Randomized trial of conservative laparoscopic treatment and methotrexate administration in ectopic pregnancy and subsequent fertility

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Methotrexate treatment was compared to laparoscopic salpingotomy for conservative management of ectopic pregnancy in a prospective randomized study. One hundred patients were randomized into two groups using random numbers. Inclusion criteria were an ectopic pregnancy visualized by ultrasound with a pre-therapeutic score <13 as assessed by the following six criteria, graded from 1 to 3: gestational age, human chorionic gonadotrophin (HCG) concentration, progesterone concentration, abdominal pain, haemoperitoneal volume and diameter of the haematosalpinx. The treatments were either 1 mg/kg of methotrexate injected transvaginally into the ectopic pregnancy without anaesthesia or administered i.m. when the pregnancy could not safely or easily be punctured (group 1), or laparoscopic salpingotomy (group 2). Success was defined as the return to normal (<10 mIU/ml) of HCG concentrations. Treatment was successful for 45 of 51 patients in group 1 (88.2%) and 47 of 49 in group 2 (95.9%). Medical treatment was significantly (P < 0.05) associated with shorter postoperative stay (24 compared with 46 h), but HCG returned to normal more quickly in the presence of a positive pregnancy test, and laparoscopy is no longer essential for diagnosis. Linear salpingotomy by laparoscopy remains the treatment of choice for tubal pregnancy (Pouly et al., 1986) and represents a significant advance over laparotomy in the duration of hospitalization, delay of recovery, and health service costs (Vermesh et al., 1989; Lundorff et al., 1991).

This procedure preserves the Fallopian tube, but carries a risk of a persistent trophoblast and of repeated tubal pregnancy. Over the past 10 years, many uncontrolled series have reported the results of conservative medical treatment. One such treatment is methotrexate, which has been administered by i.m. or i.v. injection with one to four doses (Tanaka et al., 1982; Ory et al., 1986; Sauer et al., 1987; Stovall et al., 1991, 1993), orally (Pastner and Kenigsberg, 1988) or by local injection under laparoscopic or sonographic control (Feichtinger and Kemeter, 1987; Pansky et al., 1989; Kooi and Kock, 1990; Menard et al., 1990; Fernandez et al., 1993). When appropriate inclusion criteria are used (Fernandez et al., 1991a), methotrexate failure rates have been similar to those reported in previous series of laparoscopic surgery (Pouly et al., 1986; Seifer, 1997). Moreover, follow-up and reproductive outcomes have been similar in both treatments (Pouly et al., 1986; Fernandez et al., 1991b, 1993; Pansky et al., 1993; Stovall and Ling et al., 1993). The simplicity and the results of this non-surgical approach demanded further investigation. We compared these two conservative treatments of tubal pregnancies – laparoscopic salpingotomy and methotrexate – in a prospective randomized study, with treatment success and subsequent fertility as the main outcome measures.

Materials and methods
The trial took place between 1 September 1992 and 30 October 1995 at the University Hospital of Clamart. The study was approved by the local institutional review board, and all participants signed an informed consent.

When an ectopic pregnancy was visualized by transabdominal or transvaginal ultrasound, the patient was evaluated to determine her suitability for medical treatment (Fernandez et al., 1991b). This pre-therapeutic score is based on six criteria graded on a scale from 1 to 3: gestational age, HCG and progesterone concentration, abdominal pain, haemoperitoneal volume, and diameter of the haematosalpinx, both the latter assessed by ultrasound. Previous studies (Fernandez et al., 1991a, 1993) have demonstrated that the success rate for medical treatment is greater than 90% when the pre-therapeutic score is <13. Only patients with a score <13 were included in the trial.

Of 232 women with ectopic pregnancies diagnosed during this period, 100 (43%) entered the study. The remaining 132 patients were excluded for reasons that included failure to visualize ectopic

Introduction
Early diagnosis of ectopic pregnancy is now possible, thanks to the development of radioimmunoassays and antiserum that together allow sensitive and specific assays of the β-subunit of human chorionic gonadotrophin (HCG), the use of serum progesterone, and high resolution ultrasonography with vaginal probes. Ectopic pregnancy is now often discovered before any clinical symptoms of rupture have occurred, following early clinical symptoms of abdominal pain and/or abnormal bleeding. 

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pregnancy (n = 20), score ≥ 13 (n = 52), suspicion of ruptured tubal pregnancy (n = 58), liver or kidney disease or abnormal concentrations of liver enzymes or neutropenia that contraindicated methotrexate treatment (n = 2). No eligible patient chose not to participate.

A random number table was used to assign the patients to the two treatment groups. For each next allocation of treatment, the clinicians were blinded until the patients were recruited to the trial. We have previously reported results for 20 patients in each group without inclusion of subsequent fertility (Fernandez et al., 1995). In group 1, 51 patients were treated with a single dose of methotrexate. The treatment was started immediately after diagnosis, informed consent, and randomization. This procedure was carried out without anaesthesia, under transvaginal sonographic control. Once the sac is visualized, it can easily be punctured with an 18-gauge needle inserted into a needle introducer. After penetration and aspiration, 1 mg/kg of methotrexate was injected, into the sac for 29 women, and i.m. for the 22 women whose sac could not be safely or easily punctured.

