

Success of Systemic Methotrexate Administration Versus Laparoscopic Salpingostomy in Ectopic Pregnancy

Özlem Gün ERYILMAZ¹, Özlem MORALOĞLU¹, Kerem Doğa SEÇKİN¹, Mahmut İlkin YERAL¹, Ayhan SUCAK¹
Hacer Cavidan GÜLERMAN¹

Ankara, Turkey

OBJECTIVE: In this study, we tried to compare the efficacies of laparoscopic salpingostomy and medication with a single dose of Methotrexate (50mg/m²) in ectopic pregnancy to determine the differences between the two methods in terms of treatment outcomes.

STUDY DESIGN: In this study, 64 patients with ectopic pregnancy who had been administered an MTX therapy between August 2007 and July 2010 (Group A) were compared with another 64 patients with matching ages who had undergone a laparoscopic salpingostomy (Group B). The two groups were compared in terms of age, gravida, parity, initial hCG value, hCG measured at the time of being discharged from the hospital, hCG values checked a week later and the number of hospitalization days. The number of repeating doses and the rate of undergoing a laparoscopy salpingostomy were calculated in patients receiving MTX.

RESULTS: The hCG values of the patients in the MTX and laparoscopy groups respectively were as follows: Initial hCG measurement; 670.5±1027.5 vs. 5511.3± 7293.0 (p=0.0001), hCG measured at the time of discharge; 352.3±627.0 vs. 869.7±599.1 (p=0.016), and hCG value after a week; 292.5±617.4 vs 864.1±1531.8 (p=0.023). The difference in the number of hospitalization days between the two groups came out to be significant; 2.4±4.2 for the MTX group and 1.3±1.6 for the laparoscopy group with p=0.01. Repetition of the dose became necessary in 14.1% (9/64) of the patients receiving medical treatment (MTX) as their hCG values did not decrease. Success was achieved in treating 4.7% (6/64) of these patients after the second dose and the rate of undergoing a laparoscopic salpingostomy due to MTX failure was calculated to be 4.6%.

CONCLUSION: We found in this study that MTX used as a medical treatment in ectopic pregnancy was as successful as a laparoscopic salpingostomy. MTX failure can be minimized by firmly determining the criteria for the patients who will be given a medical treatment.

Key Words: Tubal ectopic pregnancy, Medical treatment, Single dose methotrexate, Laparoscopic surgery.

Gynecol Obstet Reprod Med 2011;17:151-154

Introduction

Ectopic pregnancy with an increasing incidence is the most prevailing reason of mother deaths associated with first trimester pregnancy in the world.^{1,2}

Since patients suspected of having an ectopic pregnancy are facing the danger of death, the diagnosis and treatment stages should be fast and practices should be planned to minimize possible complications.

Despite all the efforts, mother mortality still ranges between 9 and 13%.³

Treatment of ectopic pregnancy varies depending on the clinical and laboratory data of the patient. These practices include surgical, medical and expectant treatments. Surgical treatment seems to have been reduced to laparoscopic salpingostomy or salpingostomy only. Methotrexate (MTX) is widely accepted as a medical treatment for selected cases. MTX can be administered intramuscularly in repeated doses either with a folic acid supplement on the days in between or without adding a single dose of folic acid. The logic of expectant treatment involves the belief that ectopic pregnancy can limit itself. What is expected from this treatment is tubal abortus and re-absorption.

MTX treatment may first be seen advantageous as it saves the patient from having a surgery, but resorting to surgery after

¹Zekai Tahir Burak Women's Health Research and Education Hospital
Department of Endoscopic Surgery, Ankara

Address of Correspondence: Özlem Moraloğlu
Talatpasa Bulvarı 158/5 Cebeci,
Ankara
ozlem.moraloglu@hotmail.com

Submitted for Publication: 06. 09. 2011

Accepted for Publication: 20. 09. 2011

an unsuccessful attempt creates a great disappointment and new worries in the patient. There are many studies comparing medical and surgical treatments.⁴⁻⁷ The main goal 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.

We also investigated the statuses of laparoscopy and MTX in treating ectopic pregnancy in our study. We tried to determine the differences between the two methods in terms of treatment results.

