

# Comparison of Local Injection of Methotrexate and Linear Salpingostomy in the Conservative Laparoscopic Treatment of Ectopic Pregnancy

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## Abstract

**Study Objective.** To compare local injection of methotrexate (MTX) and linear salpingostomy in the conservative laparoscopic treatment of ectopic pregnancy.

**Design.** Prospective, nonrandomized study, July 1991 to May 1994.

**Setting.** Department of obstetrics and gynecology in a university hospital.

**Patients.** Fourteen women with unruptured ectopic pregnancies without documented fetal heart motion and size below 50 mm as measured by ultrasound.

**Interventions.** All 14 women underwent the laparoscopic treatment by either local injection of MTX or linear salpingostomy (7 patients each).

**Measurements and Main Results.** Both treatments were successful in all patients. Mean length of operation was  $32 \pm 5$  minutes (range 25–35 min) in the MTX group versus  $67 \pm 15$  minutes (range 50–90 min) in the salpingostomy group. Mean length of hospital stay was 2.7 days (range 1–5 days) and 1.7 days (range 1–3 days), respectively. No intraoperative complications occurred, and the postoperative course was uneventful in all women. Mean disappearance time of serum  $\beta$ -human chorionic gonadotropin (hCG) levels was similar in both groups, although in the linear salpingostomy group the decrease was immediate. No difference in tubal patency on follow-up hysterosalpingography was observed between the two groups.

**Conclusions.** Although this is a preliminary report with a small number of patients, both types of treatment were safe and effective. An advantage of linear salpingostomy was the predictable and consistent decline of circulating  $\beta$ -hCG, and consequently a reduced need for a close follow-up. Local MTX injection was safe, economic, effective, and easy to perform, and in our experience the surgical time was statistically shorter than that for linear salpingostomy. Therefore, in selected patients, local injection of MTX could be the treatment of choice for unruptured ectopic pregnancy, avoiding a longer and potentially more dangerous procedure. Long-term outcomes do not seem to differ between the two types of treatment.

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Presented at the 24th Annual Meeting of the American Association of Gynecologic Laparoscopists, Orlando, Florida, November 8–12, 1995.

Ectopic pregnancy occurs in about 1% of all pregnancies and is responsible for 13% to 15% of maternal mortality. It is generally agreed that treatment is laparoscopic, either conservative (salpingostomy) or radical (salpingectomy), and that laparotomy is indicated only when the laparoscopic approach is contraindicated.<sup>1</sup> Several reports have shown that linear salpingostomy is safe and effective.<sup>2</sup> In the past decade, trials of systemic<sup>3-6</sup> and local treatment with methotrexate (MTX) were performed, with topical injection of MTX by laparoscopy or under ultrasound guidance proving successful.<sup>7-10</sup>

We compared two different laparoscopic approaches, topical injection of MTX versus linear salpingostomy, for the conservative treatment of ectopic pregnancy.

### Materials and Methods

The subjects were 14 women with an ampullary unruptured tubal pregnancy who were hemodynamically stable and suitable for laparoscopic treatment. The diagnosis of ectopic pregnancy was established by serum levels of  $\beta$ -human chorionic gonadotropin (hCG), ultrasound scan, and laparoscopy. Women with

an ectopic pregnancy with fetal heart motion documented by ultrasonography, larger than 50 mm, or associated with tubal rupture were excluded from the study. Only those with unruptured ampullary ectopic pregnancy were included. All patients gave informed consent to the laparoscopic procedure.

Since July 1991 the first consecutive women meeting our criteria were treated by local injection of MTX, and the next seven by linear salpingostomy. The dose of MTX was determined by the surgeon, based on ultrasound examination of the affected tube,  $\beta$ -hCG level, and the size at laparoscopy. The doses ranged between 20 and 50 mg.

