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Treatment Management of Tubal Ectopic Pregnancy: A 4-Year Retrospective Single Center Experience

Tubal Ektopik Gebelik Tedavi Yönetimi: 4 Yıllık Retrospektif Tek Merkez Deneyimi

Cem DAĞDELEN[a], Yusuf DAL[b], Fatih AKKUŞ[c], Mehmet Okan ÖZKAYA[d], Evrim ERDEMOĞLU[d]

[a]Gynecology and Obstetrics Clinic, Meddem Hospital, Isparta Türkiye
[b]Department of Obstetrics and Gynecology, Faculty of Medicine, Mersin University Mersin, Türkiye
[c]Department of Obstetrics and Gynecology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Türkiye
[d]Department of Obstetrics and Gynecology, Faculty of Medicine, Suleyman Demirel University Isparta, Türkiye

ABSTRACT

Objective: Our study aimed to retrospectively analyze the treatment of tubal ectopic pregnancy cases treated in our clinic. Material and Methods: In this study, 113 patients who were diagnosed with an ectopic tubal pregnancy and treated with methotrexate (MTX) or surgical treatment at Süleyman Demirel University Hospital between November 2015 and November 2019 were retrospectively evaluated. Patients who had a successful outcome with single-dose MTX treatment were divided into two groups to compare the baseline beta-human chorionic gonadotropin (BhCG) values of patients who needed additional surgical treatment after single-dose MTX treatment. Apart from this comparison, the treatment modalities of these 113 patients diagnosed with ectopic tubal pregnancy were determined. The Shapiro-Wilks test evaluated the conformity of continuous variables to normal distribution. Mann-Whitney U test was used to compare paired groups that did not conform to normal distribution. Results: An analysis of the characteristics of the 113 patients included in the study showed that the mean age of the patients was about 29 years (17-45), 22 of them had a history of ectopic pregnancy, and 27 patients had clinical signs and symptoms of a ruptured tubal ectopic pregnancy. In an analysis of the treatment of 113 patients who underwent medical and surgical treatment for ectopic pregnancy in a 4-year period, it was found that among 51 patients treated with a single dose of MTX, 9 of them underwent surgical treatment due to surgical indications, and 8 patients were treated with an additional dose of MTX. When the BhCG values of patients whose treatment was completed with single-dose MTX were compared with the BhCG values of patients with unsuccessful responses to single-dose MTX treatment, it was found that the BhCG values were statistically significantly higher in the unsuccessful group (p=0.033). 62 patients were evaluated according to medical treatment contraindications, and relative contraindications and surgical treatment were applied without medical treatment. In total, we had 71 patients who received surgical treatment. All surgical treatments were completed laparoscopically. Of the 71 patients who underwent surgery, 38 patients underwent laparoscopic salpingostomy, and 33 patients underwent laparoscopic salpingectomy. Conclusion: In our 4-year retrospective review, surgical methods were the most commonly used in treating ectopic tubal pregnancy. Patient selection and treatment protocols should be improved in single-dose MTX treatment management.

Keywords: Pregnancy, tubal; salpingectomy; salpingostomy; methotrexate; pregnancy, ectopic

