

# Reproductive outcome in patients treated by oral methotrexate or laparoscopic salpingotomy for the management of tubal ectopic pregnancy

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## Summary

**Objective:** To determine the reproductive outcome of women who have received methotrexate or been treated by laparoscopic salpingotomy (LS) for ectopic tubal pregnancy.

**Study Design:** The study consisted of 123 participants, all women with tubal pregnancies, who had been treated either by methotrexate per os or by laparoscopic salpingotomy. The reproductive outcome of these women was estimated after a follow-up time-period of ten years.

**Results:** In the methotrexate group, consisting of 34 women, the fertility rate was 82% with a mean interval time to conceive of 9.4 months after the treatment. In the group treated by LS, consisting of 89 women, the fertility rate was 82.6% and the mean interval time to conceive was 11.7 months.

**Conclusion:** The reproductive outcome of the women who received either per os treatment of methotrexate or LS for tubal pregnancy, remains high. Both therapeutic methods constitute reliable solutions for managing ectopic pregnancy.

**Key words:** Methotrexate; Laparoscopic salpingotomy; Reproductive outcome.

## Introduction

The proportion of ectopic pregnancy is 2-3% of the total number of pregnancies [1]. Today, modern, sensitive means allow a prompt diagnosis before symptoms and threatening the life of pregnant women occur. As a result, there has been a change in the treatment of ectopic pregnancy. We have moved from open surgery to laparoscopic techniques (salpingotomy-salpingectomy) and further to the pharmaceutical treatment of ectopic pregnancy. Both methods aim at reducing the morbidity of women and maintaining reproductive ability at high levels.

Many pharmaceutical agents are used in the treatment of ectopic pregnancy, like methotrexate, RU 486, the solution of KCL, hypertonic solution of glucose 50% and actinomycin D [2]. Methotrexate is the substance which has been mostly tested and experience in its use has been gained for this purpose. It belongs to chemotherapeutic concoctions in the category of anti-metabolites. It is an antagonist of folic acid [3], which acts by suspending the enzyme reductase of folic acid and the supply of mono-carbonate groups, which are essential for the synthesis of the dactylum of purines. It has been discovered that it suspends the reproduction of normal trophoblastic cells without affecting the salpingitic epithelium or having any teratogenic effect [4]. It acts by "derailing" the normal development of primitive trophoblastic cells and it reduces the number of the large grain-shaped cells of the destructible type [5]. In vitro cultivation of trophoblastic cells demands concentrations of methotrexate ten times

greater in order to reduce  $\beta$ -HCG to minimal levels compared to endometrial pregnancies [6].

Today, laparoscopic salpingotomy has been established as a first choice treatment for the management of tubal ectopic pregnancy for women who desire to maintain their fertility as well as for cases where rupture of the ectopic pregnancy is not imminent [7].

The objective of this study was to compare the systematic administration of methotrexate and laparoscopic salpingotomy with regard to their effectiveness for the treatment of ectopic pregnancy and the maintenance of fertility in these women.

## Materials and Methods

In this study, the participants were patients who had been admitted to the Obstetrics and Gynecology Department of the University of Ioannina for tubal ectopic pregnancy over a three-year time-period (1991-1994). The patients were asymptomatic and hemodynamically stable during their admission. The diagnosis of ectopic pregnancy was based on their medical history, the measurement of the values of  $\beta$ -HCG, and transvaginal ultrasonography (TVS).

Ten years after their treatment (2001-2004), we collected data from these patients concerning their reproductive outcomes. We registered the spontaneous pregnancies after treatment for ectopic pregnancy, the interval time within which they were accomplished, the progress of the pregnancies and the appearance of relevant fetal or neonatal anomalies, especially anomalies of the fingers or craniofacial anomalies which methotrexate has been reported to cause [3].

The age of these 123 women ranged between 19-44 years, with a mean age of 28.4 years. All the women had experienced an ectopic pregnancy for the first time and their desire was the maintenance of their fertility.

