essential for selecting the most appropriate management strategy and minimizing complications.

Management options for tubal ectopic pregnancy include expectant management, medical treatment with sys-

temic methotrexate (MTX), and surgical intervention [1,2]. While surgery remains mandatory in haemodynamically unstable patients, MTX has become an effective fertility-preserving alternative in selected clinically stable cases [1,2]. Comparative studies suggest that medical management may achieve reproductive outcomes comparable to those of conservative surgical approaches while avoiding surgical morbidity [5].

Despite its advantages, MTX treatment is associated with failure rates ranging from 10% to more than 30%, which often necessitates unplanned surgical intervention [6,7]. Identifying patients who are likely to respond successfully to MTX remains a major clinical challenge. Several studies have consistently demonstrated that elevated pretreatment β-hCG levels are associated with an increased risk of MTX failure [6,7]. Additional factors, including maternal age, pelvic pain, and the presence of fetal cardiac activity or the yolk sac on ultrasound, have also been implicated, although the results remain heterogeneous across studies [6,7,8].

Given the variability in reported predictors and the potential risk of tubal rupture during medical management, further real-world data are needed to refine patient selection for MTX therapy [9]. Improved identification of clinical, laboratory, and ultrasonographic factors associated with treatment failure may improve individualized treatment strategies, optimize patient counselling, and reduce the morbidity associated with delayed surgical intervention.

Therefore, this study primarily aimed to evaluate methotrexate treatment outcomes and identify pretreatment clinical, laboratory, and ultrasonographic factors associated with tubal rupture during MTX therapy in patients with tubal ectopic pregnancy. In addition, patients who underwent primary surgery were included to contextualize the initial treatment selection and to compare their clinical profiles with those of patients who subsequently required surgery because of rupture during MTX treatment.

2. Methods

2.1 Study Design and Ethical Approval

This single-center retrospective cohort study was conducted at the Department of Obstetrics and Gynecology, Izmir City Hospital, a tertiary referral center. The medical records of women who were diagnosed with tubal ectopic pregnancy between October 2023 and June 2025 were retrospectively reviewed.

2.2 Diagnostic Criteria

The diagnosis of tubal ectopic pregnancy was established in accordance with international guidelines by using transvaginal ultrasonography (TVUS) and serial serum β-human chorionic gonadotropin (β-hCG) measurements [1,2]. A definitive diagnosis was based on at least one of the following findings: (i) visualization of a nonovarian adnexal mass consistent with tubal ectopic pregnancy on TVUS; (ii) identification of an extrauterine gestational sac, yolk sac, or embryo with or without fetal cardiac activity; or (iii) intraoperative confirmation of tubal ectopic pregnancy [1,2]. In cases without definitive ultrasonographic findings at initial presentation, serial β-hCG measurements that were obtained approximately 48 hours apart were interpreted together with the symptoms and ultrasound findings. An increase in the serum β-hCG level of more than 63% within 48 hours was considered more suggestive of a developing intrauterine pregnancy, although ectopic pregnancy could not be excluded, whereas plateauing, declining, or otherwise nonreassuring β-hCG trends prompted continued evaluation for ectopic pregnancy in accordance with guideline-based practices [1,2]. However, such cases were included in the present study only if subsequent TVUS and/or surgical findings confirmed tubal localization. Pregnancies of unknown location without definitive tubal confirmation during follow-up were excluded from the analysis.

2.3 Eligibility Criteria

Women aged ≥18 years with a definitively confirmed tubal ectopic pregnancy and complete clinical, laboratory, ultrasonographic, treatment, and follow-up data were eligible for inclusion. Confirmation of tubal pregnancy was based on follow-up transvaginal ultrasonography and/or intraoperative findings. Patients were managed with either primary surgery or first-line systemic methotrexate according to predefined institutional protocols. The exclusion criteria included cervical, cornual, caesarean scar, ovarian, or abdominal ectopic pregnancies; pregnancies of unknown location without subsequent confirmation of tubal implantation; heterotopic pregnancies; incomplete medical records; missing serial β-hCG data; insufficient follow-up; and contraindications to methotrexate for patients considered for medical treatment, including haemodynamic instability, suspected rupture at presentation, renal or hepatic dysfunction, blood dyscrasias, active pulmonary disease, peptic ulcer disease, breastfeeding, or known hypersensitivity to methotrexate.

Accordingly, cases in which tubal laterality could not be determined on the initial ultrasonographic examination were retained only if tubal ectopic pregnancy was subsequently confirmed during follow-up and/or surgery.

2.4 Initial Treatment Allocation

The initial treatment strategy was determined according to predefined institutional management protocols, which are aligned with international guideline recommendations for tubal ectopic pregnancy [1,2]. Primary surgical management was preferred in patients with haemodynamic instability, suspected or confirmed tubal rupture, moderate-to-large haemoperitoneum (operationally defined as an estimated intraperitoneal blood volume >300 mL, when quantified, or free fluid extending beyond the pelvis on ultrasonography), worsening abdominal symptoms, contraindications to methotrexate, or when immediate surgical treat-

ment was considered more appropriate on the basis of the overall clinical, laboratory, and ultrasonographic assessments. First-line systemic methotrexate was reserved for clinically stable patients with confirmed tubal ectopic pregnancy, no contraindication to methotrexate, and who were suitable for close clinical and serial β-hCG measurement follow-up. Patients were subsequently categorized into the following two groups according to the initial management: primary surgical management or first-line systemic methotrexate therapy.

