

Management of Ectopic Pregnancy: Comparison of Systemic Methotrexate Administration and Surgical Treatment; A Retrospective Study

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OBJECTIVE: The key to preventing maternal death is early diagnosis and effective treatment of obstetric complications. Ectopic pregnancy continues to be the number one cause of maternal deaths in the first trimester of pregnancy.

Since ectopic pregnancy is the leading cause of pregnancy related death in the first trimester and accounts for 9% of all pregnancy-related deaths, the diagnosis and treatment stages should be fast and planned. In this study, our aim is to compare the results of medical treatment and surgical treatment in ectopic pregnancies.

STUDY DESIGN: A retrospective case note review was undertaken of all women who presented to Dokuz Eylül University Hospital (approximately 1800 deliveries/ year) with an ultrasonographically diagnosed ectopic pregnancy from 1st January 2008 to 1st March 2012. All patients' medical data were recorded.

RESULTS: A total of 199 patients diagnosed with ectopic pregnancy were recruited for the study. We had total of 199 patients diagnosed with ectopic pregnancy. 90 patients were given methotrexate (MTX) treatment. From 90 (45.3%) patients who were given MTX, 29 (14.6%) of the patients had urgent surgical treatment. Second dose MTX treatment was given to 14 patients. Second dose treatment was successful in 6 patients and 8 patients had surgery. 121(60.8%) patients underwent laparoscopic salpingotomy 15 (7.5%) patients underwent laparoscopic salpingostomy and 2 (1%) patients underwent diagnostic laparoscopy.

CONCLUSION: The key to preventing maternal death is early diagnosis and effective treatment of obstetric complications. Ectopic pregnancy continues to be the number one cause of maternal deaths in the first trimester of pregnancy

Key words: Pregnancy, Ectopic, Methotrexate

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Introduction

The key to preventing maternal death is early diagnosis and effective treatment of obstetric complications.¹ Ectopic pregnancy continues to be the number one cause of maternal deaths in the first trimester of pregnancy.^{1,2}

Ectopic pregnancy is a significant cause of maternal mor-

bidity and mortality, as well as fetal loss. Since ectopic pregnancy is the leading cause of pregnancy related death in the first trimester and accounts for 9% of all pregnancy-related deaths, the diagnosis and treatment stages should be fast and planned.³

Medical management has become increasingly popular in the treatment of ectopic pregnancy. Given its convenience, for many it is used as a first-line treatment, however, this is not always the optimal choice for the patient. It is important to understand the options for medical treatment and when it is appropriate to treat a particular patient with medical management, or when one should opt for surgical management.⁴ Laparoscopic salpingostomy or salpingectomy remains the preferred means of surgical removal of ectopic pregnancies.⁵ On the other hand for medical management, methotrexate (MTX) is widely accepted as a first choice. MTX can be ad-

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ministered intramuscularly in single dose or repeated doses either with folic acid supplement or not.

There are many studies comparing medical and surgical treatments. In this study, our aim is to compare different managements and treatment outcomes of patients who were diagnosed with ectopic pregnancy.

Management of ectopic pregnancy varies depending on the clinical status of the patient and serum levels of β HCG and other laboratory results. Surgical treatment, medical-methotrexate treatment or wait and watch protocols are the choices for the clinician in the convention of ectopic pregnancy. Surgical treatment seems to have been reduced to laparoscopic salpingostomy or salpingotomy. Wait and watch protocol can be administered in the case of ectopic pregnancy which is expected to limit itself with tubal abortion and re-absorption.

Methotrexate is a folate antagonist. It acts by inhibiting the enzyme dihydrofolate reductase which is essential for the de novo synthesis of purine and pyrimidine bases and interferes with DNA synthesis and cell proliferation.⁶ Methotrexate therefore stops further development of the pregnancy, which is gradually reabsorbed. The protocol is for the administration of 50 mg/m² of MTX intramuscularly, followed by serial serum β HCG levels on days 4 and 7 and administration of a second dose of MTX if these levels have failed to fall by more than 15%. Approximately %14 of patients will require more than one dose of MTX and less than %10 will undergo subsequent emergency surgical intervention.⁶

It is often difficult for clinicians and women to balance the advantages and disadvantages of each treatment modality. The aim in similar studies is to determine the reliability of MTX, to measure its success in avoiding surgery and to broaden the limits of medical treatment.