ÖZET

Amaç: Bizim çalışmamızın amacı kliniğimizde tedavi edilen tubal ektopik gebelik olgularına uygulanan tedavilerin retrospektif analizini yapmaktır. **Gereç ve Yöntemler:** Bu çalışmada Kasım 2015 ile Kasım 2019 yılları arasında Süleyman Demirel Üniversitesi Hastanesinde tubal ektopik gebelik tanısı konulan, metotreksat (MTX) tedavisi veya cerrahi tedavi uygulanan 113 hasta retrospektif olarak değerlendirildi. Tek doz MTX tedavisi ile başarılı sonuç alınan hastalarla, tek doz MTX tedavisi sonrası ek cerrahi tedavi ihtiyacı olan hastaların başlangıç beta-insan koryonik gonadotropin (BhCG) değerleri karşılaştırılmak üzere iki gruba ayrıldı. Bu karşılaştırma dışında tubal ektopik gebelik tanısı alan bu 113 hastanın tedavi yöntemleri ortaya koyuldu. Sürekli değişkenlerin normal dağılıma uyumu Shapiro-wilks testi ile değerlendirildi. Normal dağılıma uymadığı görünen ikili grupların karşılaştırılmasında Mann-Whitney U testi kullanıldı. **Bulgular:** Çalışmaya dahil edilen 113 hastanın karakteristik özellikleri incelendiğinde hastaların yaş ortalamasının yaklaşık 29 (17-45) olduğu ve bu hastaların 22'sinin daha önce ektopik gebelik öyküsü olduğu ve yine 27 hastanın da rüptüre tubal ektopik gebelik kliniği ve bulguları ile başvurduğu görüldü. 4 yıllık süreçte ektopik gebelik nedeniyle medikal ve cerrahi tedavi yapılan 113 hastanın tedavi yöntemleri incelendiğinde tek doz MTX tedavisi alan 51 hastadan 9'nun cerrahi endikasyonları nedeniyle cerrahi tedavi uygandığı, 8 hastaya ek doz MTX uygulandığı görüldü. Tek doz MTX uygulanarak tedavisi tamamlanan hastalarla, tek doz MTX tedavisine başarısız yanıt alınan hastaların BhCG değerleri karşılaştırıldığında başarısız olan grupta BhCG değerlerinin istatistiksel olarak anlamlı düzeyde yüksek olduğu bulunmuştur (p=0,033). 62 hastaya medikal tedavi kontrendikasyonlar ve rölatif kontrendikasyonlarına göre değerlendirilerek medikal tedavi uygulanmadan cerrahi tedavi uygulandı. Toplamda cerrahi tedavi alan 71 hastamız vardı. Cerrahi uygulanan 71 hastadan 38 hastaya laparoskopik salpingostomi uygulanırken 33 hastaya laparoskopik salpenjektomi yapıldı. **Sonuç:** 4 yıllık resrospektif incelememizde tubal ektopik gebelik tedavisinde en sık uyguladığımız cerrahi yöntemler oldu. Tek doz MTX tedavi yönetiminde hasta seçimi ve uygulanacak tedavi protokolleri geliştirilmedir.

Anahtar Kelimeler: Gebelik, tubal; salpinjektomi; salpingostomi; metotreksat; gebelik, ektopik

Correspondence: Cem DAĞDELEN
Meddem Hospital, Gynecology and Obstetrics Clinic, Isparta Türkiye
E-mail: cmdagdelen@gmail.com

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INTRODUCTİON

Ectopic pregnancy (EP) occurs due to the implantation of a fertilized oocyte outside the uterine cavity and is the most common cause of first-trimester morbidity and mortality.[1] Today, EP accounts for approximately 2% of all recognized pregnancies. In women between 15 and 44 years of age, the average annual EP rate is estimated to be 0.64%.[2] The most common location of EP is in the fallopian tube, predominantly in the ampullary region of the fallopian tube. Implantation outside the fallopian tube, for example, in the cervix, ovary, myometrium, abdominal, or interstitial part of the fallopian tube, occurs in less than 10% of EPs.[3] Previous pelvic infection, ectopic pregnancy, infertility, intrauterine device (IUD) use, current IUD use, and previous adnexal and previous tubal surgery can be counted as EP risk factors.[4]

