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Low-dose methotrexate treatment in ectopic pregnancy: a retrospective analysis of 164 ectopic pregnancies treated between 2000 and 2008

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Abstract
Purpose Ectopic pregnancy is an acute, potentially life-threatening condition. The aim of this study was to compare the results of surgery and methotrexate treatment in women with ectopic pregnancy, along with a review of the literature.
Methods 164 women with ectopic pregnancy, treated from 2000 to 2008 at the university gynecology department, were examined in a retrospective analysis. Patients with diagnosed ectopic pregnancy underwent one of the following treatments: Salpingotomy, salpingectomy or administration of a single dose of 30 mg methotrexate. The main outcome measures were treatment success rate, rate of patients wishing to have children after the ectopic pregnancy, and rates of pregnancy, live births, recurrent ectopic pregnancy, miscarriage, use of assisted reproduction and side effects.
Results There were no significant differences in success rates between the groups (methotrexate 83.9 %, salpingotomy 88.2 %, salpingectomy 96.8 %). Significantly more patients in the salpingotomy group wished to become pregnant afterward than in the salpingectomy group. No significant differences were observed between the groups in the rates of intrauterine pregnancy, live births, recurrences, miscarriages, or side effects.
Conclusions With defined inclusion criteria, similar results can be achieved with low-dose single administration of 30 mg methotrexate in comparison with surgical treatment for ectopic pregnancy. On the basis of the data presented here, further research to establish optimal dosages for methotrexate is needed.

Keywords Ectopic pregnancy · Methotrexate · Salpingotomy · Salpingectomy · Fertility rates

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Introduction

Ectopic pregnancy, also known as extrauterine pregnancy, occurs when the blastocyst implants outside the body of the uterus [1]. The incidence is approximately 1.5–2.0 % of all pregnancies. The most frequent location for ectopic pregnancy is the uterine tube (96–98 %), followed by the cervix (0.2–0.5 %), the ovary (0.2–2.0 %), and the abdomen (<1 %) [2–4]. High-resolution ultrasonography and quantitative assessment of human chorionic gonadotropin (hCG) allow early diagnosis. Mortalities are now therefore rare, at 0.05 % of cases [5, 6].

The causes of ectopic pregnancy include functional disturbances—e.g., disturbances of tubal mobility or of ciliary movement, dysregulation of specific adhesion molecules, morphological disturbances such as adhesions in the area of the uterine tube, or stenoses. In addition, abnormal conceptus, and chemotactic factors stimulating tubal implantation, have been considered as potential causes [1, 7].

Tubal pregnancy is the most frequent form and subject of the present article. Due to growth of the blastocyst,

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usually in the sixth to ninth gestational weeks, increasing wall tension develops in the uterine tube, with unilateral lower abdominal pain. If the uterine tube ruptures, intra-abdominal bleeding may occur, with hematoperitoneum and possible hemorrhagic shock [3]. The classic triad of symptoms—absence of menstruation, vaginal spotting, and lower abdominal pain—is often observed, but is not inevitable. The clinical findings can be extremely variable, ranging from symptom-free courses to the full picture of acute abdomen [8].

Diagnosis

In cases of suspected ectopic pregnancy, a urine test should be carried out to provide qualitative evidence of hCG and thus diagnose a pregnancy. On transvaginal ultrasound, the appropriate findings for an intrauterine pregnancy are absent [6, 9, 10]. A trophoblastic ring located outside the uterus, also known as "bagel sign", is regarded as a direct ultrasound sign [4, 11]. However, direct ultrasound evidence of ectopic pregnancy is not always possible. In this type of situation, what are known as indirect signs need to be used, such as laboratory-test evidence of pregnancy, an "empty" uterine cavity on ultrasound, free fluid in retrovesical pouch (pouch of Douglas), or a painful adnexal tumor [4, 12].

In asymptomatic patients, quantitative measurement of serum hCG may be helpful. The hCG-producing trophoblastic tissue is usually disturbed, resulting in low hCG values.

Treatment options

In the absence of symptoms and with no free fluid in the retrovesical pouch, an adnexal mass with a maximum diameter of 2 cm, and a serum hCG value below 1,000 IU/L, an expectant approach can be used. The success rates reported in the literature—although in extremely inhomogeneous groups and with varying inclusion criteria—are in the range of 57–100 % [13]. Tightly scheduled check-up examinations should be carried out until the hCG values fall below the detection limit of the relevant assay [6].

