

ORIGINAL ARTICLE

Success and spontaneous pregnancy rates following systemic methotrexate versus laparoscopic surgery for tubal pregnancies: A randomized trial

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Abstract

Objective. To determine which treatment should be offered to women with a non-ruptured tubal pregnancy: a single dose of methotrexate (MTX) or laparoscopic surgery. **Design.** Prospective, randomized, open multicenter study. **Setting.** Seven Danish departments of obstetrics and gynecology. **Sample.** A total of 106 women diagnosed with ectopic pregnancy (EP). **Methods.** Between March 1997 and September 2000, 1,265 women were diagnosed with EP, 395 (31%) were eligible, 109 (9%) were randomized of whom 106 had an EP. The study was originally powered to a sample size of 422 patients. The women were randomized to either medical (MTX; 53) or surgical (laparoscopic salpingotomy; 53) treatment. Follow-up by questionnaire and through national patient databases for a maximum of 10 years. **Main outcome measures.** Uneventful decline of plasma-human chorionic gonadotropin to less than 5 IU/L, rates of spontaneous, subsequent intrauterine, and recurrent ectopic pregnancies. **Results.** The success rates were 74% following MTX treatment and 87% after surgery (n.s.); the subsequent spontaneous intrauterine pregnancy rate was 73% after MTX and 62% after surgery; and the EP rate was 9.6% after MTX and 17.3% following surgery (n.s.). **Conclusions.** In women with an EP, who are hemodynamically stable and wishing to preserve their fertility, medical treatment with single dose MTX tends to be equal to treatment with laparoscopic surgery regarding success rate, complications, and subsequent fertility. Although the two treatment modalities seemed to be similar in outcome, it is crucial that the diagnosis is based on a high-quality ultrasonographic evaluation, as two patients had intrauterine pregnancies despite fulfilling the diagnostic algorithm for EP.

Key words: Tubal pregnancy, ectopic pregnancy, methotrexate, salpingotomy, fertility

Abbreviations: EP: ectopic pregnancy, MTX: methotrexate, plasma-hCG: plasma-human chorionic gonadotropine, IUI: intrauterine insemination, IVF: in vitro fertilization, ICSI: intracytoplasmic sperm injection.

Introduction

The incidence of ectopic pregnancy (EP) increased almost epidemically to a level of 2% in developed countries during the past decades. Now

approximately 1% of all pregnancies are extrauterine (1,2). Chlamydial infection is a major risk factor (3), in addition to previous pelvic or abdominal surgery, infertility, smoking, and a history of tubal pregnancy (2). Several treatment modalities have been applied in

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relation to EP (4). The use of transvaginal ultrasonography and sensitive plasma-human chorionic gonadotropin (plasma-hCG) assays have enabled an early diagnosis before rupture. Thereby a life-threatening situation necessitating emergency surgery has been changed to a more benign condition in sometimes even asymptomatic patients (4). Consequently, medical treatment (methotrexate (MTX)) in an outpatient setting is now a realistic option. This modality was introduced in 1991 by Stowall et al. (5,6). In 1997, the first randomized clinical trial on MTX versus laparoscopic salpingotomy was published (7). Studies on success rate after MTX treatment for EP have been conducted reporting rates in the range of 65–95%. These studies all differ in inclusion criteria and dose of MTX. A Cochrane analysis concluded that MTX treatment of EP had the highest success rate when plasma-hCG levels were below 3,000 IU/mL (4). It was stated that side effects from multiple dose MTX treatment impaired quality of life since 61% in the MTX group, compared to 12% in the laparoscopy group, experienced complications or side effects (4). In addition, MTX-treatment was more expensive than laparoscopic salpingotomy when initial plasma-hCG levels were above 3,000 IU/L (8). Treatment with a single dose of MTX had fewer side effects, but the success rate was less than following a multiple dose regimen (9). Consequently, decisions on the treatment strategy for EP are still a challenge and more randomized trials are needed (4).