2.5 Methotrexate Protocol and Definitions

Systemic methotrexate (Pfizer Inc., New York, NY, USA) was administered at 50 mg/m^2 intramuscularly according to a single-dose protocol. Serum β-hCG levels were measured on days 1, 4, and 7 after MTX administration. Treatment success was defined as a ≥15% decrease in β-hCG levels between days 4 and 7. Patients who failed to achieve this threshold but remained clinically stable received a second dose of methotrexate, followed by repeated monitoring of β-hCG levels by using the same schedule. Patients were followed up until complete β-hCG negativization was achieved.

Methotrexate treatment failure was defined as the need for surgical intervention after initial methotrexate administration for any reason, including an inadequate biochemical response, clinical deterioration, or tubal rupture. The need for a second MTX dose in clinically stable patients was considered treatment escalation rather than treatment failure. Patients who developed tubal rupture requiring emergency surgery during MTX therapy were analysed separately as a predefined treatment failure subgroup. Tubal rupture was defined as acute abdominal symptoms accompanied by ultrasonographic evidence of haemoperitoneum and/or intraoperative confirmation.

Time to β-hCG negativization was defined as the interval from initial treatment allocation to complete biochemical resolution, defined at our institution as a serum β-hCG concentration less than 5 IU/L, regardless of whether final resolution occurred after methotrexate alone or after subsequent surgical intervention.

2.6 Data Collection

Data were extracted from the hospital's electronic medical records system and entered into a structured database. The collected variables included demographic characteristics, obstetric history, main presenting features, gestational age, shock index, laboratory parameters (haemoglobin, haematocrit, and serial β-hCG levels), and ultrasonographic findings, such as the ectopic mass size, laterality, fetal cardiac activity, the presence of a pseudogestational sac, and the presence of intraperitoneal free fluid. Treatment and surgical outcomes, including methotrexate success, treatment escalation, methotrexate treatment failure, tubal rupture during MTX therapy, time to β-hCG negativization, operative duration, estimated blood loss, and blood transfusion requirement, were also documented.

To compare the primary surgery group and the group that developed rupture during MTX treatment, the gestational age, pretreatment/baseline β-hCG level, ectopic mass size, fetal cardiac activity, shock index, operation time, and estimated blood loss were analysed according to the initial diagnostic assessment at presentation. In patients who later developed rupture during the MTX follow-up, the baseline values of the β-hCG levels, the ectopic mass size, fetal cardiac activity, and the shock index were used rather than those at the time of rupture.

The shock index was calculated at admission as the heart rate divided by the systolic blood pressure and was recorded from the initial clinical assessment. For descriptive analyses, the shock index was categorized as normal (<0.7), elevated (0.7–0.9), or high (>0.9).

Treatment-related complications were identified through review of the electronic medical records. In the present study, major treatment-related complications referred to documented clinically significant adverse events that occurred during treatment or follow-up; tubal rupture requiring surgical intervention was analysed separately as a predefined study outcome.

2.7 Study Groups

Patients were analysed in predefined comparison groups. First, baseline characteristics and outcomes were compared between patients who underwent primary surgical management and those who were initially treated with methotrexate. Second, patients who received methotrexate were stratified into three subgroups as follows: a successful single-dose treatment subgroup, a subgroup requiring a second MTX dose, and a subgroup with tubal rupture requiring surgical intervention during the methotrexate follow-up. Finally, outcomes were compared between patients who underwent primary surgery and those who required emergency surgery for tubal rupture after initial methotrexate treatment.

The primary surgery group was included not as part of the medical treatment outcome analysis but to characterize baseline differences in initial treatment allocation and to enable comparison with patients who later underwent surgery because of tubal rupture during the MTX follow-up.

2.8 Statistical Analysis

Statistical analyses were performed by using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as the mean ± standard deviation when normally distributed and as the median (interquartile range, IQR) when nonnormally distributed. Categorical variables are presented as frequencies and percentages. The normality of continuous variables was assessed within each comparison group by using histograms, quantile–quantile (Q–Q) plots, skewness and kurtosis values, and the Shapiro–Wilk test. Variables that

