

Management of ectopic pregnancy in a tertiary hospital: a retrospective cohort study

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Abstract. – OBJECTIVE: The goal of this study was to manage the treatment modalities of ectopic pregnancy.

PATIENTS AND METHODS: This retrospective study included 1,103 women diagnosed and treated for ectopic pregnancy at Kanuni Sultan Suleyman Training and Research Hospital between January 1, 2017, and December 31, 2020. Serial beta-human chorionic gonadotropin (β -Hcg) measurements and transvaginal ultrasound (TV USG) findings were used to establish the diagnosis of an ectopic pregnancy. They were divided into four groups: expectant treatment, single-dose methotrexate, multidose methotrexate, and surgical treatment. All data analyses were performed using SPSS version 24.0. A receiver operating characteristic (ROC) analysis was used to determine the cut-off for change in beta-human chorionic gonadotropin (β -hCG) levels between the first and fourth day.

RESULTS: There were significant differences between groups in terms of gestational age and β -hCG changes ($p < 0.001$). In patients receiving expectant treatment, the decrease in β -hCG values on the fourth day was 35.19%, while patients receiving single-dose methotrexate treatment showed a decrease of 24%. The most common risk factor for ectopic pregnancy was the absence of risk factors. Comparison of the surgical treatment group with the other groups revealed significant differences in terms of the presence of free fluid in the abdomen, the average diameter of the ectopic pregnancy mass, and the presence of fetal cardiac activity. A single dose of methotrexate was effective in patients with β -hCG levels lower than 1,227.5 mIU/ml, with a 68.5% sensitivity and 69.1% specificity.

CONCLUSIONS: An increase in gestational age also leads to an increase in β -hCG values and the diameter of the ectopic focus. As the diagnosis period progresses, the need for surgical intervention increases.

Key Words:

β -CG, Ectopic pregnancy, Management, Methotrexate, Transvaginal sonography.

Introduction

Ectopic pregnancies are any fertilized ovum implants outside the endometrium, most commonly in the fallopian tube. Tubal ectopic pregnancies constitute more than 90% of ectopic pregnancies, especially in the ampullary region. On the other hand, non-tubal ectopic pregnancies account for less than 10% of all ectopic pregnancies, which could be cervical, ovarian, intramural abdominal, or cesarean section scar pregnancies¹. Its pathophysiology is described as early implantation caused by factors that delay or prevent the fertilized ovum from reaching the endometrial cavity². It has an incidence of 1-2% in the general population³. The incidence of ectopic pregnancy has been increasing due to increased sexually transmitted diseases, pelvic inflammatory diseases, and treatment of assisted reproductive techniques⁴. Extrauterine pregnancy is commonly associated with delayed menstruation, abdominal pain, and vaginal bleeding. Ectopic pregnancy is most common between the ages of 20 and 40, with a significant decrease in incidence observed outside this age range⁵. Previous surgery is a crucial risk factor in the etiology of ectopic pregnancy because it causes adhesions and disrupts tubal integrity, preventing the fertilized ovum from migrating at specific points⁶. For an accurate diagnosis of ectopic pregnancy, sonographic imaging of the yolk sac and the embryo in the extrauterine region is essential⁷.

Expectant treatment, medical treatment, and surgical operation are all options for extrauterine pregnancy treatment. When deciding on a treatment method, laboratory results and fertility status are critical considerations⁸. Among all the determinants of treatment success, the initial human chorionic gonadotropin (hCG) value is very important, but there is no consensus

predicting the success of the initial beta-HCG (β -hCG) level of expectant therapy and methotrexate (MTX) therapy⁹⁻¹¹.

The purpose of this study is to evaluate the treatment options for ectopic pregnancy.

