

Treatment Approaches in Ectopic Pregnancy: Retrospective Analysis of a Tertiary Referral Center

Ektopik Gebelikte Tedavi Yaklaşımları: Tersiyer Bir Referral Merkezin Retrospektif Analizi

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Abstract

Aim : We have retrospectively analyzed the patients followed-up in our department upon tentative diagnosis of EP in order to evaluate the treatment success of surgical approaches and MTX.

Method: This is a retrospective study analyzing the data of 79 patients hospitalized upon tentative diagnosis of EP at MuglaSıtkıKocman University Education and Research Hospital, Department of Obstetrics and Gynecology between 01/01/2018-01/10/2019. Success rates of surgical treatment and medical treatment were compared.

Results: 79 patients were treated upon the pre-diagnosis of EP in our department. In 10 patients (12.65%), EP regressed during follow-up. Thirty-six patients (45.56%) were treated surgically, 29 patients (39.7%) were treated medically, and the remaining 4 had CSEP, out of whom 3 (3.79%) patients underwent D&C and 1 patient (1.26%) was treated with systemic MTX injection. Disgerminoma was diagnosed in one patient who underwent surgical treatment.

Conclusion: Due to the difficulties in its diagnosis and variations in treatment methods, EP must always be well-acknowledged by the obstetricians. CSEP diagnosis must be kept in mind along with the increasing Cesarean section rates over the recent years. When surgical treatment is opted, it should be remembered that LS is the current approach to surgery.

Keywords: Ectopic Pregnancy, Methotrexate, Cesarean scar ectopic pregnancies, β -hCG

Öz

Amaç: Ektopik gebelik ön tanısı ile kliniğimizde takip edilen hastaların, cerrahi yaklaşımlarını ve Metotreksat uygulamasının tedavi başarısını değerlendirmek üzere retrospektif olarak analiz ettik.

Yöntem: 01/01/2018-01/10/2019 tarihleri arasında Muğla Sıtkı Koçman Üniversitesi Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde ektopik gebelik öntanısı ile takip edilen 79 hastanın verileri analiz edildi. Cerrahi tedavi ve tıbbi tedavi başarı oranları karşılaştırıldı.

Bulgular: Çalışmamızda, 79 hasta ektopik gebelik ön tanısı ile takip edildi. 10 hastada (% 12.65) ektopik gebelik takip sırasında spontan olarak geriledi. 36 hasta (% 45.56) cerrahi olarak tedavi edildi, 29 hasta (% 39.7) tıbbi olarak tedavi edildi. 4 hastada Sezaryen Skar ektopik gebeliği mevcuttu. Bunların 3'ü (% 3.79) D/C, 1'i (% 1.26) sistemik MTX enjeksiyonu tedavi edildi. Cerrahi tedavi uygulanan bir hastaya disgerminom tanısı konuldu.

Sonuç: Teşhisteki zorluklar ve tedavi yöntemlerindeki farklılıklar nedeniyle, ektopik gebelik her zaman kadın doğum uzmanları tarafından iyi bilinmelidir.

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Sezaryen skar ektopik gebeliği ihtimali, son yıllarda artan sezaryen oranları ile birlikte akılda tutulmalıdır. Cerrahi tedavi tercih edildiğinde, LS'nin cerrahi yaklaşımın güncel yaklaşımı olduğu unutulmamalıdır.

Anahtar Kelimeler: Ektopik Gebelik, Metotreksat, Sezaryen skar ektopik gebeliği, β -hCG

Introduction

Ectopic pregnancy (EP) is described as the implantation of a fertilized ovum outside the endometrial cavity which occurs in approximately 1.5 to 2.0% of all pregnancies(1). While EP-associated mortality significantly varies depending on the development level of relevant country, the mortality rate due to EP in the US between 2003 and 2007 was 0.5/100,000(2). Previous EP, genital infections, tubal surgery, Cesarean section, tubal pathology, in utero diethylstilbestrol (DES) exposure, infertility and relevant treatment, and a lifetime number of sexual partners >1 were associated to EP risk(3).