Fertility outcome after treatment of EP is one of the keystones when choosing treatment strategy. Only one randomized study has addressed this question (7). With a follow-up period of 18 months, Hajenius et al. reported a spontaneous intrauterine pregnancy rate of 36% following MTX and 43% after salpingotomy. The authors concluded that systemic MTX was not superior to surgery with regard to future fertility. Since the dose of MTX used was three times higher than generally recommended, it might be speculated that this dose might have induced local tissue damage leading to lower pregnancy rates. In non-randomized studies where MTX doses of 1 mg/kg were used, intrauterine pregnancy rates of up to 67% were noted (10), compared to 56–89% after surgery (11–13). This randomized study evaluated success rates and subsequent fertility following either treatment with a single dose of MTX or laparoscopic surgery in women with unruptured tubal pregnancies.

Material and methods

Women were recruited to a prospective, computer randomized multicenter study at seven departments of gynecology and obstetrics in Denmark from March

1997 to September 2000. The study was approved by the Danish Ethical Committee (j.nr. 5312-156-1996) and the Data Register (Datatilsynet j.nr 2001-41-0929), and informed written consent was obtained from all participants.

Women were included if they were hemodynamic stable, spoke Danish, and had a wish for future fertility. The diagnosis of an unruptured tubal pregnancy was based on medical history, physical examination, including transvaginal ultrasonography, and rising plasma-hCG concentrations. Only women with a rise in plasma-hCG levels by three consecutive measurements or with an extrauterine location of a live conception with a gestational sac diameter of less than 3.6 cm were eligible. Women with plasma-hCG below 2,000 IU/L were eligible for randomization only if the rate of increase was below 20%/24 hours and with no ultrasonographic sign of intrauterine pregnancy. The ultrasonography was performed by a specialist in gynecology or by the department of ultrasonography at the specific hospital. Plasma-hCG measurements were analyzed using a monoclonal-based assay at the hospital. There were no inclusion restrictions regarding upper plasma-hCG concentrations.

Women were excluded if they did not fulfill the inclusion criteria or had a heterotopic pregnancy, hepatic, renal or cardiac disease, anemia, leukocytopenia, thrombocytopenia, or abuse of alcohol. At randomization, the women accepted to participate in follow-up two years later. Individual randomization in blocks of 6–8 attached to each center was executed by phoning a computer program where a voice mail immediately communicated the treatment. The women were randomized to receive either a single dose of systemic MTX (Methotrexate[®], 1 mg/kg, Wyeth Lederle, Copenhagen, Denmark) or salpingotomy. The surgical procedure was performed laparoscopically. A linear incision was made medial to the swollen part of the tube with a monopolar microdiathermy needle. The product of conception was removed by manipulation, hydrodissection, and suction. Once hemostasis was obtained, the tubal incision was left open for spontaneous healing. If tubal rupture with intraabdominal bleeding unexpectedly was detected, the appropriate surgical technique was for the surgeon to decide.

Both study groups were monitored by using serial plasma-hCG measurements on Days 4 and 7 following treatment and weekly thereafter until the plasma-hCG concentration was below 5 IU/L. If a rise in plasma-hCG or a steady state was observed seven days after the MTX treatment, the women were advised to have a second dose of MTX, after controlling blood tests of liver and renal function and bloodcounts. MTX-treated women were advised to avoid pregnancy for a minimum of three months.

Side effects were registered. Blood counts, liver, and renal function tests were obtained if the patients presented with specific symptoms such as mouth dryness, alopecia, nausea, gastroenteritis, or dermatitis.

Women undergoing surgery were discharged according to the procedure of the individual hospital. If the woman showed signs of intraabdominal bleeding during the time of follow-up, laparoscopy or laparotomy was performed.

A successful treatment was defined as an uneventful decline in plasma-hCG to less than 5 IU/L. Persistent trophoblast was defined as rising plasma-hCG later than on Day 4.