Patients and Methods

This study retrospectively analyzed 1,103 female patients between the ages of 18 and 50 who were diagnosed and treated for ectopic pregnancy at Kanuni Sultan Suleyman Research and Training Hospital between January 2017 and December 2020. They were divided into four treatment groups: expectant, single-dose, multidose, and surgical. In the expectant group, 99 were potentially eligible and 96 were included in the study. On the other hand, in the single-dose group, 693 were potentially eligible and 681 were included in the study. In the multidose group, 95 were potentially eligible and 92 were included in the study. Moreover, in the surgical group, 246 were potentially eligible and 234 were included in the study.

All cases were classified according to the treatment option. Demographic and clinical features were evaluated, such as obstetric history, previous abdominal surgery, infertility treatment, history of ectopic pregnancy, smoking, pelvic sonography findings, clinical symptoms, β -hCG changes between day 0 (the time of presentation to the hospital) and days 4 and 7, treatment options, and length of hospital stay.

Serial β -hCG measurements and transvaginal ultrasound (TV USG) findings were used to diagnose an ectopic pregnancy, which was supported by histopathological evaluation of endometrial curettage specimens in appropriate cases. Expectant therapy was performed on patients who had stable hemodynamic parameters, no pathology detected in TV USG, and a tendency for β -hCG values to drop on their own. Medical treatment was administered to patients who could not detect intra-uterine pregnancy, gave consent to treatment, and had an increase of less than 50% or a flat plateau in serial β -hCG measurements after two consecutive days. Methotrexate (MTX) was administered intramuscularly with a dose of 50 mg/m² as a single dose or multidose with regular biochemistry tests. In patients who received a single dose of MTX, β -hCG measurement was repeated on the fourth and seventh days of the treatment, and a second

dose was administered to those whose β -hCG hormone decreased by less than 15% between the fourth and seventh days¹². A surgical approach was preferred for patients with a clinical rupture and signs of peritoneal irritation and who were hemodynamically unstable and had intra-abdominal hemorrhage on ultrasound. Salpingostomy and milking were used as fertility-preserving surgical approaches. Patients with enormous, extensive tube damage underwent salpingectomy and scalping-oophorectomies¹³. In cases where the ectopic pregnancy did not cause anatomical distortion in the tubes, the pregnancy material was removed via salpingostomy of approximately 1-2 cm opened from the antimesenteric side in the tubal segment. After hemostasis was achieved, the incision was left open. The tubal milking method was performed in the non-ruptured gestational sac near the fimbria.

All patients provided written informed consent to treatment. The requirement for patient consent to participate and publication was waived because the study was retrospective. Follow-up visits were made on the fourth and seventh days for the expectant group and the groups receiving medical MTX treatment. All groups, including the expectant treatment group, the medical treatment group, and the surgical group, were followed up for 1 month.

Inclusion Criteria

The study included ectopic pregnancy cases aged 18-50 who were diagnosed and treated between January 1, 2017, and December 31, 2020.

Exclusion Criteria

Patients with intra-uterine pregnancy and missing file information are excluded in the study.

Ethical Approval

This study conforms to the provisions of the Declaration of Helsinki and was approved by the ethics committee of Istanbul Kanuni Sultan Süleyman Training and Research Hospital KA-EK/2021.12.341.

Informed Consent

Before the treatment, the patients signed an informed consent form. For the present study, patient consent was waived because it was a retrospective analysis with no direct contact between the authors and the patients, and personal privacy was protected through anonymization.

Statistical Analysis

For statistical analysis, SPSS software version 24.0 for Windows (IBM Corp., Armonk, NY, USA) was used. Descriptive statistics were presented as mean \pm standard deviation (SD). To calculate nominal variables, one-way analysis of variance (ANOVA), Pearson's Chi-square, or Fisher's exact test was used. To confirm the need for additional MTX doses, a logistic regression analysis was performed. Moreover, a receiver operating characteristic (ROC) analysis was used to determine the cut-off for changes in β -hCG levels between the first and fourth days and between the fourth and seventh days for a further dose of MTX. The statistical significance level was $p < 0.05$ ¹⁴.