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The systematic administration of methotrexate (MTX), aiming at the management of ectopic pregnancy, was given to 34 of these women. In particular, administration of 2.5 mg MTX per os for five days with simultaneous administration of 0.1 mg/kg of folic acid was carried out [8]. The criteria for proceeding with administration of methotrexate as the first choice for the treatment of ectopic pregnancy included the hemodynamic stability of the women, values of  $\beta$ -HCG < 5000 IU/ml, no visible or less than 3 mm of gestational sac and absence of fetal cardiac function, and a quantity of free fluid in the Douglas pouch < 50 ml [9]. Moreover, renal and hepatic sufficiency were established on the basis of laboratory examinations [10]. It was decided that the rest of the 89 women would undergo laparoscopic salpingotomy. For application of laparoscopic salpingotomy the criteria included hemodynamic stability of the patient and the absence of signs of imminent ruptured ectopic pregnancy [8, 9].

## Results

Three out of 34 women in whom methotrexate had been administered, underwent laparoscopic surgery due to increased values of transaminase and persistent high values of  $\beta$ -HCG. In particular, in two women there was an increase in transaminase (5.8%) and in one woman the value of  $\beta$ -HCG continued to remain high (2.4%).

From 28 of the 34 women we collected data concerning their reproductive outcome ten years after their treatment for ectopic pregnancy. They all attempted to conceive after their treatment with methotrexate and 23 of them achieved a pregnancy, rendering a proportion of fertility of 82% (23/28). The mean interval time to conceive was 9.4 months. No relevant anomalies appeared in the fetuses born after the administration of methotrexate. The total result was 32 pregnancies, out of which 28 (28/32 or 87.5%) were intrauterine and four (4/32 or 12.5%) were again ectopic. Twenty-one pregnancies took place within the first 12 months after treatment with methotrexate (Table 1).

In 20 of the intrauterine pregnancies full-term babies were born (20/28 or 71.4%), in two cases (7.2%) there was an automatic miscarriage, whereas in six cases (21.4%) the newborns were premature.

During the same period 89 women were subjected to laparoscopic salpingotomy for ectopic gestations. During the follow-up period, we collected data from 69 women. Fifty-seven (57/69 or 82.6%) became pregnant. The mean time for conception was 11.7 months after the operation and no relevant anomalies were observed in the newborns. We had a total of 74 pregnancies for the entire duration of the study; 53 took place within the first year after the operation. Twelve out of 69 women (17.4%) could not become pregnant.

From the total of 74 pregnancies, 67 (90.5%) were intrauterine and seven (9.45%) were ectopic once again. In 52 (70.2%) cases of intrauterine pregnancies full-term babies were born, in nine cases there was an automatic miscarriage (12.1%), six newborns were premature (9%) and there were seven cases of relapse of ectopic pregnancy (9.5%) (Table 1).

Table 1. — Characteristics of the women treated by methotrexate or laparoscopic salpingotomy (LS) for ectopic pregnancy.

	Methotrexate group	LS group
Total patients with a new pregnancy (after an ectopic)	23/28 (82%)	57/69 (82.6%)
Total pregnancies	32	74
Intrauterine pregnancy	28/32 (87.5%)	67/74 (90.5%)
Repeated ectopic pregnancy	4/32 (12.5%)	7/74 (9.5%)
Full-term pregnancy	20/28 (71.4%)	52/67 (77.6%)
Premature delivery	6/28 (21.4%)	6/67 (9%)
1 <sup>st</sup> trimester miscarriage	2/28 (7.2%)	9/67 (13.4%)
Second-rate infertility	5/28 (17.8%)	12/69 (17.4%)

## Discussion

Through this study we collected data on the reproductive outcomes of women who had had at least one incident of tubal ectopic gestation in their medical history. For treatment two different options were offered; either systematic per os administration of methotrexate or laparoscopic salpingotomy. We discovered fertility rates of 82% for the methotrexate group and 82.6% for the laparoscopy respectively group. The proportions of women who faced a problem of second-time sterility were 17.8% and 17.4%, respectively (Table 1).