Surgical treatment of tubal pregnancy is necessary in hemodynamically unstable patients and patients with acute pain or ultrasound evidence of free fluid in the abdomen. The standard surgical procedure is laparoscopic salpingotomy or salpingectomy [14]. Laparotomy is now only required in 1–2 % of patients with ectopic pregnancy. Tube-preserving surgery should always be aimed for, particularly in younger patients who are still planning to have children.

Another treatment option is administration of methotrexate (MTX), a folic acid antagonist that blocks DNA/RNA synthesis and thus cell division. This treatment option is internationally recognized, although in Germany it represents an "off-label" use, as MTX is not approved for the treatment of ectopic pregnancy. As in the expectant approach, there are strict exclusion criteria for methotrexate therapy. Hemodynamically unstable patients, those with evidence of a ruptured ectopic pregnancy with persistent lower abdominal pain and/or >300 mL of free fluid in the abdomen, patients who are breastfeeding, cases of positive cardiac activity in a tubal ectopic pregnancy, and sonographic findings >3.5–4.0 cm are all absolute contraindications. An hCG value >5,000 IU/L is a relative contraindication [15–19]. Further closely scheduled specialist care should also be ensured.

In the single-dose protocol, methotrexate 50 mg/m^2 body surface is administered on day 1 intramuscularly or intravenously [16]. The hCG value is measured on days 4 and 7. If a drop in the hCG value by at least 15 % has not yet occurred, a second MTX dosage of 50 mg/m^2 body surface should be administered. If there is a drop of >15 %, weekly hCG check-ups are carried out until the value is below the detection threshold of the relevant assay [13]. Patients treated with the single dose require a second MTX injection in 13.5 % of cases, and less than 1 % required three or more MTX injections [20]. However, there have been no dose-finding studies on the administration of MTX in patients with ectopic pregnancy, and several groups have reported good success rates of between 85.4 and 98.7 % using much lower dosages [21].

Studies have reported pregnancy rates of 79.6–100 % [22–24]. Schäfer et al. [21] showed fertility rate at 69.2 % with low-dose MTX therapy (20–40 mg absolute). In series the cumulative intrauterine pregnancy rate after salpingostomy ranged from 53 to 88 % [25–28], and after salpingectomy from 49.3 to 66 % [25, 27, 29, 30].

The most common side effects of MTX are mild and self-limited. They include nausea, vomiting, stomatitis, diarrhea, and elevated liver function tests, stomatitis and conjunctivitis. Rare side effects are nephrotoxicity, interstitial pneumonitis, and alopecia dermatitis. Side effects with methotrexate therapy occurred in approximately 36 % of women. Using a single-dose protocol is associated with fewer side effects [17, 20]. Maybe with a low-dose single-dose MTX regime it is possible to reduce the side effects.

The aim of the present study was to compare the success rates and the rates of fertility, recurrence, live birth and side effects after salpingotomy, salpingectomy, and medical treatment with 30 mg methotrexate in patients with ectopic pregnancies.

Patients and methods

The data for all patients treated for tubal ectopic pregnancy using salpingotomy, salpingectomy, or MTX at the

Department of Gynecology in Erlangen University Hospital between January 2000 and December 2008 were analyzed retrospectively for this study. During that period, a single dose of 30 mg MTX was used to treat ectopic pregnancy. A single intravenous injection of 30 mg MTX was administered, or otherwise the treatment followed the scheme described above. Any surgical procedure that became necessary in addition, or more than two MTX injections, was regarded as representing treatment failure after medical therapy. Further surgical interventions or additional MTX therapy following surgical treatment were regarded as representing treatment failure after surgery. MTX was used when no absolute or relative contraindications (see treatment options) were found. If there were contraindications for MTX or the patients did not agree to MTX therapy, we offered the surgical treatment option.

The basic data for the patients and details of their medical histories, diagnoses, and treatment were taken from the patients' files. All 164 patients received an information letter and were asked to complete a questionnaire inquiring about their desire for children, pregnancies, live births, repeat ectopic pregnancies, miscarriages, use of assisted reproduction techniques (ART), and side effects. If necessary patients got a telephone call to answer further questions. The patients were also asked whether they would opt for the chosen treatment again. Approval from the local ethics committee for the retrospective data analysis and patient survey was received (no. 3939).

Statistics

This retrospective study statistically tested whether the three treatment methods differed from each other in relation to the parameters being investigated. All of the tests were two-sided, with the significance level set at 5 %. Differences between the treatment methods were compared on a paired basis using Fisher's exact test. The means for the parameters of age and follow-up were compared using one-way analysis of variance (ANOVA), and the post hoc analysis was carried out using the Mann–Whitney *U* test.