Material and Method

A retrospective case note review was undertaken of all women who presented to Dokuz Eylul University Hospital (approximately 1800 deliveries/year) with an ultrasonographically diagnosed ectopic pregnancy from 1st January 2008 to 1st March 2012. A total of 199 patients diagnosed with ectopic pregnancy were recruited for the study. The study data was obtained from patient files and information recorded on the computers. The criteria of suitability for MTX therapy were determined as follows:

- 1- An ectopic gestational lump of < 4 cm in transvaginal ultrasonography.
- 2- Lack of fetal cardiac activity in transvaginal ultrasonography
- 3- The β HCG value being <6.000

Exclusion criteria for MTX treatment were: uncertain diagnosis, presence of fetal heart beat, hemodynamic instability; severe abdominal pain; active pulmonary, renal or liver disease, inability to return for follow ups and refusal of medical treatment.

The patients were grouped as Group A: Methotrexate group, Group B: Surgical Treatment Group C: Failed medical treatment and patients who went urgent surgical treatment.

All patients age, gravida, parity, initial β HCG, β HCG measurements at discharge, hospitalization days, need of blood transfusion were recorded. The number of repeating doses and β HCG values on day 4 and 7 and the rate of undergoing a laparoscopy salpingostomy were calculated in patients receiving MTX.

If there was any suspicion of tubal rupture at any time during the treatment or follow-up period, a salpingotomy was performed via laparoscopy or laparotomy. The main indications for emergency surgery were hemodynamic instability and severe abdominal pain.

Statistical analyses of data were made using the SPSS for Windows 11.5 package program. Arithmetical mean \pm Standard deviation was used as the descriptive value. The limit of significance was set at 0.05.

Results

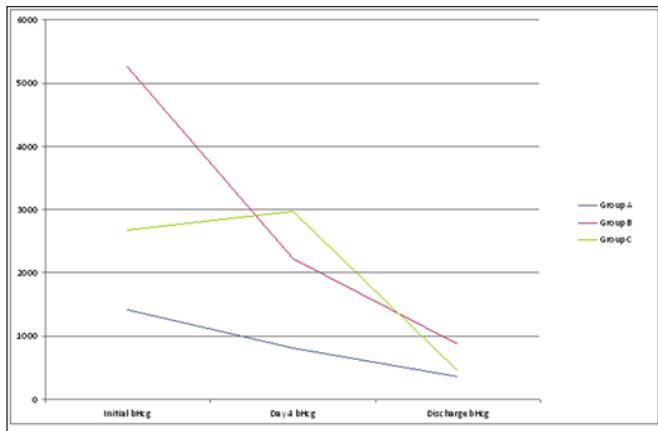
We had total of 199 patients diagnosed with ectopic pregnancy. 90 patients were given MTX treatment. From 90 (45.3%) patients who were given MTX, 29 (14.6%) of the patients had urgent surgical treatment. Second dose MTX treatment was given to 14 patients. Second dose treatment was successful in 6 patients and 8 patients had surgery. 121 (60.8%) patients underwent laparoscopic salpingotomy 15 (7.5%) patients underwent laparoscopic salpingostomy and 2 (1%) patients underwent diagnostic laparoscopy. Group A was formed from 61 patients who had only medical treatment. Group C was formed from 29 patients who had medical treatment but failed, and underwent surgery. Group B: 121 patients underwent laparoscopic surgery.

The demographic characteristics of patients are summarized in Table 1. The age distributions for Group A and Group B and Group C were 28.4 \pm 5.48 and 31.1 \pm 4.92 and 29.8 \pm 4.53 respectively. The gravidity distributions for Group A and B and C were 2.31 \pm 1.39 and 2.64 \pm 1.43 and 2.53 \pm 1.68 respectively. The parity distributions for Group A and Group B and Group C were 0.49 \pm 0.80, 0.77 \pm 0.90 and 0.41 \pm 0.56 respectively.