Therefore, it is obvious that the women who were subjected to laparoscopic salpingotomy presented slightly better fertility percentages than those who were treated by methotrexate. Moreover second-time infertility occurred in a smaller percentage and relapses of ectopic pregnancy were fewer as well. However the differences expressed in percentages were not statistically significant (Table 1).

Based on the relevant international literature several studies have been published reporting fertility rates after laparoscopic surgery for ectopic pregnancy ranging between 30-80% and between 62-82% after administration of methotrexate [11-14]. Furthermore, the proportion of patients who had an intrauterine pregnancy or ectopic relapse after surgical treatment for ectopic pregnancy ranged between 30-66% and 7-23%, respectively [12, 14]. Our percentages are among the highest being reported. In our project among patients who tried to conceive we had 87.5% intrauterine pregnancies and 12.5% relapses of ectopic pregnancy in the methotrexate group. The percentages after laparoscopic salpingotomy were 90.5% and 9.5%, respectively.

The data we collected also describe the outcome of these pregnancies. Specifically, in the methotrexate group we had 71.4% of full-term newborns, 7.2% of spontaneous miscarriages, and 21.4% of premature newborns. In the laparoscopy group there were 77.6% of full-term newborns, 13.4% of automatic miscarriages and 9% of births of premature babies.

A wide variety of factors have an effect on a woman's fertility and in order to maintain it the functional and anatomic integrity of her genital system is extremely

important [2, 15]. Based on one of our previous studies it was ascertained that maintenance of the fallopian tube carrying the ectopic pregnancy is possible after laparoscopic salpingotomy in a proportion that reaches even 100% in certain cases [16]. We are also aware of the fact that administration of methotrexate does not cause any harm to the epithelium of the fallopian tube and acts selectively on ectopic trophoblastic tissue [5, 6]. As a result, we believe that the treatment method that is followed has a slight or no effect on the fertility of women [17]. It seems that what is most significant is the previous existence of infertility case-histories, the functional integrity of the other fallopian tube, as well as the presence of pelvic disease, such as endometriosis, inflammation and the presence of pelvic adhesions [1, 2, 17, 18].

Concerning the effectiveness of each method and the treatment of ectopic pregnancy, in the methotrexate group we were forced to administer a second dose of methotrexate to one woman 1/34 (2.9%) because of the high values of  $\beta$ -HCG after the initial dose. In three out of 34 women we were forced to proceed with laparoscopic surgery. Two of them had an increase in transaminases, a reduction in renal function with relevant symptoms of headache and gastrointestinal disorders which were attributed to the methotrexate, while in the third woman there was a rise in the values of  $\beta$ -HCG and a laparoscopy was performed. In the methotrexate group a decrease in the values of  $\beta$ -HCG was more delayed, something which led to a longer stay of the patients in the hospital compared to those who underwent laparoscopy. There were no toxic indications due to the use of methotrexate, such as neutropenia because of suppression of the bone marrow [19] or other serious and harmful side-effects.

In the laparoscopic salpingotomy group there were 2/89 (2.2%) women who had persistent activity of the trophoblastic tissue with persistent high values of  $\beta$ -HCG postoperatively. In the international literature the proportion of persistence of ectopic pregnancy after laparoscopic surgery is reported to be between 3-20% [20]. In the first patient this activity was interrupted after per os administration of methotrexate 2.5 mg for five days, while the second patient was subjected to laparoscopy and salpingotomy for removal of the remaining trophoblastic tissue.

Methotrexate, as well as laparoscopic salpingotomy, rendered high levels of fertility after their application. Both methods of treatment are effective and reliable for the management of tubal pregnancy, as long as diagnosis is timely. The choice of method must be made on the basis of strict criteria.

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