### Operative Procedures

#### Local Injection of MTX

After meticulous examination of the whole pelvis, the affected tube was grasped with an atraumatic forceps through a second 5-mm cannula. A 18-gauge spinal needle was introduced into the ectopic gestational sac under laparoscopic guidance. After as much fluid as possible was aspirated, MTX diluted in 4 ml of saline solution was injected in the affected tube

TABLE 1. Characteristics of the Two Groups

	Age (yrs)	Gravida	Para	Previous Ectopic Pregnancy	Weeks of Amenorrhea	$\beta$ -hCG (mIU/ml)	Largest Ultrasound Diameter (mm)	Largest Laparoscopic Diameter (mm)	
MTX	24	0	0	0	4	100	10	10	
	32	0	0	0	7	750	16	25	
	29	0	0	0	6	440	16	30	
	25	0	0	0	11	80	15	15	
	28	0	0	0	8	120	20	30	
	33	5	2	0	6	1260	40	30	
	37	2	0	1	7	210	22	35	
	Mean	29.7				7	421.4	19.86	25
	SD	4.61				2.16	437.8	9.67	9.13
	LS	42	1	1	0	7	83	16	30
29		2	1	1	8	700	50	45	
28		0	0	0	9	90	30	25	
29		2	0	1	7	648	39	40	
25		0	0	0	6	2500	48	25	
30		3	0	0	10	105	50	20	
30		0	0	0	7	6300	40	40	
Mean		30				7.71	1489.4	39	32.1
SD	5.5				1.38	2285.7	4.71	9.5	

through the same needle. Oral calcium folinate 16.2 mg/day was administered for a week after laparoscopy, starting the day of the intervention.

**Linear Salpingostomy**

A 10- to 15-mm longitudinal incision was made in the antimesenteric edge of the tube with scissors. Trophoblastic tissue and clots were gently removed by repeated suction and lavage. The tubal incision was left open with no suturing. If necessary, hemostasis was achieved by bipolar coagulation. No antibiotics were given prophylactically.

**Postoperative Care**

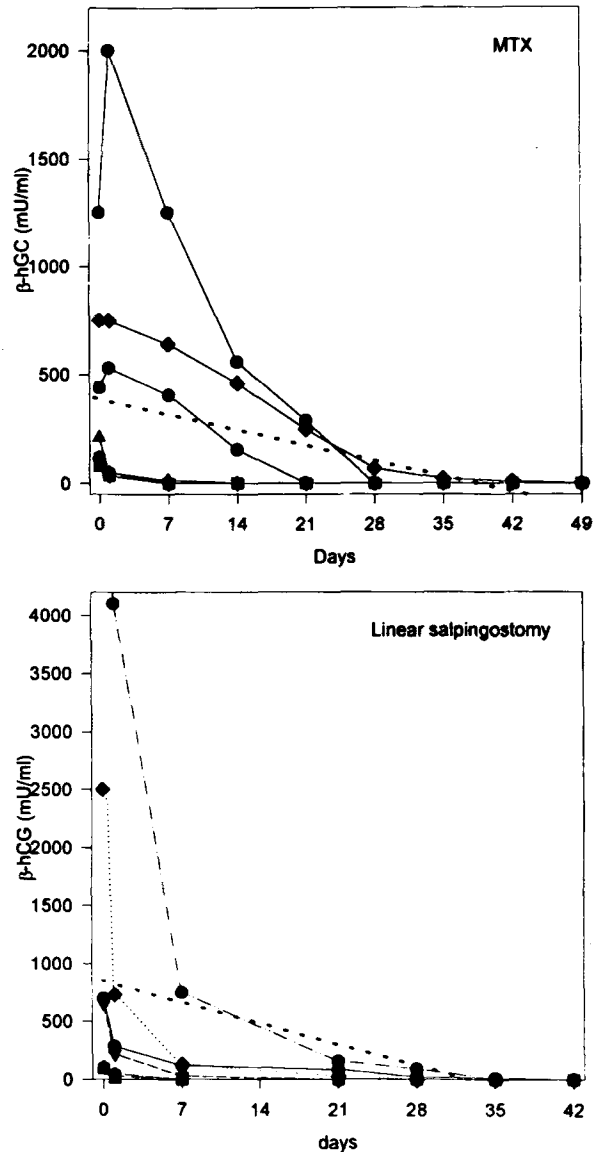
After the operation, vital signs were monitored closely for 24 hours. In the MTX group hemogram, hematocrit, and renal and hepatic function were checked to discover any toxic effect of the drug. Therefore these women were hospitalised at least for 2 days. In both groups, patients were discharged from the hospital only when serum  $\beta$ -hCG levels fell below preoperative values. The levels were monitored at 24 and 48 hours, and weekly until they disappeared. The women were advised to avoid pregnancy for at least 3 months, and to undergo a hysterosalpingogram (HSG) in 3 to 6 months to assess tubal patency.