Results

There were 24 non-participants, 3 in the expectant group, 12 in the single-dose MTX, 3 in the multidose MTX, and 6 in the surgical treatment. Further, 1,103 ectopic pregnancy cases were included in the study. The characteristics of the cases and β -hCG levels of groups between 0 and 7 days are shown in Table I.

The mean age of the patients in the expectant group was 30.29 ± 6.02 years, the mean parity (number of children delivered) was 1.29 ± 1.04 , the body mass index was 24.76 ± 1.84 , and the average gestational age was 37.87 ± 6.1 days. On the other hand, the mean age of the patients in the single-dose MTX group was 30.31 ± 5.96 years, the mean parity was 1.32 ± 1.13 years, the body mass index was 24.71 ± 1.82 , and the average gestational age was 44.98 ± 8.63 days. Moreover, the mean age of the patients in the multidose MTX group was 30.8 ± 4.69 years, the

mean parity was 1.47 ± 8.9 , the body mass index was 22.92 ± 1.16 , and the average gestational age was 61.07 ± 7.44 days. Further, the mean age of the patients in the surgical treatment group was 31.28 ± 5.22 years, the mean parity was 1.43 ± 1.13 , the body mass index was 22.80 ± 4.77 , and the average of gestational age was 68.87 ± 4.77 days. There were no statistically significant differences in median age, parity, and body mass index, but there were in gestational age. The differences in β -hCG values between groups were statistically significant ($p < 0.001$). In patients treated with expectant treatment, the decrease in β -hCG values on the fourth day was 35.19% and 24% in patients treated with single-dose MTX. The risk factors for ectopic pregnancy of the groups are shown in Table II. The most common risk factors for ectopic pregnancy were the absence of risk factors, previous pelvic surgery, smoking, the presence of an intra-uterine device, assisted reproductive technique, previous ectopic pregnancy, and history of miscarriage. Table III shows the clinical features and ultrasound findings of the groups. The most common symptoms of ectopic pregnancy were pain, vaginal bleeding, and menstrual delay. There were significant differences between Group 4 and the other groups in terms of the presence of fetal cardiac activity, the presence of free fluid in the abdomen, the presence of gestational sac, and the average diameter of ectopic pregnancy mass. Figure 1 shows how a ROC analysis was used to determine the cut-off for changes in β -hCG levels between the first and fourth day and between the fourth and seventh day for a further dose of MTX. Patients benefited from a single-dose of MTX in β -hCG levels lower than 1,227.5 mIU/ml with a 68.5% sensitivity and 69.1% specificity.

Table I. Characteristics and β -hCG levels of groups between 0 and 7 days.

	Group 1 Expectant treatment	Group 2 Single-dose methotrexate	Group 3 Multidose methotrexate	Group 4 Surgical treatment	p-value
	n = 96	n = 681	n = 92	n = 234	
Age	30.29 ± 6.02	30.31 ± 5.96	30.8 ± 4.69	31.8 ± 5.22	0.635
Parity	1.29 ± 1.04	1.32 ± 1.13	1.47 ± 8.9	1.47 ± 1.13	0.153
Body mass index	24.76 ± 1.82	$24.71 (1.82)$	22.92 ± 1.16	22.92 ± 6.88	0.167
Gestational age (day)	37.87 ± 6.1	44.98 ± 8.63	61.07 ± 7.44	62.2 ± 4.77	0.0001*
Average diameter of ectopic pregnancy (mm)	3.67 ± 0.9	10.41 ± 2.36	26.93 ± 7.44	38.79 ± 7.39	0.0001*
Day 0 β -hCG level	520.94 ± 240.52	817 ± 633.18	$2,003.91 \pm 1,064.68$	$2,851.28 \pm 1,571.24$	0.0001*
Day 4 β -hCG level	337.66 ± 64.29	616 ± 640	$1,788.73 \pm 1,106.76$	$2,153.53 \pm 872.95$	0.0001*
Day 7 β -hCG level	201.18 ± 120.88	444 ± 524	$1,375.28 \pm 904.89$	$1,572.38 \pm 681.52$	0.0001*

*Statistical significance.