A posted questionnaire was used to collect information regarding subsequent fertility. Non-responders were contacted by telephone. The Danish Birth Registry and the Danish Registry of in vitro fertilization (IVF)-pregnancies were scrutinized to obtain further information in relation to pregnancies, abortion, EP, and/or any assisted reproduction procedures. The spontaneous intrauterine pregnancy rate included IUI, but not IVF or ICSI-treated women.

Statistical methods

The power calculation estimated that a sample size of 422 patients was needed to establish a difference in spontaneous pregnancy rates of 10% between the two treatments (rate after conservative surgery = 59% and after MTX = 69%) with a power of 80% and type II error (β) of 0.05 and a expected dropout due to failure in the randomization process of 10%. Analysis of the outcomes was made on an intention-to-treat basis. The inclusion was stopped after three years and six months due to recruitment problems. Consequently this study was underpowered.

Results are given as mean values with 95% confidence intervals (CI) or as median and range. A χ^2 -test was used for nominal unpaired data, while a Mann-Whitney *U*-test was used for comparison of ordinal unpaired variables and *T*-test for unpaired parametric data. Cumulative probability of spontaneous intrauterine pregnancy over time was calculated for each group by use of Proportional Regression Model (Cox Regression Models and Life-Tables) and analyzed following the intention-to-treat principle. The starting point for the calculation was the date of treatment. The endpoint was the primary outcome measure, i.e. the date of accomplished spontaneous intrauterine pregnancy, whereafter the women were censored. The endpoint for the women who did not conceive, was the date of the enquiry to the Danish Birth Registry.

Results

A total of 1,265 women were diagnosed with a tubal pregnancy and 395 (31.2%) were eligible for randomization (Figure 1). Of these, 106 (8.4%) gave written informed consent and were randomized, 53 in each study group. The baseline characteristics for all women are given in Table I and reasons for exclusion in Table II. There were no significant differences between the two study groups in the baseline characteristics.

The success rate following laparoscopic surgery was 87% (46/53 patients) and not significantly different from that in the MTX group (74%; 39/53 patients). A total of nine (17%) women in the surgical group were seen at the clinic either due to pain ($n = 3$) or persisting trophoblastic tissue ($n = 6$). In the MTX-treated group, 24 (45%) women were re-examined due to pain ($n = 21$) or persistent trophoblast ($n = 3$). In the surgically treated group, 32 (60%) had tubal preservation surgery (salpingotomy) and 21 (40%) had a salpingectomy. Fifteen women had a second surgical procedure, 13 from the MTX group and two from the laparoscopic group (Figure 1).

Five in the MTX group and one in the surgical group complained of nausea. Among the less common side effects, vomiting, diarrhea, constipation, dizziness, loss of hair, and sleeping problems occurred in the MTX-treated group. Side effects to surgery were a tooth broken during induction of anesthesia, one bladder perforation, one urinary tract infection, and one esophageal lesion necessitating transfusion.

The group of women who had a second treatment procedure displayed significantly higher plasma-hCG values (median 4,065 IU/L) with 71% having a plasma-hCG $\geq 3,000$ IU/L compared to the group that did not need a secondary treatment (median = 2,269 IU/L).

The median follow-up period was 8.6 years (range 6.9–10.3 years). Among the 106 women, two were lost to follow-up and 85 had conceived at least once (Table III). Fourteen of the 19 women who did not conceive reported at the two-year follow-up, that they did not plan further pregnancies. Thirty-eight of 52 women (73%) had achieved a spontaneous pregnancy in the MTX group and 32 of 52 (62%) in the surgical group.

The cumulative rates of spontaneous intrauterine pregnancy for both groups are shown in Figure 2. Using a Cox Proportional Regression Model, we found no difference in spontaneous intrauterine pregnancy rate (hazard ratio: 1.41; 95% CI 0.88–2.26; $p = 0.15$).