did not conform to the normality assumption were compared by using the Mann–Whitney U test for two-group comparisons and the Kruskal–Wallis test for comparisons among more than two groups. Levene's test was used to assess the homogeneity of variance. When the assumptions of normality and homogeneity of variance were met, the independent samples *t*-test was used for comparisons between two groups, and analysis of variance (ANOVA) was used for comparisons among more than two groups. Categorical variables were compared by using appropriate statistical tests, which were selected according to the table structure and expected cell counts. Pearson's chi-square test was used for categorical variable comparisons when the expected cell count assumptions were satisfied, and the continuity-corrected chi-square test was applied for 2 × 2 contingency tables when appropriate. Fisher's exact test was used for sparse 2 × 2 contingency tables or when the expected cell count was less than 5, whereas the Fisher–Freeman–Halton exact test was used for sparse R × C contingency tables or when the expected cell count was less than 5. Receiver operating characteristic (ROC) curve analysis was performed as an exploratory approach to identify clinically applicable pretreatment thresholds for tubal rupture during MTX therapy. Optimal cut-off values were determined by using the Youden index, and sensitivity and specificity were calculated at the selected cut-off points. Although other pretreatment continuous variables were available, the primary ROC curve analysis was restricted a priori to the baseline β-hCG level and ectopic mass size because these variables are most directly related to the trophoblastic burden and tubal distension and are key indicators that are commonly used for treatment selection according to guidelines and previous studies. Categorical or ordinal variables were evaluated in subgroup comparisons but were not entered into the primary ROC curve analysis. A two-sided p-value < 0.05 was considered to indicate statistical significance.

3. Results

3.1 Study Population

A total of 194 women diagnosed with tubal ectopic pregnancy were included in the analysis. Initial management consisted of primary surgical treatment in 54 patients (27.8%) and first-line methotrexate (MTX) therapy in 140 patients (72.2%). The baseline demographic, clinical, laboratory, and ultrasonographic characteristics of the study population, together with initial management allocation, are presented in Table 1.

3.2 Comparison According to the Initial Treatment Strategy

When the patients were stratified according to the initial treatment strategy, demographic variables, including age, gravidity, parity, gestational age, and history of ectopic pregnancy, did not significantly differ between the primary surgery and MTX groups (all $p > 0.05$; Table 2). The haemoglobin and haematocrit values also did not differ significantly between the two groups, whereas the baseline serum β-hCG levels were significantly higher in the primary surgery group (Table 2). Regarding clinical and ultrasonographic characteristics, several clinical and ultrasonographic features differed significantly between the groups. The patients who underwent primary surgery more frequently presented with abdominal pain, a larger ectopic mass size, the presence of free intraperitoneal fluid, a pseudogestational sac, and greater fetal cardiac activity. In addition, the high shock index category at presentation and the requirement for blood transfusion were significantly more common in the surgical group. The time to complete β-hCG negativization was significantly shorter in patients who received primary surgical management than in those who received MTX (median: 10.0 [IQR, 8.25–12.0] vs. 27.0 [IQR, 23.0–30.0] days; $Z = –10.044$; $p < 0.001$). Initial sonographic laterality also differed significantly between the groups ($p < 0.001$; Table 2). In the primary surgery group, all cases were localized to the right or left tube at presentation, whereas in the MTX group, a substantial proportion of cases were not localized on initial ultrasonography, despite subsequent confirmation of tubal ectopic pregnancy during follow-up and/or surgery.

3.3 Treatment Outcomes in the Methotrexate Cohort

Among the 140 patients who were initially treated with MTX, the treatment outcomes varied (Table 3). Single-dose MTX was successful in 94 patients (67.1%); 24 patients (17.1%) required a second dose of MTX because of an inadequate biochemical response; and tubal rupture requiring surgical intervention during MTX therapy occurred in 22 patients (15.7%).

Patients who developed rupture had significantly higher baseline ($p < 0.001$), day-4 ($p = 0.003$), and day-7 ($p = 0.006$) β-hCG levels, a larger ectopic mass size ($p = 0.001$), and a markedly greater frequency of free intraperitoneal fluid ($p < 0.001$) than those successfully treated with MTX. The decrease in β-hCG levels between days 4 and 7 was significantly lower in patients who required treatment escalation or developed rupture ($p < 0.001$). Although fetal cardiac activity was more frequent in the rupture subgroup, the difference was not statistically significant after analysis with the Fisher–Freeman–Halton exact test ($p = 0.084$).

Significant differences among the MTX outcome subgroups were also observed for gestational age ($p = 0.005$), haemoglobin level ($p = 0.023$), haematocrit level ($p = 0.010$), the presence of a pseudogestational sac ($p = 0.014$), and blood transfusion requirement ($p = 0.024$). The subgroup that experienced rupture during MTX therapy had a higher median gestational age and lower median haemoglobin and haematocrit values. A pseudogestational sac was more frequent in the rupture subgroup than in both the single-dose success subgroup and the second-dose subgroup. Histories of ectopic pregnancy did not differ significantly among the MTX outcome subgroups ($p = 0.095$).

Table 1. Baseline clinical, laboratory, and ultrasonographic characteristics of the study population and selected outcomes (N = 194).