**Data Analysis**

Statistical difference between the two groups were calculated by Student's *t* test. Mann-Whitney test was performed when indicated. Probability below 0.05 was considered significant.

**Results**

Women in the two groups were similar with respect to age, gestational age, size of tubal pregnancy by ultrasound, and  $\beta$ -hCG level at admission (Table 1). Ultrasound showed an ectopic pregnancy with a largest diameter that ranged between 10 and 50 mm; on the day of laparoscopy the  $\beta$ -hCG levels ranged between 80 and 6300 mIU/ml. The last menstrual period to diagnosis ranged between 4 and 11 weeks. Risk factors for ectopic pregnancy were present in 78.5% of women, and included a history of abdominal surgery in three, a previous ectopic pregnancy treated with salpingectomy in



**FIGURE 1.** Time course of disappearance of  $\beta$ -hCG in individual women. (Top) Patients treated by linear salpingostomy. (Bottom) Women treatment with MTX. Dotted lines = regression lines. Intercept with x axis identifies median zeroing time for both treatments (36.6 MTX vs 21.1 LS). MTX = methotrexate; LS = linear salpingostomy; US = ultrasonography; EP = ectopic pregnancy; IUP = intrauterine pregnancy; HSG = hysterosalpingography.

three, and past use of an intrauterine device in four. One patient had an intrauterine septum that was associated with three miscarriages. Only three women (25%) were parous before this ectopic pregnancy.

At laparoscopy the largest ectopic gestation ranged between 15 and 40 mm (mean  $27.1 \pm 9.5$  mm) in the MTX group and between 20 and 45 mm (mean  $28.5 \pm 10.2$  mm) in the salpingostomy group.

Both laparoscopic treatments were successful in all patients. In four patients 50 mg of MTX was used; in three women with minimal involvement of the tube and low  $\beta$ -hCG levels, the dose was lower. Mean operative time was  $32.1 \pm 4.8$  minutes (range 25–35 min) in the MTX group and  $67.5 \pm 15.4$  minutes (range 50–90 min) in the linear salpingostomy group ( $p < 0.001$ ). There were no intraoperative complications, and the postoperative course was uneventful in all women. No toxic side effects of MTX (stomatitis, elevated liver enzymes) were observed. Mean hospital stay was 2.7 days (range 2–5 days) in the MTX group and 1.7 days (range 1–3 days) in the linear salpingostomy group, with no statistically significant difference.

Serum  $\beta$ -hCG disappeared in 7 to 42 days after laparoscopy (Figure 1). In women treated by linear sal-

pingostomy, a notable decline the levels, even if not statistically significant, was observed 48 hours after the intervention (median 648 vs 220 mU/ml,  $p = 0.159$ ). By contrast, in the MTX group,  $\beta$ -hCG levels on the second postoperative day did not differ from preoperative levels (421 vs 492 mU/ml,  $p = 0.827$ ). In fact, they were higher in three patients as a result of a temporary increase, and in one patient the level was unchanged.

The regression lines for both treatments, although not statistically different, showed an immediate decrease of  $\beta$ -hCG levels in the linear salpingostomy group. However, the mean disappearance time was 18.3 days for MTX versus 18 days for linear salpingostomy.

In six women (3 in each group) HSG performed between 3 and 6 months after laparoscopy showed normal patency of the treated tube. The remaining patients refused HSG or become pregnant before it was performed. One woman treated with MTX, who had documented contralateral tubal occlusion, successfully conceived 4 months after the procedure and delivered a healthy baby at term. Three more patients, two in the MTX group and one in the linear salpingostomy group, achieved pregnancy within 6 months after laparoscopy; two of them delivered a healthy baby at term and the