Table 1: Demographic characteristics of the Group A-B-C.

	Group A N= 61	Group B N=109	Group C N= 29	P
Age	28.4 ± 5.48	30.9 ± 4.92	29.8 ± 4.53	>0.05
Gravida	2.31 ± 1.39	2.64 ± 1.43	2.53 ± 1.68	>0.05
Parity	0.49 ± 0.80	0.77 ± 0.90	0.41 ± 0.56	>0.05

The respective initial β HCG values of the patients of Group A, B, C were 1405.6 ± 1483.3, 5249.5 ± 4857.6 and 2670.4 ± 2073.6 (p= 0.001) (Figure 1) and table 2 shows the results. The number of hospitalization days was statistically significant between Group A and B (Table 2).

Figure 1: The declining β HCG levels Group A, B, and C.

A repetition of the dose was necessary in 15.5% (14/90) of the patients receiving medical treatment. Success was achieved in treating 6.6% (6/90) of these second dose. The rate of undergoing a laparoscopic surgery after the second dose of MTX was 8.8% (8/90). The β HCG values were observed to hit a plateau in 6 of these patients. The other two patients had acute abdominal symptoms and tubal rupture. Laparoscopic surgery was applied to these eight patients.

23.3% (21/90) patients who were under medical treatment with MTX underwent surgery after the first dose MTX because of hemodynamic instability and severe abdominal pain.

Discussion

The key to preventing maternal death is early diagnosis

and effective treatment of obstetric complications.¹ Ectopic pregnancy continues to be the number one cause of maternal deaths in the first trimester of pregnancy^{1,2}

Superiorities of medical treatment and surgical treatment over each other are an issue being discussed and studied for many years.³ It is often difficult for clinicians and women to balance the advantages and disadvantages of each treatment modality. The aim in similar studies is to determine the reliability of MTX, to measure its success in avoiding surgery and to broaden the limits of medical treatment.

As Göktolga mentioned earlier in his studies³ expectant management, medical treatment with methotrexate (MTX) and surgery are treatment options in unruptured ectopic pregnancy. Expectant management is especially suitable for patients with decreasing β hCG levels or in cases with small titers of β hCG. Initial level of β hCG is important for follow-up of patients. Surgery is indicated in patients with ruptured ectopic pregnancies and in hemodynamically unstable patients. Fallopian tubes are the most common location (97%) for ectopic pregnancies which is followed by abdomen, ovaries, and cervix. Tubal pregnancies are the most commonly encountered in ampulla (55%) followed by isthmus (25%), fimbria (17%). Ruptured ectopic pregnancy is responsible for 10-15% of all maternal deaths.⁴⁻⁶

In Alper and Büyükbayrak's 2009 study;⁴ 441 patients were treated surgically, 70 patients were treated with systemic methotrexate and 3 patients were treated with local methotrexate injection due to cervical ectopic pregnancy. Among surgically treated patients, 82.2% (n=365) was treated with laparotomy, 17.1% (n=76) was treated with laparoscopy. Surgical procedures performed by laparotomy were salpingectomy (58.3%), salpingostomy (8.2%), milking (3.7%), cornual resection (0.6%) and oophorectomy (0.2%). 10.9% of surgically

Table 2: Clinical outcomes of the patients of Group A-B-C

	Group A N= 61	Group B N=109	Group C N= 29	P
Initial β HCG value (mIU/mL)	1405.6 ± 1483.3	5249.5 ± 4857.6	2670.4 ± 2073.6	0.001
Day 4 β HCG (mIU/mL)	809.2 ± 844.8	-	2966.8 ± 2667.8	0.031
β HCG at discharge (mIU/mL)	352.5 ± 106.6	869.3 ± 286.7	442.2 ± 847.4	0.121
Hospitalization time (days)	4.6 ± 2.7	2.4 ± 2.9	4.7 ± 3.2	0.001

treated patients were treated with laparoscopic salpingectomy and 3.9% by laparoscopic salpingostomy. Systemic methotrexate treatment was applied to 70 patients. The success rate of single dose methotrexate treatment was 94.2%; overall success rate of systemic methotrexate treatment was 97.1%.⁴