Results

During the above period, a total of 164 patients with ectopic pregnancy were treated at the Department of Gynecology in Erlangen. A total of 133 patients underwent surgery, with 102 patients (62.2 %) receiving salpingotomy and 31 (18.9 %) salpingectomy. Thirty-one patients (18.9 %) received medical treatment with 30 mg MTX (Table 1). Surgical treatment was carried out if the patient declined methotrexate therapy or in the presence of contraindications (see above). Laparoscopic salpingotomy was attempted primarily in all of the patients. Salpingectomy was only carried out when the tube was completely destroyed or there was uncontrollable bleeding.

Success rate

In the patients treated with MTX, the mean initial hCG value was 2004 IU/L. Twenty-six patients (83.9 %) received no further interventions, and the success rate was thus 83.9 % in the MTX group. Twenty-seven patients (87.1 %) received a single dose of MTX. Four patients (12.9 %) required a second MTX injection, and none of the patients received more than two doses of MTX. Overall, treatment was considered to have failed in five patients (16.1 %), as they had to undergo surgery as well. The initial hCG value in these five patients was <1,000 IU/L in four cases and 14,000 IU/L in one case.

In the salpingotomy group, 90 of 102 patients (88.2 %) were successfully treated. Treatment failure was noted in 12 of the patients (11.8 %), as they required additional treatment for the ectopic pregnancy after the salpingotomy. Nine patients still had an hCG plateau after salpingotomy, and MTX treatment was therefore carried out. At the

Table 1 Success rate, age at diagnosis and follow-up in the methotrexate (MTX), salpingotomy (SO), and salpingectomy (SE) groups

	MTX ($n = 31$)	Salpingotomy (SO) ($n = 102$)	Salpingectomy (SE) ($n = 31$)	p value
Success rate	26 (83.9 %)	90 (88.2 %)	30 (96.8 %)	MTX vs. SO $p = 0.54$ MTX vs. SE $p = 0.20$ SO vs. SE $p = 0.30$
Age at diagnosis (years)	30.8 (SD 6.4; 19–41)	30.8 (SD 5.2; 19–42)	33.7 (SD 4.5; 23–43)	$p = 0.031$ (ANOVA)
Follow-up (months)	56.0 (SD 22;13–95)	39.1 (SD 23.1; 4–110)	41.0 (SD 27.9; 6–102)	$p = 0.012$ (ANOVA)

Figures shown are means with standard deviation (SD), as well as minimum and maximum values

The success rates between the different groups were compared using Fisher's exact test

The other parameters were compared using ANOVA and post hoc analysis were performed

Age: MTX vs. SO, $p = 0.800$; MTX vs. SE, $p = 0.114$; SO vs. SE, $p = 0.007$

Follow-up: MTX vs. SO, $p = 0.004$; MTX vs. SE, $p = 0.089$; SO vs. SE, $p = 0.880$

second intervention, one patient underwent salpingotomy and two patients had salpingectomies.

Salpingectomy was successful in 30 of 31 patients (96.8 %). In one patient, additional treatment with 30 mg MTX was necessary, as an adequate drop in hCG did not take place. No significant differences were observed with regard to the different treatment regimens (Table 2). Table 3 lists the side effects observed with the treatments; here again, there were no significant differences between the treatment options.

Patient questionnaire

The response rates to the questionnaire were 77.4 % in the MTX group, 71.6 % in the salpingotomy group, and 74.2 % in the salpingectomy group. The patients in the salpingectomy group were significantly older than those in the salpingotomy group ($p = 0.007$), but there were no significant differences between the MTX group and the salpingotomy group or between the MTX group and the salpingectomy group (Table 1). The follow-up period was significantly longer in the MTX group in comparison with the salpingotomy group ($p = 0.004$). There were no significant differences between the salpingotomy group and the salpingectomy group with regard to the follow-up period. Nor were there any significant differences between the groups with regard to the response rate to the questionnaire (Table 2).

Fertility after treatment for ectopic pregnancy

Eighteen patients (75.0 %) in the MTX group, 63 patients (86.3 %) in the salpingotomy group, and 13 patients (56.5 %) in the salpingectomy group still wanted to have children afterward. Significantly, more patients in the salpingotomy group than in the salpingectomy group still wanted children. During the follow-up period, intrauterine pregnancies occurred in 12 patients (66.7 %) in the MTX group, 41 (65.1 %) in the salpingotomy group, and 6 (46.2 %) in the salpingectomy group. There were no significant differences between the groups with regard to the rates of live birth, recurrent ectopic pregnancy, miscarriage, or use of ART (Table 2).