Despite a very meticulous inclusion strategy, we found that three women (3%) were falsely considered

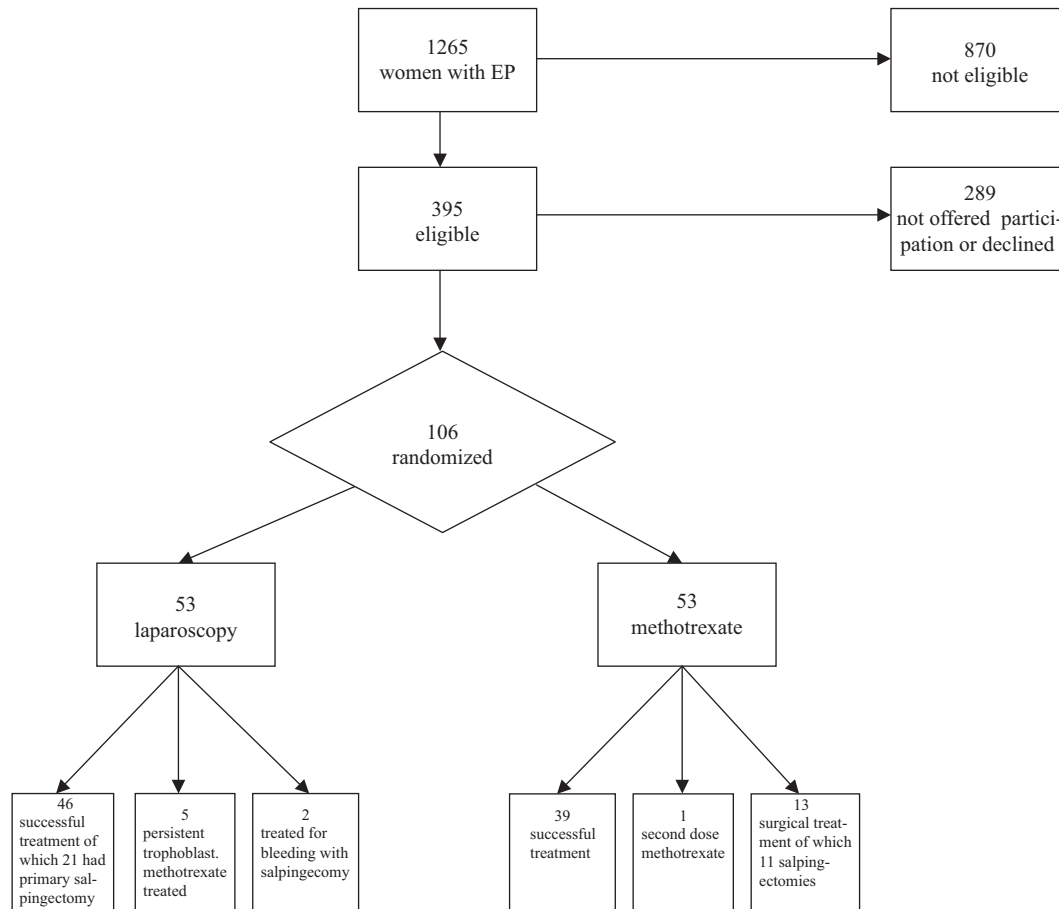


Figure 1. Study flowchart of women with an ectopic pregnancy (EP).

to have an EP. In one woman treated with MTX, a live intrauterine pregnancy was diagnosed by ultrasound one week after the MTX treatment. Plasma-hCG was declining, dilatation and curettage were done and histology confirmed the presence of an intrauterine pregnancy. The second woman was randomized to laparoscopy, which did not reveal any pathology and the patient subsequently delivered a healthy child. The third woman had slowly increasing plasma-hCG levels and displayed at ultrasonography a presumed pseudogestational sac. She was randomized to surgery. No pathology was observed. The pregnancy showed signs of waning and chorionic villi were observed at the histological examination.

Discussion

A single dose of MTX and laparoscopic surgery seemed to be comparable in the management of tubal pregnancy in a general hospital setting. The two treatments displayed similar outcomes regarding success rates and future fertility. In addition, we found

that when MTX is offered it is of utmost importance to have an exact diagnosis eventually confirmed by repeated ultrasound examinations.