Evaluation of treatment modalities of ectopic pregnancy

Table II. Risk factors of four groups.

Risk factors	Group 1 n%	Group 2 n%	Group 3 n%	Group 4 n%	p-value
Absence of risk factors	30 (31.3%)	262 (38.5%)	28 (30.4%)	66 (28.2%)	0.922
Previous pelvic surgery	7 (7.3%)	79 (11.6%)	10 (10.9%)	28 (12%)	0.676
Smoking	21 (21.9%)	122 (17.9%)	20 (21.7%)	50 (1.4%)	0.876
Presence of an intra-uterine device	19 (19.8%)	109 (16.0%)	19 (20.8%)	50 (21.4%)	0.234
Assisted reproductive technique	6 (6.3%)	27 (4.0%)	4 (4.3%)	12 (5.1%)	0.323
Previous ectopic pregnancy	2 (2.1%)	15 (2.2%)	2 (2.2%)	5 (2.1%)	0.765
History of miscarriage	11 (11.5%)	67 (9.8%)	9 (9.7%)	23 (9.8%)	0.987
Total	96 (100%)	681 (100%)	92 (100%)	234 (100%)	0.676

Table III. Clinical features and ultrasound findings.

Clinical features	Group 1 n%	Group 2 n%	Group 3 n%	Group 4 n%	p-value
No clinic finding	46 (48%)	109 (16%)	16 (17.39%)	13 (5.55%)	0.0001*
Pain	10 (10.4%)	211 (31%)	28 (30.43%)	101 (43.16%)	0.0001*
Vaginal bleeding	27 (28.1%)	206 (30.3%)	26 (28.26%)	65 (27.77%)	0.0001*
Menstrual delay	13 (13.54%)	155 (22.76%)	22 (23.91%)	55 (23.5%)	0.0001*
Total	96 (100%)	681 (100%)	92 (100%)	234 (100%)	
Ultrasound findings					
Presence of fetal cardiac activity	0 (0%)	1 (0.15%)	0 (0%)	54 (23.07%)	0.0001*
Presence of free fluid in the abdomen	0 (0%)	23 (3.38%)	5 (5.4%)	94 (40.17%)	0.0001*
Presence of gestational sac	0 (0%)	82 (12%)	44 (47.8%)	124 (53%)	0.0001*
Average diameter of ectopic pregnancy mass (mm)	3.67 ± 0.9	10.41 ± 2.36	26.93 ± 7.44	38.79 ± 7.39	0.0001*

One-way ANOVA statistical test was performed among groups. *Statistical significance.

Discussion

As gestational age progresses, β -hCG values increase, as does the diameter of the ectopic focus. As the diagnosis period progresses, the rate of surgical intervention increases. In patients treated with expectant treatment, the decrease in β -hCG values on the fourth day was 35.19% and 24% in patients treated with single-dose methotrexate treatment. Patients who received a single dose of methotrexate treatment had β -hCG levels lower than 1,227.5 mIU/ml with a 68.5% sensitivity and 69.1% specificity. Ectopic pregnancy is a serious condition that affects sexually active women during their reproductive period. It is crucial to diagnose and treat the patients as soon as possible; otherwise, the patient's future fertility and life are jeopardized.

Although β -hCG is 1,500 mIU/L or higher, ectopic pregnancy should be suspected in patients whose intra-uterine gestational sac cannot be seen on transvaginal ultrasound. In the diagnosis of extrauterine pregnancy, not only is β -hCG measurement important but also transvaginal ultrasound¹⁵.