Table 2 Questionnaire response rate and fertility parameters after treatment for ectopic pregnancy in the methotrexate (MTX), salpingotomy (SO), and salpingectomy (SE) groups (absolute and percentage)

	MTX ($n = 31$)	Salpingotomy ($n = 102$)	Salpingectomy ($n = 31$)	p value
Questionnaire response rate	24 (77.4 %)	73 (71.6 %)	23 (74.2 %)	MTX vs SO $p = 0.65$
				MTX vs SE $p = 1.00$
				SO vs SE $p = 0.82$
Wanting children after ectopic pregnancy	18 (75.0 %)	63 (86.3 %)	13 (56.5 %)	MTX vs SO $p = 0.21$
				MTX vs SE $p = 0.23$
				SO vs SE $p = 0.01$
Intrauterine pregnancy after ectopic pregnancy	12 (66.7 %)	41 (65.1 %)	6 (46.2 %)	MTX vs SO $p = 1.00$
				MTX vs SE $p = 0.29$
				SO vs SE $p = 0.22$
Live birth after ectopic pregnancy	12 (66.7 %)	36 (57.1 %)	6 (46.2 %)	MTX vs SO $p = 0.59$
				MTX vs SE $p = 0.29$
				SO vs SE $p = 0.55$
Recurrent ectopic pregnancy	1 (5.6 %)	9 (14.3 %)	0	MTX vs SO $p = 0.44$
				MTX vs SE $p = 1.00$
				SO vs SE $p = 0.34$
Miscarriage after ectopic pregnancy	3 (16.7 %)	9 (14.3 %)	1 (7.7 %)	MTX vs SO $p = 0.72$
				MTX vs SE $p = 0.62$
				SO vs SE $p = 1.00$
Use of ART	2 (11.1 %)	8 (12.6 %)	4 (30.8 %)	MTX vs SO $p = 1.00$
				MTX vs SE $p = 0.21$
				SO vs SE $p = 0.20$
Would opt for same treatment again	17 (70.8 %)	34 (46.6 %)	10 (43.5 %)	MTX vs SO $p = 0.06$
				MTX vs SE $p = 0.08$
				SO vs SE $p = 0.82$

ART assisted reproduction techniques

Pairwise comparisons were carried out using Fisher's exact test

Table 3 Details of side effects of the treatment options relative to all questionnaires received in each group (methotrexate, $n = 24$; salpingotomy, $n = 73$; salpingectomy, $n = 23$)

Reported side effects	Methotrexate	Salpingotomy	Salpingectomy
Photosensitization	0	1 (1.4 %)	0
Nausea	2 (8.3 %)	3 (4.1 %)	2 (8.7 %)
Stomatitis	0	3 (4.1 %)	0
Enteritis	0	1 (1.4 %)	0
Depression/dejection	4 (16.7 %)	11 (15.1 %)	3 (13.0 %)
Period of depression/dejection (weeks)	24.0 (range 8–52)	24.7 (range 10–52)	25.0 (range 24–26)
Pneumonia	0	0	0
Alopecia	3 (12.5 %)	2 (2.7 %)	1 (4.3 %)

Patient satisfaction

Seventeen patients (54.9 %) in the MTX group, 34 patients (46.6 %) in the salpingotomy group, and 10 patients (43.5 %) in the salpingectomy group stated that they would opt for the chosen form of treatment again.

Comments

This retrospective study examined success rates and fertility after various methods of treating ectopic pregnancy. Almost identical success rates were observed after MTX treatment, salpingotomy, and salpingectomy. Differences were only noted in relation to a subsequent wish to have a child and fertility. However, the groups were inhomogeneous because of different inclusion criteria, and the follow-up periods varied in length. This is a pilot study to generate preliminary results; therefore, no power analysis was done. These limitations are the result of the retrospective study design and need to be taken into account when interpreting the results.

The study also compared low-dose MTX treatment with two surgical methods. It presents the longest follow-up period reported to date after low-dose MTX therapy, and the lowest recurrence rate. Only two other studies have previously been published on the treatment of ectopic pregnancy with low-dose MTX.