EP occurs in various locations, given in order of decreasing frequency: tubal pregnancy [ampulla (70%), isthmus (12%), fimbria (11.1%)], interstitial pregnancy (2%-4%), cornual pregnancy (<1%), ovarian pregnancy (3%), cervical pregnancy (<1%), Cesarean scar pregnancy (<1%), intra-abdominal pregnancy (very rare), and heterotopic pregnancy (very rare)(4). However, the gradual increase in Cesarean sections in recent years raises the concern that number of Cesarean scar ectopic pregnancies (CSEP) may also increase gradually.

Diagnosis of EP critically requires an increased awareness and understanding of the associated risk factors. Advances in ultrasound (USG) technology as well frequent and sensitive follow-up of serum beta-human chorionic gonadotropin (β -hCG) levels are essentially useful in diagnostics. Although certain serum biomarkers are suggestive of EP diagnosis, gold standard method is diagnostic laparoscopy (DL)(5). Treatment modalities are expectant management (success rate: 47%-82%)(6), single or multiple dose methotrexate (MTX) (success rate: 88%-93%)(7), and surgical treatment including laparotomic (open) surgery (LT), laparoscopic surgery (LS), salpingectomy, or salpingostomy.

We have retrospectively analyzed the patients followed-up in our department upon tentative diagnosis of EP between 01/01/2018 and 01/10/2019 in order to evaluate the treatment success of surgical approaches and MTX.

Methods

This is a retrospective study analyzing the data of 79 patients hospitalized upon tentative diagnosis of EP at Mugla Sıtkı Kocman University Education and Research Hospital, Department of Obstetrics and Gynecology between 01/01/2018 and 01/10/2019. Ethical approval for the study was obtained from the Ethics Committee of Mugla Sıtkı Kocman University (Ethics Committee protocol code: 14/11/2019-3). The study was conducted in accordance with the Helsinki declaration.

Age, gravidity, parity, symptoms, gestational age by last menstrual period (LMP), β -hCG levels, and USG findings were evaluated retrospectively for all patients. In our department, the diagnosis of ectopic pregnancy is made based on a serum β -hCG level of >1500 mIU/mL in addition to unobserved intrauterine (IU) gestational sac through transvaginal (TV) USG or no more than 66% increase in β -hCG values at 48-hour intervals during follow-up and/or unobserved trophoblastic tissue in endometrial sampling.

MTX treatment was performed on patients who were not scheduled to undergo surgery and who were not apply surgery; and was not performed in the presence of a known MTX allergy or a significant hepatic, pulmonary, renal or hematological disease. Prior to MTX treatment, informed consent was obtained from all subjects. Treatment regimen composed of a single 50 mg/m² dose of intramuscular MTX (METHOTREXATE-KOÇAK 50 mg/5 ml Vial Containing Solution for Injection, KOÇAK Farma İlaç ve Kimya Sanayi A.Ş.) administered to all eligible subjects. Before the administration of the first dose, all patients were tested for blood group typing, complete blood count, liver function tests, blood urea, and creatinine levels. Any patients with a known history of lung disease were evaluated through chest radiography due to the risk of interstitial pneumonitis. In case of Rhesus (Rh) factor incompatibility, Rh-immunoglobulin (RhoGAM Ultra-Filtered PLUS 300 μ g (1500 IU), Ortho-Clinical Diagnostics, Inc. NJ, USA) was applied. Day of MTX administration was considered as Day 0, thereafter, β -hCG was re-tested at Day 4 and Day 7. A 2nd dose of MTX treatment was administered where decrease in β -hCG level was <15% between Day 4 and Day 7. In the event of a decrease by >15% in β -hCG levels between Day 4 and Day 7, those were followed-up with weekly β -hCG levels and a β -hCG level of 25 IU/mL was considered treatment success.