If EPs are not diagnosed in time, they may lead to significant complications such as rupture of the fallopian tube or other structures and intraabdominal hemorrhage. Therefore, treatment should be initiated as soon as the diagnosis is made.[5] After appropriate patient selection, it can be treated medically with methotrexate (MTX), targeting the trophoblastic tissue of the embryo. Surgical treatment is another option in ruptured EP where medical treatment has failed or is contraindicated. Laparoscopic surgery, instead of laparotomy, is the recommended and gold standard method.[6,7] There are two surgical approach options for tubal pregnancy. Salpingectomy and salpingostomy (cutting the tube to eliminate the tubal pregnancy but leaving the rest of the tube intact) seem to result in similar fertility outcomes in subsequent pregnancies. Traditionally, salpingectomy has been the standard procedure, but salpingostomy offers a conservative option.[8,9]

Our study aimed to retrospectively analyze the treatment of tubal EP cases treated in our clinic and to evaluate the success rate of a single-dose MTX treatment protocol.

MATERIALS AND METHODS

In this study, we retrospectively evaluated 113 patients diagnosed with tubal EP who underwent single-dose MTX therapy or surgical treatment at Süleyman Demirel University Hospital between November 2015 and November 2019. Some demographic characteristics of the patients, treatment modalities, and beta-human chorionic gonadotropin (BhCG) data were recorded on the first day of treatment and day 7. Surgical treatment (laparoscopic salpingectomy and salpingostomy) was applied in case of MTX contraindication in treatment management, and medical treatment was applied to other patients. The diagnosis of ectopic pregnancy was made when the intrauterine pregnancy could not be visualized by transvaginal ultrasound at serum BhCG levels above 1500 mIU/ml, and when there was an increase of less than 60% in serial BhCG measurements taken at 48-hour intervals at values below 1500 mIU/ml or when the ectopic focus was visualized by transvaginal ultrasound.

For the treatment of ectopic pregnancy, liver and renal function tests, hemodynamic stability, presence of ruptured ectopic pregnancy and the embryonic cardiac activity of the ectopic pregnancy, and presence of ectopic pregnancy >4 cm in size visualized by transvaginal ultrasonography should be determined before medical treatment of the patients with MTX. These conditions were considered as MTX contraindications or relative contraindications (Table 1). EPs located outside the tuba, ectopic pregnancies treated with multiple doses of MTX, and expectorant approach were excluded from the study.

Patients who had successful results with single dose MTX treatment and patients who needed additional surgical treatment after single dose MTX treatment were divided into two groups to compare baseline BhCG values.

Patients with a decrease of less than 15 percent in BhCG value at week 1 after MTX administration and patients who underwent emergency operations due to hemodynamic instability after MTX administration were considered unsuccessful in single-dose MTX treatment (Table 2).

Apart from this comparison, the treatment modalities of these 113 patients diagnosed with tubal EP were revealed.

The Suleyman Demirel University Faculty approved the study of Medicine Clinical Research

TABLE 1: MTX contraindications.[9]

Absolute Contraindications	Relative Contraindications
Intrauterine pregnancy	Ectopic pregnancy >4 cm in size visualized by transvaginal ultrasonography
Evidence of immunodeficiency	Refusal to accept a blood transfusion.
Moderate to severe anemia, leukopenia, or thrombocytopenia	Embryonic cardiac activity detected by transvaginal ultrasonography
Sensitivity to MTX	High baseline BhCG concentration (>5,000 mIU/mL)
Active lung disease	Inability to participate in monitoring
Active peptic ulcer disease	
Clinically significant liver dysfunction	
Clinically significant renal dysfunction	
Breastfeeding	
Ruptured ectopic pregnancy	
Hemodynamically unstable patient	

TABLE 2: Failure criteria for single dose MTX administration.

BhCG value decreased by less than 15 percent in the 1st week after MTX administration
Emergency operation due to hemodynamic instability after MTX administration

Ethics Committee with the decision dated 07.07.2022 and numbered 14/189. All patients included in the study were informed, and a voluntary consent form was obtained. This study was conducted in accordance with the Helsinki Declaration Principles.