Variable	Mean ± SD or median (IQR)/n (%)
Initial management	
Primary surgery	54 (27.8%)
First-line methotrexate (MTX)	140 (72.2%)
Age (years)	31.81 ± 5.85
Gravida	2.5 (1.0–4.0)
Parity	1.0 (0.0–2.0)
History of ectopic pregnancy	
No	172 (88.7%)
Yes	22 (11.3%)
Main presenting feature	
Abnormal β-hCG rise	92 (47.4%)
Abdominal pain	102 (52.6%)
Gestational age (days)	44.18 ± 10.37
Haemoglobin (g/dL)	11.86 ± 1.45
Haematocrit (%)	35.76 ± 3.93
Shock index at admission	
Normal	149 (76.8%)
Elevated	40 (20.6%)
High	5 (2.6%)
Initial sonographic laterality*	
Not localized on initial ultrasonography	61 (31.4%)
Right tube	61 (31.4%)
Left tube	72 (37.1%)
Pseudogestational sac	
Absent	158 (81.4%)
Present	36 (18.6%)
Fetal cardiac activity	
Absent	179 (92.3%)
Present	15 (7.7%)
Ectopic mass size† (mm)	25.84 ± 11.25 (n = 138)
Free intraperitoneal fluid	
Absent	129 (66.5%)
Present	65 (33.5%)
Baseline β-hCG (mIU/mL)	1216 (411–3285)
Blood transfusion requirement	
No	181 (93.3%)
Yes	13 (6.7%)

Note: Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are presented as a number (percentage). Percentages are rounded to one decimal place. Baseline and selected clinically relevant treatment/surgical variables are shown. Blood transfusion requirement is included as a documented treatment/surgical outcome.

* Cases categorized as "Not localized on initial ultrasonography" were subsequently confirmed as tubal ectopic pregnancies during follow-up and/or surgery. † Ectopic mass size was calculated only in patients with a measurable ectopic adnexal mass on initial ultrasonography; cases without measurable localization on initial ultrasonography were excluded from this analysis. SD, standard deviation; β-hCG, β-human chorionic gonadotropin; IQR, interquartile range.

The time to β-hCG negativization also differed significantly among the MTX subgroups ($p = 0.002$; Table 3). The shorter interval observed in the rupture subgroup should be interpreted in the context of subsequent surgical interven-

Table 2. Comparison of primary surgery and methotrexate groups.

Variable	Primary surgery (n = 54)	Methotrexate (n = 140)	Test statistic	*p*-value
	Mean ± SD or median (IQR)/n (%)	Mean ± SD or median (IQR)/n (%)		
Age (years)	32.35 ± 5.84	31.61 ± 5.86	$t = 0.794$	0.428
Gravida	2.0 (1.0–4.0)	3.0 (2.0–4.0)	Z = –1.141	0.254
Parity	1.0 (0.0–1.8)	1.0 (0.0–2.0)	Z = –1.497	0.135
Gestational age (days)	42.48 ± 11.15	44.83 ± 10.02	$t = –1.417$	0.158
History of ectopic pregnancy	No: 47 (87.0%); Yes: 7 (13.0%)	No: 125 (89.3%); Yes: 15 (10.7%)	$\chi^2 = 0.196$	0.658
Haemoglobin (g/dL)	11.54 ± 1.63	11.98 ± 1.36	$t = –1.935$	0.054
Haematocrit (%)	34.94 ± 4.29	36.07 ± 3.76	$t = –1.798$	0.074
Ectopic mass size† (mm)	30.0 (24.2–31.5)	20.0 (16.0–28.5)	Z = 4.831	<0.001
Baseline β-hCG (mIU/mL)	3682 (1230–6656)	932 (284–2452)	Z = 5.337	<0.001
β-hCG negativization (days)	10.0 (8.2–12.0)	27.0 (23.0–30.0)	Z = –10.044	<0.001
Main presenting feature	Abnormal β-hCG rise: 8 (14.8%); Abdominal pain: 46 (85.2%)	Abnormal β-hCG rise: 84 (60.0%); Abdominal pain: 56 (40.0%)	$\chi^2 = 31.910$	<0.001
Shock index	Normal: 42 (77.8%); Elevated: 7 (13.0%); High: 5 (9.3%)	Normal: 107 (76.4%); Elevated: 33 (23.6%); High: 0 (0.0%)	Fisher–Freeman–Halton exact	0.001
Pseudogestational sac	Absent: 36 (66.7%); Present: 18 (33.3%)	Absent: 122 (87.1%); Present: 18 (12.9%)	$\chi^2 = 10.811$	0.001
Fetal cardiac activity	Absent: 42 (77.8%); Present: 12 (22.2%)	Absent: 137 (97.9%); Present: 3 (2.1%)	Fisher's exact	<0.001
Free intraperitoneal fluid	Absent: 11 (20.4%); Present: 43 (79.6%)	Absent: 118 (84.3%); Present: 22 (15.7%)	$\chi^2 = 71.455$	<0.001
Blood transfusion requirement	No: 43 (79.6%); Yes: 11 (20.4%)	No: 138 (98.6%); Yes: 2 (1.4%)	Fisher's exact	<0.001
Initial sonographic laterality	Not localized on initial ultrasonography: 0 (0.0%); Right tube: 28 (51.9%); Left tube: 26 (48.1%)	Not localized on initial ultrasonography: 61 (43.6%); Right tube: 33 (23.6%); Left tube: 46 (32.9%)	Fisher–Freeman–Halton exact	<0.001

Note: Continuous variables were compared using the independent samples *t*-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using Pearson's chi-square test, Fisher's exact test, or Fisher–Freeman–Halton exact test according to expected cell counts and table structure. Test statistic represents *t*, Z, χ^2, Fisher's exact test, or Fisher–Freeman–Halton exact test. † Ectopic mass size applies only to patients with a measurable adnexal mass on initial ultrasonography.

tion, which likely accelerated biochemical resolution compared with follow-up after medical treatment alone.