Yalcinkaya et al. carried out a double-blind, randomized study on MTX therapy in ectopic pregnancy in 100 patients. A slightly lower success rate was noted with MTX 25 mg/m^2 body surface, at 85.4 %, in comparison with 88.5 % in patients who were treated with MTX at 50 mg/m^2 body surface. The rates of recurrent ectopic pregnancy were similar, at 4.2 and 7.7 %, and there were also no significant differences between the two treatment regimens with regard to subsequent intrauterine pregnancies. There were significantly fewer side effects with low-dose MTX treatment. The rate of side effects after low-dose MTX therapy was half the rate observed with the higher dosage [31].

In a study by Schäfer et al. [21], also with low-dose MTX therapy (20–40 mg absolute), the success rate was 92.5 %. However, the 40 patients also included 11 patients who had persistent ectopic pregnancies and had therefore undergone other forms of treatment previously. A single dose of MTX at the low dosage was successful in all 11 patients. In the 29 patients who received MTX as the first treatment, the success rate was 89.7 %. Twenty-three patients required only one dose of MTX (79.3 %) and six patients (20.7 %) needed a second dosage. MTX therapy was unsuccessful in three patients, who underwent surgery. The initial hCG values were below 1,000 IU/L in half of the women, between 1,000 and 10,000 IU/L in 17, and over 10,000 IU/L in three. The authors did not report a mean for the initial hCG values.

A success rate of more than 80 % was also observed in the present study, along with a very low rate of side effects following low-dose MTX therapy. Two patients (8.3 %) reported nausea, and three patients (12.5 %) reported temporary alopecia. One patient was treated with MTX whose initial hCG value (14,000 IU/L) was outside of the inclusion criteria. With stricter observation of the recommendations published by the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine [16, 18] on the treatment of ectopic pregnancy with MTX (hCG value <5,000 IU/L, etc.), this patient would not have been able to receive MTX. In that case, an even higher success rate with MTX therapy (86.7 %) would have been possible.

In a meta-analysis by Barnhart et al. [20], 1,067 patients from various studies using the single-dose protocol (50 mg/m^2 body surface) were analyzed and compared with the multi-dose protocol. A total of 940 patients (88.1 %) were successfully treated with the single-dose protocol (one or two doses). The mean initial hCG value was 2,778 IU/L.

The success rate with low-dose MTX therapy in the present study was not much lower, at 83.9 %. In the group studied here, the mean initial hCG value was 2,004 IU/L. The rate of patients who required a second MTX dose was 12.9 % in the present study, in comparison with 13.5 % in the meta-analysis mentioned above. The rate of patients

who required more than two MTX injections was also low in the meta-analysis, at 0.9 %, and in the present group none of the patients required more than two doses. The fertility rate after MTX treatment was lower at 66.7 % than in other studies, which have reported pregnancy rates of 79.6–100 % [22–24]. A comparable fertility rate, at 69.2 %, with a comparable MTX dosage, was reported by Schäfer et al. [21]. In other series the cumulative intrauterine pregnancy rate after salpingostomy ranged from 53 to 88 % [25–28], and after salpingectomy from 49.3 to 66 % [25, 27, 29, 30] and is comparable to our results.

The rate of recurrent tubal pregnancies after MTX administration was low in the Erlangen group, at 5.6 %, and the rate of recurrent ectopic pregnancy in the study by Schäfer et al. was also low, at 7.7 % [21]. At higher dosages, recurrence rates of 3.7–16.1 % have been reported [22–24]. Literature shows recurrence rates from 10.2–17.3 % after salpingotomy [25–28] and 10–22 % after salpingectomy [25, 27, 29, 30]. We saw a comparable recurrence rate in the salpingotomy group (14.3 %) and a lower recurrence rate in the salpingectomy group. There was no significant difference in patient satisfaction between the treatment options.

A review of literature shows side effects in 31.3 % of patients using the single-dose protocol with 50 mg/m^2 body surface. With the limitation that there was no standardized liver enzyme check after MTX treatment we found lower side effects (20.8 %) in our study.

Success rates comparable with those of surgical methods can thus also be achieved with low dosages of MTX. Most data on MTX therapy are available for a dosage of 50 mg/m^2 body surface. This dosage appears to be high. Consistent with the findings of the other studies mentioned above, the present study showed similarly good success rates, with lower rates of side effects, after administration of low-dose MTX therapy. Some authors have proposed a "cut-off" for the hCG value of <2,000 IU/L before MTX therapy [32]. As four of the five cases of treatment failure in the present study occurred with an initial hCG value <1,000 IU/L, this study does not support that view.

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