Fernandez et al. demonstrated that a single dose of MTX administration could be an effective alternative for laparoscopic salpingostomy.⁷ In that study, the rate of repeating the MTX dose was found to be 13.7%. This is similar in our study which is 15.5%. Again, Fernandez showed that the rate of undergoing laparoscopy after MTX administration was found to be 11.7% and in our study this rate was 14.6%.

In a meta-analysis carried out by Mol et al. regarding the treatment of ectopic pregnancy, a single dose MTX treatment administered to patients who were stable hemodynamically was found statistically unsuccessful compared to surgical treatment.⁸

Operative management is the most widely used treatment for ectopic pregnancy. There has been debate about which surgical procedure is best. Laparoscopic salpingostomy is currently the procedure of choice when the patient has an unruptured ectopic pregnancy and wishes to retain her potential for future fertility.

Medical management has become increasingly popular in the treatment of ectopic pregnancy. Given its convenience, for many it is used as a first-line treatment, however, this is not always the optimal choice for the patient. It is important to understand the options for medical treatment and when it is appropriate to treat a particular patient with medical management, or when one should opt for surgical management.⁹

In conclusion, although duration and the likelihood of emergency surgical intervention all increase with serum β HCG concentration at presentation, our results suggest that medical management of ectopic pregnancy using MTX is still safe and successful. It should therefore be more readily considered as a viable treatment option for asymptomatic, hemodynamically stable women with ectopic pregnancies regardless of their initial serum β HCG level.

Ektopik Gebeliklerde Yönetim Metotreksat Uygulamas ve Cerrahi Tedavinin Karşılaştırılması Retrospektif Çalışma

AMAÇ: Ektopik gebelik, erken tanı ve tedavi metodlarının artmasına rağmen maternal mortalite ve morbiditenin önemli bir sebebidir. Bu çalışmada; ektopik gebelik tanısı almış hastalarda cerrahi ve medikal tedavi sonuçlarının karşılaştırılması ve metotreksat tedavisinin cerrahiye önlemedeki güvenilirliğinin

saptanması; böylece ektopik gebeliklerin yönetiminde metotreksat tedavisinin sınırlarının genişletilmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Ocak 2008-Mart 2012 tarihleri arasında Dokuz Eylül Üniversitesi'nde ektopik gebelik tanısı konmuş 199 hastanın dosyaları retrospektif olarak incelenmiştir. Hastaların demografik özellikleri, uygulanan tedavi yöntemi, β hcg değerleri kaydedilmiştir.

BULGULAR: Toplam 199 hastadan 90 hastaya (%45,3) metotreksat verildi. Metotreksat verilen 90 hastanın 61'i medikal tedaviden fayda görürken, 29 hastaya cerrahi müdahale uygulanmıştır. Metotreksat tedavisi alan hastaların 14'üne ikinci doz metotreksat uygulanmış olup 6 hastada tedavi başarısı sağlanırken, 8 hastaya cerrahi tedavi uygulanmıştır.

SONUÇ: Ektopik gebelik, erken tanı ve tedavi metodlarının artmasına rağmen maternal mortalite ve morbiditenin önemli bir sebebidir. Modern tanısal metodlar sayesinde ektopik gebelik tanısı daha erken konularak konservatif tedavi yaklaşımları uygulanabilmektedir. Cerrahi ve medikal tedavinin birbirine olan üstünlüğü halen tartışmalıdır. Bu nedenle, avantaj ve dezavantaj dengesini sağlamak açısından klinisyenler karar vermekte zorlanmaktadır.

Anahtar Kelimeler: Gebelik, Ektopik, Metotreksat

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