No major treatment-related complications, other than the predefined outcome of tubal rupture requiring surgical intervention, were documented during the recorded follow-up period.

3.4 Comparison Between the Primary Surgery and MTX-Treated Rupture Groups

A focused comparison between the patients who underwent immediate surgery at presentation and those who required surgery due to rupture during MTX treatment is shown in Table 4. In this comparison, gestational age, pretreatment β-hCG level, ectopic mass size, operation time, estimated blood loss, shock index, and fetal cardiac activity were evaluated. The gestational age at presentation was significantly greater in the group that experienced rupture during MTX treatment. No statistically significant differences were observed between these groups in terms of the pretreatment β-hCG levels, ectopic mass size, operation duration, estimated blood loss, shock index, or fetal cardiac activity.

3.5 ROC Curve Analysis for Predicting Tubal Rupture During MTX Treatment

The results of the receiver operating characteristic (ROC) curve analysis, which was performed to assess the predictors of tubal rupture during MTX treatment are shown in Fig. 1. The baseline β-hCG concentration demonstrated excellent discriminative ability (area under the curve [AUC] = 0.869; 95% confidence interval [CI], 0.769–0.970; $p < 0.001$), with an optimal cut-off value of 1670 mIU/mL. At this cut-off, the sensitivity was 95.2%, and the specificity was 77.1%. The ectopic mass size also showed good predictive performance (AUC = 0.766; 95% CI, 0.632–0.900; $p = 0.001$), with a cut-off value of 30 mm. At this cut-off, the sensitivity was 68.4%, and the specificity was 87.7%.

Table 3. Clinical and laboratory factors according to methotrexate treatment outcome subgroups.

Variable	MTX-1 (single-dose success) (n = 94)	MTX-2 (second dose required) (n = 24)	MTX-related rupture (rupture during MTX) (n = 22)	Test statistic	*p*-value
	Median (IQR)/n (%)	Median (IQR)/n (%)			
Age (years)	31.5 (27.0–35.0)	31.0 (27.0–34.2)	32.0 (27.5–36.7)	H = 0.212	0.899
Parity	1.0 (0.0–2.0)	0.5 (0.0–1.0)	1.0 (0.0–2.0)	H = 4.454	0.108
Gravida	3.0 (2.0–4.0)	2.0 (1.0–3.2)	3.0 (1.2–4.0)	H = 3.795	0.150
History of ectopic pregnancy	No: 87 (92.6%); Yes: 7 (7.4%)	No: 21 (87.5%); Yes: 3 (12.5%)	No: 17 (77.3%); Yes: 5 (22.7%)	Fisher–Freeman–Halton exact	0.095
Gestational age (days)	43.0 (38.2–49.0)	46.5 (38.7–53.0)	48.5 (44.2–55.7)	H = 10.782	0.005
Haemoglobin (g/dL)	12.0 (11.1–13.00)	12.0 (11.4–13.6)	11.2 (10.7–12.3)	H = 7.552	0.023
Haematocrit (%)	36.0 (34.0–38.7)	37.0 (35.7–40.0)	33.0 (32.0–38.2)	H = 9.304	0.010
Main presenting feature	Abnormal β-hCG rise: 52 (55.3%); Abdominal pain: 42 (44.7%)	Abnormal β-hCG rise: 15 (62.5%); Abdominal pain: 9 (37.5%)	Abnormal β-hCG rise: 17 (77.3%); Abdominal pain: 5 (22.7%)	$\chi^2 = 3.656$	0.161
Shock index	Normal: 73 (77.7%); Elevated: 21 (22.3%)	Normal: 19 (79.2%); Elevated: 5 (20.8%)	Normal: 15 (68.2%); Elevated: 7 (31.8%)	$\chi^2 = 1.009$	0.604
Pseudogestational sac	Absent: 82 (87.2%); Present: 12 (12.8%)	Absent: 24 (100.0%); Present: 0 (0.0%)	Absent: 16 (72.7%); Present: 6 (27.3%)	Fisher–Freeman–Halton exact	0.014
Initial sonographic laterality	Not localized on initial ultrasonography: 45 (47.9%); Right tube: 19 (20.2%); Left tube: 30 (31.9%)	Not localized on initial ultrasonography: 12 (50.0%); Right tube: 4 (16.7%); Left tube: 8 (33.3%)	Not localized on initial ultrasonography: 4 (18.2%); Right tube: 10 (45.5%); Left tube: 8 (36.4%)	$\chi^2 = 9.396$	0.052
Ectopic mass size† (mm)	19.0 (15.0–23.2)	18.0 (14.0–18.0)	30.0 (22.0–40.0)	H = 13.124	0.001
Baseline (day-1) β-hCG (mIU/mL)	717.0 (244.5–1522.8)	575.5 (231.2–1245.0)	2856.0 (2455.0–7078.0)	H = 29.528	<0.001
β-hCG day-4 (mIU/mL)	400.0 (201.0–1045.5)	579.0 (224.5–1437.0)	2857.0 (1776.0–3094.0)	H = 11.639	0.003
β-hCG day-7 (mIU/mL)	218.5 (96.9–743.3)	542.0 (206.5–1363.5)	2337.0 (1922.0–2397.8)	H = 10.348	0.006
Free intraperitoneal fluid	Absent: 94 (100.0%); Present: 0 (0.0%)	Absent: 23 (95.8%); Present: 1 (4.2%)	Absent: 1 (4.5%); Present: 21 (95.5%)	Fisher–Freeman–Halton exact	<0.001
β-hCG decline days 4–7 (%)	35.3 (25.7–54.8)	10.4 (6.0–12.6)	20.4 (18.2–32.1)	H = 58.544	<0.001
Blood transfusion requirement	No: 94 (100.0%); Yes: 0 (0.0%)	No: 24 (100.0%); Yes: 0 (0.0%)	No: 20 (90.9%); Yes: 2 (9.1%)	Fisher–Freeman–Halton exact	0.024
Time to β-hCG negativization (days)	27.0 (24.0–30.8)	27.0 (23.0–29.2)	15.5 (12.2–27.8)	H = 12.764	0.002
Fetal cardiac activity	Absent: 93 (98.9%); Present: 1 (1.1%)	Absent: 24 (100.0%); Present: 0 (0.0%)	Absent: 20 (90.9%); Present: 2 (9.1%)	Fisher–Freeman–Halton exact	0.084