**TABLE 2. Type of Treatment and Outcome**

Size of Ectopic Pregnancy at Laparoscopy (mm)	Treatment	Operative Time (min)	Hospital Stay (days)	Time to Disappearance of $\beta$ -hCG (days)	Outcome at Follow-up
10 x 10	MTX 20 mg	30	2	7	HSG: tubal patency, intrauterine pregnancy <sup>a</sup>
25 x 15	MTX 30 mg	35	5	49	HSG: tubal patency
30 x 20	MTX 50 mg	35	3	21	Term pregnancy
15 x 15	MTX 25 mg	30	1	2	—
30 x 10	MTX 50 mg	25	2	7	Term pregnancy
30 x 20	MTX 50 mg	30	3	28	—
40 x 40	MTX 50 mg	40	2	14	HSG: tubal patency
30 x 10	LS	60	1	7	HSG: tubal patency
45 x 15	LS	55	1	35	—
25 x 10	LS	90	2	7	—
40 x 15	LS	80	1	14	HSG: tubal patency
25 x 20	LS	70	2	21	—
20 x 20	LS	50	2	14	Term pregnancy
40 x 25	LS	70	1	28	HSG: tubal patency

<sup>a</sup>Legal induced abortion.

The immediate outcome in all patients was resolution of the ectopic pregnancy.

other chose abortion. Type of treatment and outcome are described in Table 2.

### Discussion

The laparoscopic approach is of great importance in the diagnosis and treatment of ectopic pregnancy, comparing favorably with laparotomy in better results, less discomfort to the patient, shorter hospital stay and reduced costs.<sup>1-11</sup> Endoscopic treatment can be radical or conservative, depending on several factors that should be considered before and during surgery.<sup>2</sup> Studies show that conservative surgery offers the best results in terms of subsequent pregnancy rate,<sup>12-13</sup> even if the procedure is not the only variable affecting the possibility of conceiving.<sup>12-14</sup> Moreover, salpingectomy does not reduce the risk of recurrent ectopic pregnancy.<sup>15</sup>

In our experience, local injection of MTX in selected patients who met strict criteria proved to be an easy, fast, safe, effective and economic laparoscopic procedure. In fact, it can be easily performed even by a less-skilled endoscopic surgeon. Despite the small number of patients, the shorter surgical time required for the injection of MTX compared with linear salpingostomy was statistically significant. Moreover, it was cost effective in that it did not require expensive instruments such as laparoscopic scissors, monopolar or bipolar instruments, laser, and endobag.

The hospital stay was longer in the MTX group than in the linear salpingostomy group. This was not due to postoperative complications, but to the fact that patients were discharged only when  $\beta$ -hCG levels declined below preoperative levels and any potential toxic side effect was excluded. From the experience we gained in this study, we have adopted a more liberal approach to these women, discharging them 24 hours after the treatment, with close supervision.

One way to monitor the immediate success of the treatment for an ectopic pregnancy is to determine the rate of decrease of  $\beta$ -hCG level on the second or the third postoperative day. In this study we found that after MTX treatment, the levels on the second postoperative day were unchanged or even increased in some patients, whereas linear salpingostomy resulted in a dramatic decrease in all women. The reason that MTX does not lead to an immediate drop in  $\beta$ -hCG levels after the procedure is due to its release from "dying"

trophoblastic cells from the cytotoxic effects of MTX.<sup>16</sup> Therefore it seems useless to evaluate the levels sooner than 3 days after the injection.

Reported failure rates of conservative endoscopic surgery are between 4% and 6%,<sup>1-17</sup> and after MTX injection about 11%.<sup>7</sup> No major complications occurred during or after either treatment, and the ectopic pregnancy was removed successfully in all patients.

Hysterosalpingogram was performed in three women in both groups and showed patency in all of them. One patient in the linear salpingostomy group had a viable intrauterine pregnancy 6 months after the treatment. In the MTX group, a woman who had tubal obstruction on the contralateral tube conceived after 4 months and delivered a healthy baby, and two others had a viable intrauterine pregnancy 1 year after treatment. These results are in agreement with the 90.5% tubal patency at HSG in 21 patients treated with local MTX, of whom 6 became pregnant.<sup>18</sup>

According to previous studies, MTX treatment should not be undertaken if fetal heart motion is noted on ultrasound, because these women are at high risk for uncontrolled hemorrhage at the time of pregnancy disruption and failure of the treatment.

Despite its longer operative time, linear salpingostomy for unruptured ectopic pregnancy offers the advantage of a predictable and consistent decline of circulating  $\beta$ -HCG that allows immediate evaluation of the result. Nonetheless, local injection of MTX is a safe and effective alternative, easy to perform, less traumatic and less expensive. We believe that it is the treatment of choice for interstitial and cornual pregnancy in selected women who cannot undergo a potentially long operation, and in those with extensive pelvic adhesions that can make a surgical approach difficult.

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