Patients ineligible for medical treatment (patients with unstable hemodynamics, suspected to have ruptured EP, ineligible for or unwilling to get MTX treatment) were treated surgically. All LS and LT were performed under general anesthesia by multiple gynecologist in a single center. The decision to perform LS or LT and type of the procedure performed during the operation (salpingectomy, salpingostomy, etc.) was made depending on the experience of the attending/responsible physician. The exclusion criterion for the study was patients who have received MTX treatment after that have no other control and follow-up after surgery.

Results

Throughout the study, 79 patients were treated upon the pre-diagnosis of EP in our department. In 10 patients (12.65%), EP regressed during follow-up. Thirty-six patients (45.56%) were treated surgically, 29 patients (39.7%) were treated medically, and the remaining 4 had CSEP, out of whom 3 (3.79%) patients underwent D&C and 1 patient (1.26%) was treated with systemic MTX injection. Demographic data (age, gravidity, parity, height, weight, β -hCG) of patients treated medically and surgically were shown in Table 1.

Table-1 :Demographic data of the patients

	Operated (n=36)	Medically Treated (n=32)
Age (years)	29.6 ± 4.9	26.7 ± 10.2
Gravidity (n)	2.4 ± 1.0	1.9 ± 1.0
Parity (n)	0.8 ± 1.0	0.5 ± 0.7
Height (cm)	168.1 ± 6.1	148.4 ± 48.8
Weight (kg)	70.4 ± 9.8	61.7 ± 22.8
β-hCG (IU/mL)	5509.0 ± 4442.6	1181.2 ± 1170.0

Of patients treated surgically, 77.7% (n=28) were treated using LS, and 22.2% (n=8) were treated with LT. Of 28 patients treated with LS, 24 (85.71%) underwent salpingectomy while 4 (14.28%) underwent salpingo-oophorectomy. Among the 8 LT patients, 5 (62.5%) underwent salpingectomy, 2 (25%) underwent salpingo-oophorectomy, and 1 (12.5%) underwent cornual resection. One of the patients who underwent LT salpingo-oophorectomy was diagnosed with dysgerminoma. Treatment modalities performed on patients were shown in Table 2.

Table-2: Treatment modalities of the patients

		n (79)	%
Observation		10	12.65
Surgical Treatment		36	45.56
Laparoscopy		28	35.44
	Laparoscopic Salpingectomy	24	30.37
	Laparoscopic Salpingo-oophorectomy	4	5.06
Laparotomy		8	10.12
	Laparotomic Salpingectomy	5	6.32
	Laparotomic Salpingo-oophorectomy	2	2.52
	Laparotomic Cornual Resection	1	1.26
Systemic Methotrexate		29	36.7
	Successful Outcome	25	31.64
	Multiple Dose Methotrexate	3	3.79
	Post-methotrexate Surgery	1	1.26
Cesarean Scar Pregnancy		4	5.06
	Dilatation/Curettage	3	3.79
	Methotrexate	1	1.26

During the specified period, systemic MTX treatment was administered to 29 patients (39.7%) in our department. Among 29 MTX receivers, 25 (86.2%) had a β-hCG level <20 mIU/mL. Due to the development of signs of acute abdomen and disruption of hemodynamics in 3 patients (10.34%), treatment could not be continued, and surgery was performed. A second dose of MTX treatment was administered to 1 patient (3.44%) with less than 15% decrease in β-hCG levels between Day 4 and Day 7, and thus, resolution in β-hCG level was attained.

In our series, the success of single-dose MTX treatment was found to be 86.2%, and the success of overall systemic MTX treatments was found to be 89.65%.

Our cohort of patients was including 4 patients followed-up with the diagnosis of CSEP, among them, 2 (50%) underwent D&C and 1 (25%) was given MTX. For the last patient, D&C was applied at another center after which the patient was transferred to our department due to abundant bleeding and needed blood transfusion and intrauterine balloon tamponade.