Note: Continuous variables were compared using the Kruskal–Wallis test. Categorical variables were compared using Pearson's chi-square test or Fisher–Freeman–Halton exact test, as appropriate. Test statistic represents H, χ^2, or Fisher–Freeman–Halton exact test. † Ectopic mass size applies only to patients with a measurable adnexal mass on initial ultrasonography. Day-7 β-hCG values and the days 4–7 decline percentage were calculated only for patients with available measurements before emergency surgery; rupture patients who underwent surgery before scheduled day-7 assessment did not contribute to these variables.

Table 4. Baseline clinical comparison between patients undergoing primary surgery and those who later developed MTX-related tubal rupture.

Variable	Primary surgery (n = 54)	MTX-related rupture (n = 22)	Test statistic	*p*-value
	Mean ± SD or median (IQR)/n (%)			
Gestational age (days)	42.48 ± 11.15	49.41 ± 7.01	$t = -2.699$	0.009
Pretreatment/baseline β-hCG (mIU/mL)	3681.5 (1230.0–6656.0)	2856 (2455–7078)	Z = –0.342	0.737
Ectopic mass size† (mm)	30.0 (24.2–31.5)	30.0 (22.0–40.0)	Z = –0.462	0.648
Operation time (min)	90.0 (71.2–115.0)	84.5 (56.0–105.0)	Z = 0.969	0.336
Estimated blood loss (mL)	400.0 (220.0–537.5)	250.0 (212.5–337.5)	Z = 1.876	0.061
Shock index	Normal: 42 (77.8%); Elevated: 7 (13.0%); High: 5 (9.3%)	Normal: 15 (68.2%); Elevated: 7 (31.8%); High: 0 (0.0%)	Fisher–Freeman–Halton exact	0.069
Fetal cardiac activity	Absent: 42 (77.8%); Present: 12 (22.2%)	Absent: 20 (90.9%); Present: 2 (9.1%)	Fisher's exact	0.327

Note: Continuous variables were compared using the independent samples *t*-test or Mann–Whitney U test, as appropriate. Categorical variables were compared using Fisher's exact test and Fisher–Freeman–Halton exact test, as appropriate. Test statistic represents *t*, Z, Fisher's exact test, or Fisher–Freeman–Halton exact test. For the primary surgery group, pretreatment/baseline β-hCG refers to the preoperative β-hCG value measured before surgical management. For the MTX-related rupture group, it refers to the baseline day-1 β-hCG value measured before the first methotrexate dose. † Ectopic mass size applies only to patients with a measurable adnexal mass on initial ultrasonography.

4. Discussion

In this retrospective cohort study, we evaluated the clinical, laboratory, and ultrasonographic factors associated with the success and failure of methotrexate (MTX) treatment in patients managed for tubal ectopic pregnancy. Our principal findings demonstrated that the occurrence of tubal rupture during MTX therapy was associated with a higher baseline β-human chorionic gonadotropin (β-hCG) level, a larger ectopic mass size, and the presence of free intraperitoneal fluid. In addition, receiver operating characteristic (ROC) curve analysis revealed that the determined cut-off values for the β-hCG levels and ectopic mass sizes had clinically meaningful discriminative performance. Collectively, these findings highlight the importance of a risk-based approach to patient selection for MTX treatment [10,11].