The study was originally designed to include 422 women. However, inclusion was stopped after three years and six months. During the trial period more and more women became reluctant to take part in randomized controlled trials. Increasing knowledge about the different existing treatment modalities in relation to EP was collected by the patient, such as from the internet, magazines, and general practitioners. Consequently, more and more women preferred to discuss and have a major influence themselves on the decision of treatment strategy. Doctors not considering MTX as a safe option when treating EPs may also have been a contributing factor. We are convinced that the situation would be the same now and that in the future reliance has to be placed on follow-up and subsequent quality assessment of prospective data collected in specific databases.

It is of the utmost importance that diagnostic accuracy is optimal when women suspected with an

Table I. Baseline characteristics. Patients randomized for methotrexate or laparoscopy as well as the group of eligible, but not randomized and not eligible women. Values are given as median [range] or number (%).

Characteristics	Methotrexate (n = 53)	Laparoscopy (n = 53)	Eligible, but not randomized (n = 289)	Not eligible (n = 870)
History				
Age	30.8 [21.1–40.9]	32.7 [24.3–41.2]	31.9 [18.7–43.2]	31.4 [19–46]
Parity	2 [0–5]	2 [0–6]	2 [0–9]	2 [0–8]
Weight in kg	64.5 [45–122]	64 [50–95]	63 [45–165]	63 [38–165]
Fertility surgery	2 (4)	4 (8)	12 (4)	81 (9)
Pelvic inflammatory disease (PID)	15 (28)	13 (25)	72 (25)	199 (23)
Two tubes at randomization	49 (92)	49 (92)	248 (86)	779 (90)
At least one tube after end of treatment	52 (100)	53 (100)	253 (88)*	805 (93)
Previous spontaneous abortion	12 (23) 0 [0–2]	15 (28) 0 [0–1]	75 (26) 0 [0–4]	205 (24) 0 [0–7]
Former induced abortion	16 (30)	10 (19)	79 (27) 0 [0–4]	212 (24) 0 [0–4]
Former ectopic pregnancies	5 (9)	8 (15)	61 (21)	155 (18)
Clinical symptoms				
Pain				
No pain	24 (46)	27 (51)	116 (40)	133 (15)
Mild pain	27 (52)	26 (49)	139 (48)	219 (25)
Constant pain	1 (2)	0	28 (10)	496 (57)
No report of pain	1 (2)	0	6 (2)	22 (3)
β-hCG before treatment in IU/L	2,259 [176–41,000]	3,200 [72–42,859]	3,144 [131–67,828]	1,621 [3–114,669]
Hemoperitoneum at surgery in ml	–	31 [0–400]	50 [0–1,000]	100 [0–3,700]
Number of patients with ≥50 mL of hemoperitoneum	–	24 (45)	126 (44)	602 (69)
Number of patients with ≥100 mL of hemoperitoneum	–	11 (21)	81 (28)	500 (57)
Ultrasound findings				
Gestational sack	12 (23)	15 (28)	52 (18)	119 (14)
Gestational sac diameter in mm	12 [5–25]	14 [7–29]	15 [5–59]	16 [1–60]
Adnexal mass	21 (40)	24 (45)	170 (59)*	455 (52)
Adnexal mass diameter in mm	20.5 [6–48]	23 [10–51]	21 [3–72]	25 [2–91]
Pseudogestational sac	2 (4)	3 (6)	17 [6]	31 (4)
Pseudogestational sac in mm	8.5 [2–15]	4 [4–4]	13 [3–41]	9 [2–37]

*Indicate $p < 0.05$ between the two randomized groups and the not randomized eligible group.