STATISTICAL ANALYSIS

The data obtained from the study were analyzed with PASW Statistics 18 program. As a result of the analysis, categorical variables were presented as percentage and frequency, and continuous variables were presented as mean, standard deviation, median, and quartiles. The Shapiro-Wilks test evaluated the conformity of continuous variables to normal distribution. Mann-Whitney U test was used to compare paired groups that did not fit the normal distribution. $p<0.05$ was accepted as the significance level.

MEDICAL TREATMENT PROTOCOL

With a single-dose regimen, MTX is administered at a dose of 50 mg/m^2. When using a "single dose" MTX regimen, additional doses of MTX may be administered if the response is deemed inadequate (Table 2). In both single and multiple-dose MTX treatment protocols, once BhCG levels meet the criteria for the initial decline, BhCG levels are serially monitored at weekly intervals to ensure that concentrations steadily decline and become undetectable.[10]

SURGICAL TREATMENT PROTOCOL

Laparoscopic surgery has become the gold standard in the surgical treatment of EP. It appears to have advantages over laparotomy in terms of operative time, hospital stay and recovery time, analgesic requirement, and hospital cost.[11]

Salpingectomy is based on the total or partial removal of the tuba on the side of the ectopic focus. During this procedure, it is recommended to use bipolar electrosurgery that wraps the tube from the upper edge of the mesosalpinx to minimize the spread of thermal energy that may adversely affect ovarian blood flow.[12]

Salpingostomy involves making a linear incision over the tubal EP focus and removing the ectopic focus, aiming to preserve the tube for future pregnancy.[13]

RESULTS

In an analysis of the treatment methods and characteristics of 113 patients who underwent medical and surgical treatment for ectopic pregnancy at the Clinic of Gynecology and Obstetrics, Süleyman Demirel University Hospital in a 4-year period, the mean age of the patients included in the study was about 29 years (17-45) and the mean gestational week was 6 weeks (3-10) (Table 3). While 11 patients had a tubal

TABLE 3: Demography and obstetrical history

	Mean	Std. Deviation	Minimum	Maximum
Age	29,47	5,951	17	45
Gravida	2,78	1,624	1	11
Parite	,97	,977	0	5
Abortus	,72	1,089	0	8
Gestational week	6,09	1,873	3	10

surgery history, the number of patients who underwent abdominal surgery other than tubal surgery was 45. In addition, 22 of these patients had a history of ectopic pregnancy, and 27 patients had clinical signs and symptoms of a ruptured tubal ectopic pregnancy (Table 4).

51 patients were started on single-dose MTX treatment. After single dose MTX treatment, 9 of these 51 patients underwent surgical treatment due to surgical indications, while 8 patients received an additional dose of MTX. 62 patients were evaluated according to the contraindications, and relative contraindications of medical and surgical treatment were applied without medical treatment. In total, we had 71 patients who received surgical treatment. All surgical treatments were completed laparoscopically. Of the 71 patients who underwent surgery, 38 patients underwent laparoscopic salpingostomy, and 33 patients underwent laparoscopic salpingectomy (Table 5).

When the BhCG levels of patients whose treatment was completed with single dose MTX were compared with the BhCG levels of patients whose treatment was completed with surgery (unsuccessful response to single dose MTX treatment), it was found that BhCG levels were statistically significantly higher in the unsuccessful group (p=0.033) (Table 6).

TABLE 4: Ectopic pregnancy and operation history.

	n	Percent (%)
Abdominal operation history	45	39,82
Tubal operation history	11	9,7
Ectopic pregnancy history	22	19,46

TABLE 5: Applied treatment methods.