Material and Method

This study was conducted on the patients who had been diagnosed as having tubal ectopic pregnancy and were being treated in the endoscopic surgery clinic of Zekai Tahir Burak Women's Health Education and Research Hospital between August 2007 and July 2010. The patients were screened retrospectively. The study data was obtained from patient files and information recorded on the computers. 64 patients with ectopic pregnancy who had been administered an MTX therapy (Group A) were compared with another 64 patients with matching ages who had received laparoscopic salpingostomy (Group B). The criteria of suitability for MTX therapy were determined as follows:

1. An ectopic gestational lump of < 4 cm in transvaginal ultrasonography (TVU)
2. Lack of fetal cardiac activity in TVU
3. The hCG value being < 15000. All the patients were administered a single dose of 1mg/kg MTX

The two groups were compared in terms of age, gravida, parity, initial hCG value, hCG measured at discharge and hCG

values checked a week later as well as the number of hospitalization days. The number of repeating doses and the rate of undergoing a laparoscopy salpingostomy were calculated in patients receiving MTX.

An ethical approval was obtained for our study from the education planning and coordination committee of our hospital.

Statistical analyses of data were made using the SPSS for Windows 11.5 package program. When evaluating intergroup comparisons, the t-test was used for the variables with a normal distribution in independent samples and the Mann-Whitney U test for those without a normal distribution; whether or not the temporal changes in hCG values showed any differences between the groups was examined using a two-way variance analysis in repeated measurements. Arithmetical mean \pm standard deviation was used as the descriptive value. The limit for significance was set at 0.05.

Results

The demographic characteristics of patients are summarized in Table 1. The age distributions for the MTX and laparoscopy groups were 29.5 ± 5.0 and 28.6 ± 5.4 respectively ($p>0.05$). The gravida and parity distributions were considered significant for again the MTX and laparoscopy groups; 2.2 ± 1.6 vs. 2.8 ± 1.8 and 0.6 ± 0.9 vs. 1.0 ± 1.1 ($p=0.03$; $p=0.013$, Table 1). The respective hCG values of the patients in the MTX and laparoscopy groups were as follows: initial hCG measurement; 670.5 ± 1027.5 vs. 5511.3 ± 7293.0 ($p=0.0001$), hCG values measured at the time of discharge; 352.3 ± 627.0 vs. 869.7 ± 599.1 ($p=0.016$), hCG values a week later; 292.5 ± 617.4 vs. 864.1 ± 1531.8 ($p=0.023$) (Table 2, Figure 1). The number of hospitalization days was found to be statistically significant between the two groups; 2.4 ± 4.2 for the MTX group and 1.3 ± 1.6 for the laparoscopy group; $p=0.01$ (Table 2).

Table 1: Demographic characteristics of the group treated with methotrexate (MTX) (Group A) and the group undergone a laparoscopic salpingostomy (Group B).

	MTX (n=64)	Laparoscopic salpingostomy (n=64)	p value
Age	29.5 ± 5.0	28.6 ± 5.4	>0.05
Gravida	2.2 ± 1.6	2.8 ± 1.8	0.03
Parity	0.6 ± 0.9	1.0 ± 1.1	0.013

Table 2: Clinical outcomes of the patients treated with methotrexate (MTX) (Group A) and those undergone a laparoscopic salpingostomy (Group B).

	MTX (n=64)	Laparoscopic salpingostomy (n=64)	p value
Initial hCG value (mIU/mL)	670.5 ± 1027.5	5511.3 ± 7293.0	0.0001
hCG at discharge (mIU/mL)	352.3 ± 627.0	869.7 ± 599.1	0.016
hCG a week later (mIU/mL)	292.5 ± 617.4	864.1 ± 1531.8	0.023
Hospitalization time (days)	2.4 ± 4.2	1.3 ± 1.6	0.01

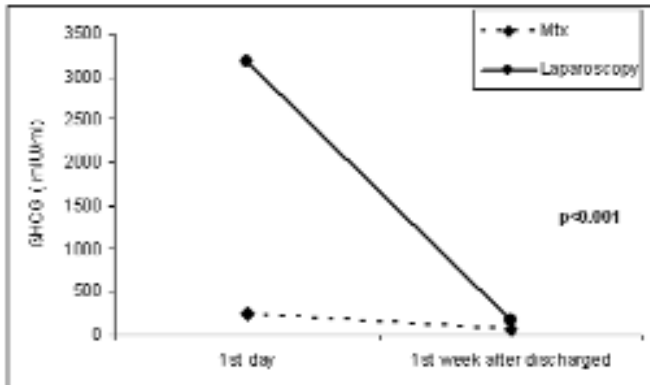


Figure 1: The declining beta-hCG trend a week later in the patients treated with methotrexate (MTX) (Group A) and those undergone a laparoscopic salpingostomy (Group B).