extrauterine pregnancy are offered medical treatment. In our study, diagnostic failures were reported in three women, two in the MTX-group and one in the laparoscopic group. Similar misdiagnosis has been reported by others (2,9). Our study included seven departments of gynecology and obstetrics throughout Denmark, including both county and university hospitals, thereby reflecting the diagnostic and treatment

procedures during daily clinical work. This might, however, have influenced the results when compared to smaller studies from one specialized center. Not only the diagnostic capabilities but also the threshold for second line treatment may differ from one department to another, as well as between individual doctors. An example was the high number of women undergoing follow-up due to pain, of whom a large proportion had surgery. On the other hand the multicenter design and the problems mentioned above also lead to some rather robust conclusions and high external validity. The minimal differences between the women randomized and those eligible but not randomized, also strengthens the external validity (Table I). Our study also supports the use of expectant management in women with negative sonographic findings and low plasma-hCG concentrations (14,15). The visualization of an ectopic gestational sac containing a yolk sac or embryo is diagnostic of EP, but this combination of findings is detected in only a small proportion of cases (16). However, in expert ultrasound units, abnormalities suggestive of the diagnosis will be identified in more than 90% of EPs (2).

Table II. Patients excluded from the study: some women had more than one reason for exclusion.

Not eligible	870
Immediate treatment needed	497
Younger than 18 years	3
Not Danish spoken	59
Liver or kidney disease	7
Planned sterilization	74
Liver and renal test out of range	22
P-hCG declining	193
Other reasons	15
Eligible, but not randomized	289
Declined	174
Not offered participation	115
Total not entering the study	1,159

Table III. The grand total number of pregnancies in the randomized groups (including assisted reproduction).

	Methotrexate		Surgery		Total	
	n	Percentage (%)	n	Percentage (%)	n	Percentage (%)
Number of spontaneous pregnant women	38	73	32	62	70	67
Number of pregnant women IVF included	44	85	41	79	85	82
Spontaneous pregnancies	67	85	65	86	132	86
Live births	49	62	38	50	87	56
Spontaneous abortions	14	18	19	25	33	21
Ectopic pregnancies	4	5	8	11	12	8
IVF-pregnancies	12	15	11	15	23	15
Live births	9	11	8	11	17	11
Spontaneous abortions	3	4	1	1	4	3
Ectopic pregnancies	0	0	2	3	2	1
Total	79	100	76	100	155	100

Note: The term 'spontaneous pregnancies' includes all pregnancies, except the IVF-treated women. There were no significant differences in fertility outcome between the two treatments.

The success rates following laparoscopy and medical treatment of 87% and 74%, respectively, are similar to the results reported by others (12,17,18). The surgical procedure allowed confirmation of the diagnosis and visualization of the contralateral salpinx, allowing advice and planning of strategy for any subsequent pregnancy. The laparoscopic group of women also benefited from fewer follow-up visits and thereby potentially less cost (8).

This study had an exceptional long follow-up period with a maximum of 10 years and we observed relatively high spontaneous pregnancy rates after both treatments. These figures most likely underestimate the potential fertility in this group, since several women in the two-year questionnaire reported not to have plans for any further pregnancies.

Although the study was underpowered, we can conclude that medical treatment with a single dose of MTX and laparoscopic surgery seems to be equal treatment modalities for an EP in a woman who is hemodynamically stable and has a wish for future

fertility. It is crucial that the diagnosis is based on a high-quality ultrasonographic evaluation.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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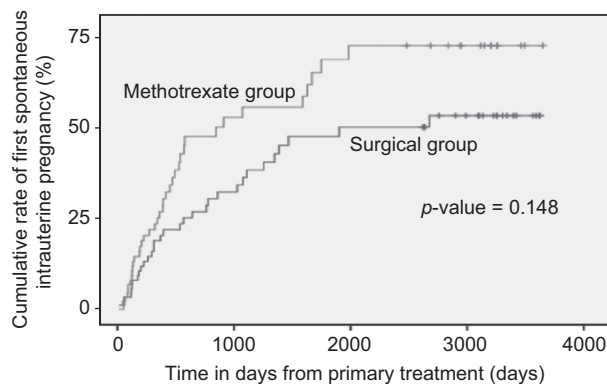


Figure 2. The cumulative rates of spontaneous pregnancy for women receiving either medical treatment using methotrexate (1 mg/kg) or laparoscopic surgery.

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