There is no consensus in the literature on the β -hCG cut-off level for expectant therapy that results in the highest success rate. It ranges from 200 to 1,500 mIU/L¹⁶⁻¹⁹. It has been reported that the spontaneous resolution rate in patients with initial serum β -hCG levels lower than 1,500 mIU/L was 21%²⁰. In this study, patients with β -hCG less than 520 were treated with expectant management, and 41.17% of patients recovered completely. Methotrexate prevents the formation of tetrahydrofolate, a vital compound for DNA and RNA synthesis, by blocking the catalyst enzyme dihydrofolate reductase. In ectopic pregnancies, it inhibits trophoblastic cell division. It can cause gastroenteritis, alopecia, elevated liver enzymes, stomatitis, pneumonia, and bone marrow depression. It has been reported that the treatment success rate with MTX is dependent on factors such as the initial β -hCG concentration, the size of the extrauterine mass, and previous extrauterine pregnancy history²¹. Thus, the most commonly used treatment is the single-dose methotrexate treatment. The literature had a success rate of up to 94%^{22,23}. Low

Single-dose MTX group	AUC (95%)	Cut-off value	p-value	Sensitivity	Specificity
Day 4 β -hCG	0.725 (0.672-0.777)	1,227.5	0.0001	68.5%	69.1%

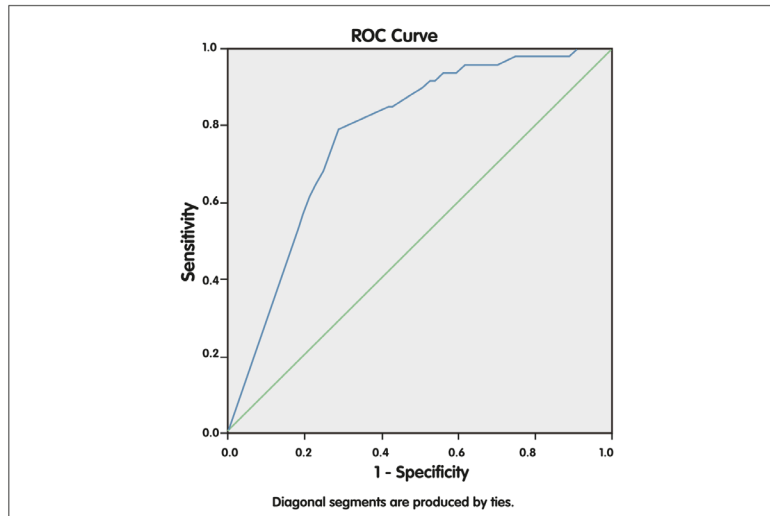


Figure 1. ROC curve of β -hCG value on day 4 of the single-dose methotrexate group.

baseline β -hCG levels can predict success with single-dose methotrexate therapy for ectopic pregnancy^{24,25}. Completely different initial β -hCG levels for successful treatment have been reported, such as 2,141 mIU/L, 1,790 mIU/L, and 2,000 mIU/L²⁶⁻²⁸. The initial hCG level is the most important parameter in determining treatment success²⁹. However, β -hCG levels were found to have no effect on treatment success³⁰. We found that patients with β -hCG values less than 1,227.50 mIU/L (68.33%) had the highest success rate with single-dose methotrexate.

Regardless of ectopic mass diameter and β -hCG level, the decrease in β -hCG level between day 1 and day 4 has been reported to be a good and early predictor of the success of MTX therapy for extrauterine pregnancy³¹. There is no consensus among the β -hCG threshold values reported within the literature. It has been reported³² that a decrease of more than 22% in β -hCG levels between 0 and 4 days can predict treatment success rate with a 97% positive predictive value.

Another study³³ reported a decrease in β -hCG levels of more than 20% between the first and fourth days, which could predict treatment success rate with a 100% positive predictive value. However, it was found that the decrease in β -hCG levels between the fourth and seventh days was more effective in reducing the need for additional doses of methotrexate than the decrease in β -hCG levels between the first and fourth

days³⁴. In our study, a 24% decrease between the first and fourth days resulted in 68.5% sensitivity and 69.1% specificity.