Discussion

Of 69 patients treated in our study, 28 (40.57%) was operated by LS, with 24 (34.78%) undergoing LS salpingectomy and 4 (5.78%) undergoing LS salpingo-oophorectomy. LS ratio in the study by Turhan et al. was 20% and in another study by Özyapı Alper et al. it was done in 14.8% of patients. Compared to named studies which were also performed in our country, our ratio of LS is higher. We believe that such a higher figure is attributable to the increasing experience of surgeons as a result of LS operations being performed more frequently in the recent years, and the consistent availability of equipment and staff in our hospital to perform LS.

Success rate with a single dose of MTX varies between 64-90% in the literature (8, 9). In our study, successful outcomes were obtained in 86.2% of the patients who received MTX treatment. The need for surgical treatment arose due to the development of hemodynamic instability in 10.34% of the patients treated with MTX. In the study by Kılıç BS et al., hemodynamic instability was highlighted as the most important parameter in making decision of surgery, where single-dose MTX treatment has failed (10). This principle corroborates the results of our study. In the study by Pulatoglu C et al., the cut-off β-hCG value, which determined the failure of methotrexate treatment, was found to be 1362 mIU/mL (11). In our study, we didn't calculate cut-off β-hcg value related to methotrexate failure.

In the surgery sub-group made of 36 patients, 29 underwent salpingectomy, 6 underwent salpingo-oophorectomy, and one underwent cornual resection. Salpingostomy is among the surgical treatments modalities for EP (12). In the study by Lagana AS et al., EP recurrence at the end of 2 years was 3-fold higher in patients who underwent salpingostomy than in those who underwent salpingectomy (12). Therefore, salpingostomy method is unpreferable for us.

In the study by Condous P et al., the sensitivity and specificity of TV USG in the diagnosis of EP were 90.9% and 99.9%, respectively. In the same study, its positive predictive value was found to be 93.5% and negative predictive value as 99.8% (13). Among the patients included in our study, one patient who experienced LT due to preliminary diagnosis of EP was diagnosed to have dysgerminoma. In 2% of the dysgerminoma patients, pregnancy-associated pathologies are considered due to β-hCG hormone secreted by isolated syncytiotrophoblast cells, and thus, misdiagnoses may be encountered (14).

Cornual EP is a rare form of EP. Its diagnosis is more difficult than other types of EP, particularly compared to tubal ectopic pregnancy (15). Angular pregnancy must also be kept in mind for differential diagnosis(16). In our cohort, cornual pregnancy was detected in one case and diagnostic LT + cornual resection was performed. In the literature, there are many publications in which cornual EP was treated with LS (15, 17).

Cesarean section rates show a significant increase both in our country and around the world (18) which eventually leads to an increase in CSEP incidence. In the review by Bodur S. et al., CSEP incidence in general obstetric population was 1/3.000, whereas it was 1/531 in patients who had undergone at least one Cesarean section (19). Of 79 patients included in our study, 4 had CSEP. We attribute this high incidence to the fact that our hospital is a tertiary center. In previous experience reported by another center, surgical treatment or combined systemic and intra-gestational MTX were both successful in the management of CSEP(20). In our experience, likewise, CSEP patients were treated by systemic MTX and D&C in one and 2 cases, respectively. Another patient underwent intracervical balloon placement due to the abundant bleeding as a result of D&C performed in another hospital and was followed-up with blood transfusion.

Conclusion

Ectopic pregnancy maintains its importance as it is the most common cause of mortality during the first trimester. Due to the difficulties in its diagnosis and variations in treatment methods, EP must always be well-acknowledged by the obstetricians. CSEP diagnosis must be kept in mind along with the increasing Cesarean section rates over the recent years. When surgical treatment is opted, it should be remembered that LS is the current approach to surgery.

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