A repetition of the dose was necessary in 14.1% (9/64) of the patients receiving medical treatment (MTX) as their hCG values had not decreased. Success was achieved in treating 4.7% (6/64) of these patients after the second dose. The rate of undergoing a laparoscopic salpingostomy due to MTX failure was found to be 4.6% (3/64). The hCG values were observed to hit a plateau in two of these patients. In one patient, acute abdominal symptoms developed on the fifth day of medical treatment and all of them were taken out through a surgery and a one-sided salpingostomy was applied.

Discussion

Ectopic pregnancy is still a major cause of the first trimester mother deaths.¹ Success in treatment reaches up to 90% with early diagnosis.⁸ Superiorities of medical treatment and surgical treatment over each other are an issue being discussed and studied for many years.

In their prospective and randomized study, Fernandez et al. demonstrated that a single dose of MTX administration could be an effective alternative for laparoscopic salpingostomy.⁹

In that study, the rate of repeating the MTX dose was found to be 13.7%. This result is quite similar to 14.1%, the rate we obtained in our study. Again in that study, the rate of undergoing laparoscopy after MTX administration was found to be 11.7%. This rate, however, was found to be as low as 4.6% in our study. The reason for this difference is because the study conducted by Fernandez et al. included cases where the patients using MTX had an ectopic pregnancy with an ultrasonographic size of >4 cm, which means that the criteria for medical treatment was kept broader; in our study, on the other hand, the MTX criteria were evaluated more firmly and we had a pleasingly low rate of undergoing surgery. In a similar study, the decreasing rates of hCG and progesterone, two of the serum reagents of ectopic pregnancy, were compared between a group treated with MTX and another that had undergone a laparoscopic salpingostomy.¹⁰ Laparoscopy was found

superior in all aspects in that study and the rate of undergoing laparoscopic salpingostomy due to MTX failure was calculated to be 15.8%. This result is also very close to the value we obtained in our study. Saraj et al. also reported that an MTX treatment can be administered at least as confidently as a laparoscopic salpingostomy. 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 significantly unsuccessful as compared to a laparoscopic salpingostomy.¹¹ In this meta-analysis which compared a total of four prospective and randomized studies, the rate of repeating the MTX dose was found to be 19.1% and the rate of undergoing surgery to be 3.3%. Both of these values are similar to the ones in our study. Medical treatment is as successful as laparoscopic salpingostomy in patients who have undergone a good selection with firmer administration criteria and may considerably reduce the need for a surgery.

Another notable point in this study was the gravida and parity values of the patients. The MTX therapy has been preferred in a significantly higher rate in patients with no previous delivery. The underlying reasons include elimination of the worry of an organ loss due to the risk of a salpingectomy during a laparoscopic surgery and avoidance of risking future fertility by protecting the fallopian tube.

The hCG values measured before and after the treatment and in the first week following the discharge were lower in the group using MTX. Such low values resulted from the fact that the patient group treated with MTX had already had lower hCG values from the very beginning. Since one of the MTX administration criteria was to have an ectopic pregnancy with an ultrasonographic size of >4 cm, less trophoblast existence may have caused less hCG release.

With regard to the duration of stay in the hospital, our study showed that laparoscopy was more advantageous. While no difference was found regarding the duration in the study of Fernandez et al.⁹ the group taking MTX had almost twice as much hospitalization time in our study. This result may have originated from the fact that the patient group in the study was referred from distant sites. Considering that the post-treatment hCG monitoring cannot be carried out in a sound way and the possibility of ectopic pregnancy producing a rupture, the patients coming from distant towns had been hospitalized until a decreasing hCG trend could be observed.

In summary, we found in this study that MTX used as a medical treatment in ectopic pregnancy was as successful as a laparoscopic salpingostomy. MTX failure can be minimized by specifying firmer criteria for the patients who will be administered a medical treatment.

Ektopik Gebelik Tedavisinde Laparoskopik Salpingostomiye Karşı Sistemik Metotreksat Uygulamasının Başarısı

AMAÇ: Çalışmamızda, ektopik gebeliğin tedavisinde laparoskopik salpingostomi ve tek doz metotreksat (50mg/m²) ile tıbbi tedavinin etkinliğini karşılaştırarak, tedavi sonuçları açısından her iki yöntemin farklılıklarını belirlemeye çalıştık.