Methotrexate is widely used as a fertility-preserving alternative to surgery in haemodynamically stable and carefully selected patients with tubal ectopic pregnancy [2,12]. In our study, tubal rupture requiring surgery occurred in 15.7% of patients who were initially treated with MTX, whereas 17.1% of patients required a second MTX dose because of an inadequate biochemical response. These findings indicate that a substantial proportion of patients required treatment escalation or surgery, despite the initial medical management, which is consistent with the 10–30% proportion reported in the literature [6,13]. The relatively high success rate achieved with single-dose MTX in our cohort supports the critical role of appropriate patient selection and adherence to standardized follow-up protocols in optimizing clinical outcomes [14,15]. Nevertheless, the occurrence of treatment escalation or tubal rupture in a substantial proportion of patients underscores that MTX cannot be considered a completely risk-free therapeutic option [16]. The apparently greater decrease in the median days 4–7 β-hCG level in the subgroup with rupture during MTX therapy than in the second-dose subgroup should be interpreted with caution because day-7 values were available only for rupture patients who remained clinically stable long enough to complete the scheduled biochemical follow-up. Therefore, early ruptures did not contribute to this variable, creating a likely selection effect. Although elevated β-hCG levels and ectopic mass sizes are recognized as risk indicators in the literature, the present study adds clinically relevant real-world data by specifically examining tubal rupture during the MTX follow-up and by providing cohort-based threshold estimates within a standardized institutional treatment pathway. In addition, the comparison between primary surgical cases and those who experienced rupture during MTX treatment offers practical insights into whether delayed surgery after failed medical treatment represents a less severe surgical scenario.

In our study, the ultrasonographically measured ectopic mass size was strongly associated with MTX failure, particularly with the development of tubal rupture. Consistent with previous evidence identifying gestational sac diameter as an important predictor of methotrexate treatment success, our findings highlight that patient selection should not rely solely on biochemical parameters but should also incorporate detailed morphological assessment [11]. In addition, the markedly higher percentage of free intraperitoneal fluid in the rupture group is consistent with previous reports identifying abdominal free fluid as a poor prognostic factor for methotrexate treatment success [17].

Although the association between fetal cardiac activity and MTX failure remains controversial in the literature [6], fetal cardiac activity was observed more frequently in the rupture group in our study. This finding supports the

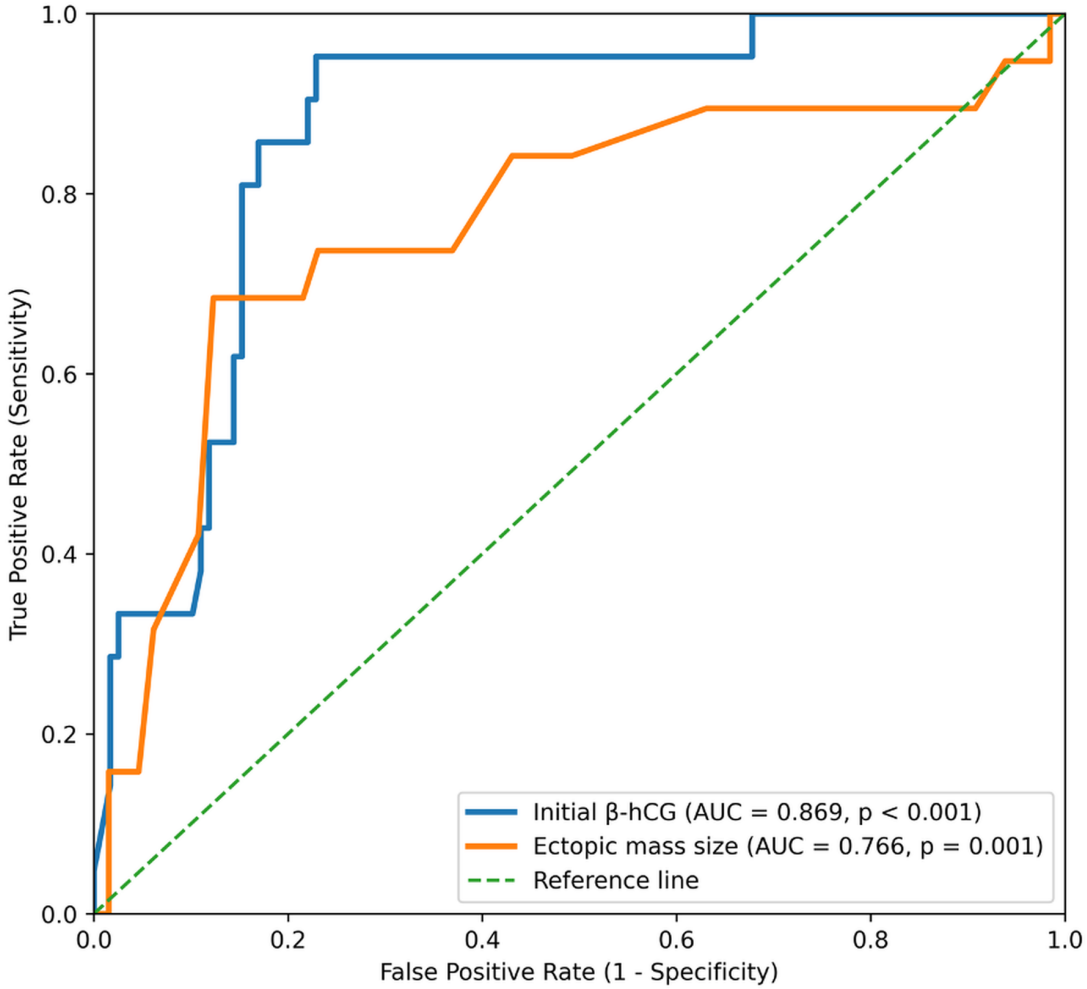

Fig. 1. ROC analysis for predicting tubal rupture during methotrexate treatment. ROC, receiver operating characteristic; AUC, area under the curve.