Treatment method applied	n	Percent (%)
Methotrexate	34 (single dose) 8 (multiple doses)	37,2
Laparoscopic salpingostomy	35	31
Laparoscopic salpingectomy	27	23,9
Laparoscopic salpingostomy after failed methotrexate	3	2,7
Laparoscopic salpingectomy after failed methotrexate	6	5,3

TABLE 6: BhCG levels after single dose MTX treatment

	Median	Quadrant	p value
Successful treatment with MTX (N:34)	1445	294-1966	0,033
Unsuccessful treatment with MTX (N:9+8)	4649	653-7557	

DISCUSSION

In this study, we aimed to retrospectively analyze the treatment of tubal EP cases treated in our clinic and to evaluate the success rate of the single-dose MTX treatment protocol.

In the literature, it has been observed that single-dose MTX achieved a success rate of 80-88% in treating tubal EP.[14,15] In our study, the treatment success rate was 66% in patients treated with single-dose MTX. Compared to the studies in the literature, it was observed that our success rate in single-dose MTX treatment could be improved. When alternative medical methods to single-dose MTX treatment are investigated, two-dose MTX and letrozole treatments come to the forefront in the literature. Although there are studies suggesting that two-dose MTX treatment is therapeutic with similar success rates as single-dose MTX, Gupta et al. showed in a meta-analysis study that two-dose MTX protocol in EP treatment was more successful than single-dose protocol in terms of treatment success.[16,17] In another study by Rezaei et al., MTX+letrozole was found to be a safer

and more effective alternative treatment method than MTX+placebo in treating clinically stable women diagnosed with tubal EP.[18] Studies on developing medical treatments that keep us away from surgery, preserve the patient's fertility, and reduce treatment costs are increasing.[19]

Surgical treatments are recommended in cases where medical treatment is contraindicated or relatively contraindicated, and laparoscopy is considered the gold standard. In a study of 52 patients who underwent salpingectomy due to EP, no difference was observed in ovarian function tests when laparotomy cases were compared with laparoscopy cases.[20] In our study, 71 patients underwent surgical treatment for tubal EP, and all completed laparoscopically. The type of operation, conservative or radical, is determined according to the patient's clinical condition, desire for fertility, tubal status, and previous history of EP. In the meta-analysis study of Tian et al. investigating the effects of salpingostomy and salpingectomy on fertility, no difference was found in fertility.[9] In Laganà's study on 132 patients, in addition to the opinion that salpingectomy should generally be preferred to salpingostomy in women with a healthy contralateral tube, a conservative treatment approach such as salpingostomy is recommended in women who have risk factors for infertility, have an unhealthy contralateral tuba and want tuba protection.[21] In our study, salpingostomy was performed in 38 patients and salpingectomy in 33 patients. The literature suggests that there is no difference between the odds of pregnancy formation after medical and surgical treatment for ectopic pregnancy.[22,23] As a limitation of our study, the probabilities of pregnancy formation after treatment were not assessed.

The low success rate of the medical treatments we applied in our clinic in our study leads us to search for different methods in the medical treatment plan. For example, there are studies with more successful results in multiple-dose MTX treatment protocol. Laparoscopy is the standard gold method for patients who cannot be treated medically. Conservative (salpingostomy) and radical (salpingectomy) surgical approaches are determined according to the patient's fertility desire and clinical condition.

CONCLUSION

In our 4-year retrospective review, surgical methods were the most commonly used in treating ectopic tubal pregnancy. Patient selection and treatment protocols should be improved in medical treatment management.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Yusuf Dal, Cem Dağdelen;* ***Design:*** *Cem Dağdelen;* ***Control/Supervision:*** *Evrim Erdemoğlu, Mehmet Okan Özkaya;* ***Data Collection and/or Processing:*** *Cem Dağdelen, Yusuf Dal;* ***Analysis and/or Interpretation:*** *Cem Dağdelen;* ***Literature Review:*** *Cem Dağdelen, Fatih Akkuş;* ***Writing the Article:*** *Cem Dağdelen, Yusuf Dal;* ***Critical Review:*** *Cem Dağdelen, Fatih Akkuş;* ***References and Fundings:*** *Cem Dağdelen, Yusuf Dal;* ***Materials:*** *Yusuf Dal.*

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