GEREÇ VE YÖNTEM: Bu çalışmada, 2007 Ağustos ve 2010 Temmuz tarihleri arasında MTX tedavisi verilen 64 ektopik gebelik hastası (Grup A), yaşa göre eşleştirilen laparoskopik salpingostomi yapılan 64 hasta (Grup B) ile karşılaştırıldı. Her iki grup; yaş, gravida, parite, ilk hCG değeri, taburcu olurken ölçülen hCG ve bir hafta sonrasındaki kontrol hCG değerleri ve hospitalizasyon gün sayısı açısından karşılaştırıldı. MTX alan hastalarda tekrarlayan doz sayısı ve laparoskopik salpenjektomiye gidiş oranı hesaplandı.

BULGULAR: Hastaların hCG değerleri sırasıyla MTX ve laparoskopi grubu için şu şekildeydi: ilk hCG ölçümü; 670,5±1027,5 vs 5511,3±7293,0 (p=0,0001), taburcu olurken ölçülen hCG değeri; 352,3±627,0 vs 869,7±599,1 (p=0,016), bir hafta sonraki hCG değeri; 292,5±617,4 vs 864,1±1531,8 (p=0,023). Hospitalizasyon gün sayısı her iki grup arasında istatistiksel olarak anlamlı çıktı; MTX grubu için 2,4±4,2 ve laparoskopi grubu için 1,3±1,6; p=0,01. Medikal tedavi (MTX) alan hastaların %14,1'inde (9/64) hCG değerinin düşmemesi sonucu doz tekrarı gerekti. Bu hastaların %4,7'sinde (6/64) ikinci dozdan sonra tedavide başarı sağlandı ve MTX başarısızlığı ile laparoskopik salpingotomiye gidiş oranı %4,6 olarak hesaplanmıştır.

SONUÇ: Bu çalışmada, ektopik gebelik'te medikal tedavi olarak kullanılan MTX'in laparoskopik salpingostomi kadar başarılı olduğunu tespit ettik. Medikal tedavi verilecek hasta kriterleri sıkı belirlenerek, MTX başarısızlığı en aza indirgenebilir.

Anahtar Kelimeler: Tubal ektopik gebelik, Metotreksat, Laparoskopi, Salpingostomi

References

1. Lewis G, Drife J. Why mothers die. Triennial Report 2000-2002. The sixth report of the confidential enquiries into maternal deaths in the United Kingdom. RCOG Pres, London. 2004
2. Ankun WM, Van der Veen F, Hamerlynk JV, Lammes FB. Transvaginal sonography and human chorionic gonadotropin measurements in suspected ectopic pregnancy: a detailed analysis of a diagnostic approach. *Hum Reprod* 1993;8:1307-11
3. Sara H, Garmel MD. Early pregnancy risks. *Current Obstetrics & Gynecologic Diagnosis & Treatment*. Ninth Ed., Mc Graw Hill Companies, 2010:256-71
4. Hajenius PJ, Engelsbel S, Mol BWJ, Van der Veen F, Ankun WM, Bossuyt PMM. Randomised trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy. *Lancet* 1997;350:774-9
5. Mol BW, Hajenius PJ, Engelsbel S, Ankun WM, Hemrika DJ, Van der Veen F. The treatment of tubal pregnancy in The Netherlands: an economic evaluation of systemic methotrexate and laparoscopic salpingostomy. *Am J Obstet Gynecol* 1999;181:945-51
6. Sowter MC, Farquar CM, Gudex G. A randomised trial comparing single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured ectopic pregnancy. *Br J Obstet Gynaecol* 2001;108:192-203
7. El-Sherbiny MT, El G, Mera IM. Methotrexate versus laparoscopic surgery for the management of unruptured tubal pregnancy. *Middle East Fertil Soc J* 2003;8:256-62
8. Fernandez H, Yves Vincent SC, Pauthier S, Audibert F, Frydman R. Randomized trial of conservative laparoscopic treatment and methotrexate administration in ectopic pregnancy and subsequent fertility. *Hum Reprod*. 1998;13:3239-43
9. Saraj AJ, Wilcox JG, Najmabadi S, Stein SM, Johnson MB, Paulson RJ. Resolution of hormonal markers of ectopic gestation: a randomized trial comparing single-dose intramuscular methotrexate with salpingostomy. *Obstet Gynecol*. 1998;92:989-94
10. Mol BW, Hajenius PJ, Engelsbel S, Ankun WM, Hemrika DJ, Van der Veen F. The treatment of tubal pregnancy in The Netherlands: an economic evaluation of systemic methotrexate and laparoscopic salpingostomy. *Am J Obstet Gynecol* 1999;181:945-51.