Risk factors for ectopic pregnancies are absent in up to 50% of cases³⁵. Any exposure that could damage the fallopian tubes, such as prior ectopic pregnancy, prior tubal surgery, history of pelvic inflammatory disease, and salpingitis node isthmica, is a risk factor for tubal pregnancy. The potential causes for such damage include abdominal surgery, smoking, a history of sexually transmitted infection, endometriosis, in-utero exposure to diethylstilbestrol, and use of ART³⁶. An increase in telocyte count in the fallopian tube may reduce tubal motility, affecting blastocyst transfer to the uterus and possibly contributing to EP pathogenesis³⁷. The results showed that although an isthmocele does not seem to increase the risk of cesarean scar pregnancy (CSP), embryo transfer on day 3 does. In patients with isthmocele, a single embryo transfer should be performed on day 5, which might reduce the risk of CSP³⁸. Although the risk of pregnancy is low in patients with an IUD, the risk of ectopic pregnancy is relatively high³⁹. Broad-based polyps near the tubal ostia or internal cervical OS may impair sperm transport and cause infertility⁴⁰.

The risk of recurrent ectopic pregnancy is approximately 10% in women who have had one prior ectopic pregnancy and up to 25% in women

who have had two or more prior ectopic pregnancies⁴¹. The use of ultrasound has significant medical and legal implications. It allows for objective documentation of the findings that lead to a clinical decision or specific obstetric intervention⁴². For a suspected ectopic pregnancy, a transvaginal ultrasound evaluation and pregnancy confirmation is the bare minimum. Serial evaluation using transvaginal ultrasonography or serum hCG level measurement or both are frequently required to confirm the diagnosis⁴³. The most common symptom of a tubal ectopic pregnancy is an extraovarian heterogeneous mass, which is usually a hematoma at the site of ectopic implantation. Tubal ectopic pregnancy is also distinguished by the presence of an echogenic ring in the adnexa surrounding an unruptured ectopic pregnancy, known as the tubal ring. The presence of an extrauterine gestational sac with an embryo confirms an ectopic pregnancy, but this finding is uncommon⁴⁴. In our study, approximately 30% of the groups had no identifiable risk factors. Laparoscopic treatment of extrauterine pregnancy is superior to laparotomy in terms of less hospital stay, less blood loss, less cost, less need for analgesics, and fewer postoperative intra-abdominal adhesions⁴⁵.

Strengths and Limitations of the Study

The data were meticulously collected, and the sample size was sufficient in comparison with the studies in the literature. This study determined the consequences of experience that could be beneficial to each group. The study was retrospective and was conducted in a single Turkish tertiary care hospital. This limitation may limit the ability to establish causal relationships and the generalizability of the study.

Conclusions

Patients with β -hCG levels lower than 1,227.5 mIU/L benefited from a single dose of methotrexate treatment. On the other hand, patients with β -hCG levels lower than 520 mIU/L benefited from the expectant treatment. Treatment options for ectopic pregnancy should be tailored to each individual case.

As gestational age progresses, β -hCG values increase, as does the diameter of the ectopic focus. As the diagnosis period progresses, the rate of surgical intervention increases.

In patients receiving methotrexate treatment, if the decrease in β -hCG values on the fourth day is

more than 24%, the success of the treatment increases significantly. On the other hand, if the decrease in β -hCG values on the fourth day is more than 35% in patients receiving expectant treatment, the treatment success is quite high. The need for additional doses for ectopic pregnancy can be predicted early based on the difference in the β -hCG values on the first and fourth days.

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Authors' Contributions

AB, OU: Conceptualized and designed the study.
AB, OU: Conducted statistical analysis, wrote the article.
AB, OU: Contributed to the interpretation of results.
AB, OU: Completed the final approval and had the manuscript ready for publication.

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Conflict of Interest

The authors declare they have no conflict of interest to declare.

Availability of Data and Materials

Data are available on request from the authors.

Ethics Approval

This study conforms to the provisions of the Declaration of Helsinki and was approved by the ethics committee of Istanbul Kanuni Sultan Süleyman Training and Research Hospital KAEK/2021.12.341.

Informed Consent

Informed consent was waived due to the retrospective design of the study.

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