hypothesis that more advanced trophoblastic activity and increased vascularity may limit the effectiveness of MTX therapy [6,17]. Similarly, the higher prevalence of abdominal pain and clinical symptoms in the surgically managed group underscores the importance of integrating clinical assessments with laboratory findings when determining the optimal treatment strategy [1,2]. Although fetal cardiac activity was more frequent in the rupture group, the difference was not statistically significant after analysis with the Fisher–Freeman–Halton exact test. Therefore, these findings should be interpreted with caution.

One of the noteworthy findings of our study is that the intraoperative and clinical profiles of patients who required surgery due to tubal rupture during MTX treatment were largely comparable to those of patients who underwent primary surgical management at initial presentation. This observation indicates that the rupture occurring during MTX therapy does not represent a surgically "milder" condition but rather has a risk profile similar to that of patients requiring immediate surgical intervention. These findings underscore the importance of carefully evaluating the risk of rupture when planning MTX treatment in patients with tubal ectopic pregnancy [18,19].

The present findings indicate that MTX treatment should not be regarded as a universal "one-size-fits-all" solution but rather as a strategy that requires individualized risk assessment [1,2]. In particular, patients with a baseline β-hCG concentration above 1670 mIU/mL or an ectopic mass size exceeding 30 mm should be considered to have an increased risk of rupture during MTX therapy [20,21]. In this subgroup, closer surveillance, discussion of alternative treatment options, or consideration of primary surgical management may represent a clinically rational approach.

The strengths of this study include the evaluation of a relatively homogeneous patient population, the use of a standardized MTX treatment protocol, and the application of clinically meaningful ROC analyses. However, several limitations should be acknowledged. The retrospective design, single-center setting, and limited sample size may restrict the generalizability of the findings. In addition, long-

term fertility outcomes were not assessed, and some clinical variables were inherently constrained by the retrospective nature of data collection.

5. Conclusion

In conclusion, our study demonstrates that baseline β-hCG level and ectopic mass size are clinically robust predictors of tubal rupture during MTX treatment in patients with tubal ectopic pregnancy. The combined evaluation of these parameters may facilitate safer and more individualized patient selection and treatment planning. Prospective, multicenter studies are warranted to validate these threshold values and to support their integration into clinical decision-making algorithms.

Key Points

• In this cohort of women with tubal ectopic pregnancy, single-dose methotrexate was successful in most MTX-treated patients (67.1%), while 17.1% required a second dose and 15.7% experienced tubal rupture requiring surgery.

• Patients who developed tubal rupture during MTX follow-up had significantly higher baseline, day-4, and day-7 β-hCG levels, larger ectopic mass size, and a markedly higher frequency of free intraperitoneal fluid.

• The percentage decline in β-hCG between days 4 and 7 was significantly lower in patients requiring treatment escalation or developing rupture.

• Baseline β-hCG and ectopic mass size showed clinically relevant predictive performance for tubal rupture during MTX therapy, with cut-off values of 1670 mIU/mL and 30 mm, respectively.

• Although fetal cardiac activity was numerically more frequent in the rupture subgroup, this difference was not statistically significant after reanalysis with the Fisher–Freeman–Halton exact test.

• Patients who later required surgery because of MTX-related rupture had baseline clinical profiles broadly comparable to those undergoing primary surgery, supporting careful pretreatment risk assessment before selecting medical management.

Availability of Data and Materials

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

EGÖ contributed to the conception and design of the study, data analysis and interpretation, literature review, drafting of the manuscript, and management of references. HSS contributed to the study concept, methodological design, and critically revised the manuscript for important intellectual content. SÖ was responsible for statistical analysis, contributed to interpretation of the data, and provided substantial support during the writing and revision of the manuscript. BKK and ŞBT were responsible for acquisition of data, clinical material management, and actively contributed to data interpretation and drafting sections of the manuscript. YKA contributed to the methodological framework, supervised the overall study process, and critically reviewed and revised the manuscript for important intellectual content. AGK contributed to the interpretation of data, assisted in drafting and revising the manuscript, and provided critical intellectual input during manuscript development. All authors contributed to revising the manuscript critically for important intellectual content. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved. All authors read and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

The study protocol was approved by the Institutional Ethics Committee of Izmir City Hospital (Approval No: 2025/120) and conducted in accordance with the Declaration of Helsinki. Because the study was retrospective and based exclusively on routinely collected medical records, ethical approval was obtained before the data were extracted and the final analysis was completed. This study involved no direct patient contact, additional intervention, or influence on clinical management, and all the data were deidentified before analysis. Therefore, the requirement for individual informed consent was waived by the Ethics Committee on the grounds that the study posed minimal risk to participants.

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Conflicts of Interest

The authors declare no conflicts of interest.

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