The 49 patients in group 2 were treated by laparoscopy, using a triple suprapubic puncture technique with a 5 mm trocar and a 10 mm non-operative laparoscope that was introduced through the umbilicus and connected to a video camera. A monopolar linear salpingotomy was performed over the bulging antimesenteric portion of the tube, and an irrigation probe and grasping forceps were used to flush the tube once the ectopic sac was removed.

Patients in group 1 were monitored on an outpatient basis unless they lived too far from the hospital or when the procedure was performed after 4 p.m. (n = 21). Patients in group 2 were hospitalized for 2 days as is recommended in France (and reimbursed by the French national health insurance system). Patients were followed up by telephone after each HCG assay. All patients were aware of the possibility of treatment failure, defined by the persistence of high HCG concentrations or by the onset of abdominal pain, or both. In such cases, patients in group 1 were treated either by laparoscopy, or by a second injection of methotrexate when the patients were asymptomatic, and patients in group 2 by an i.m. injection of methotrexate.

Assays of HCG concentrations (International Reference Preparation) were required (RIA gnost-HCG, Behring, Marburg, Germany) on days 2, 5, and 10 after the procedure and then weekly until normalization (<10 mIU/ml). Treatment success was defined as completed elimination of the tubal pregnancy (serum HCG <10 mIU/ml). Liver function tests and red and white cell counts were obtained on day 10 to test for possible side-effects. Other information collected for each patient included demographic and obstetric characteristics and risk factors for ectopic pregnancy (Coste et al., 1991): age, parity, gravidity, smoking habits, history of tubal surgery and of ectopic pregnancy, history of pelvic inflammatory disease, pregnancy occurring despite contraceptive use, history of infertility, use of infertility drugs, fetal cardiac activity (observed by transvaginal ultrasonography).

Neither the vaginal scan nor the pelvic examination was repeated, to avoid an iatrogenic tubal rupture. The rate at which HCG concentrations returned to normal was compared with the reference curve (Pouly et al., 1991; Fernandez et al., 1993).

We calculated success rates after primary treatment (i.e. one methotrexate dose or salpingotomy alone) and after primary treatment plus additional therapeutic intervention. Patients were seen or contacted by telephone every 6 months to update the fertility and obstetric history. All patients in this series were followed up for at least 1 year to evaluate their spontaneous reproductive performance and any pregnancies occurring after IVF.

Patient characteristics are expressed as mean ± SD. The two groups were compared using Student’s t-test and the χ² test as modified by Yates, as appropriate.

### Results

No patient was excluded after initial inclusion. Indeed, the inclusion criteria proved extremely relevant for both groups. In the salpingotomy group, all patients had a haematosalpinx (sensitivity of pelvic ultrasound for the ectopic pregnancy diagnosis: 100%) for which conservative treatment was indicated.

Treatment was effective for 45 patients in the methotrexate group and 47 patients in the laparoscopic group. The success rates were very similar (respectively 88.2 and 95.9%, P = 0.15).

Table I shows baseline demographics and characteristics. The methotrexate group contained more patients with a past history of ectopic pregnancy.

Table II shows characteristics of the tubal pregnancies in both groups.

The methotrexate group was subdivided for the results between local and i.m. administration of methotrexate. However, there were no statistical differences between the two groups.

In the methotrexate group, although the success rate for local and for i.m. administration did not differ significantly, four of the six failures took place among patients who received an i.m. injection. One of the i.m. patients, with an initial score of 12, had an HCG concentration that had quintupled 6 days after injection; she required a salpingotomy. The HCG concentrations of three i.m. patients reached a plateau on day 10 to test for possible side-effects. Other information collected for each patient included demographic and obstetric characteristics and risk factors for ectopic pregnancy (Coste et al., 1991): age, parity, gravidity, smoking habits, history of tubal surgery and of ectopic pregnancy, history of pelvic inflammatory disease, pregnancy occurring despite contraceptive use, history of infertility, use of infertility drugs, fetal cardiac activity (observed by transvaginal ultrasonography).

### Table I. Characteristics of 100 patients with ectopic pregnancies

<table>
<thead>
<tr>
<th></th>
<th>Methotrexate (n = 51)</th>
<th>Salpingotomy (n = 49)</th>
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<tbody>
<tr>
<td>Age (mean ± SD years)</td>
<td>30.8 ± 5.6 (20–43)</td>
<td>30.3 ± 4.6 (18–43)</td>
</tr>
<tr>
<td>Parity (mean ± SD)</td>
<td>0.6 ± 0.9 (0–3)</td>
<td>0.7 ± 0.8 (0–4)</td>
</tr>
<tr>
<td>Gravidity (mean ± SD)</td>
<td>2.4 ± 1.2 (0–6)</td>
<td>2.3 ± 1.3 (0–8)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>19 (37.2)</td>
<td>19 (38.8)</td>
</tr>
<tr>
<td>Appendectomy (%)</td>
<td>17 (33.3)</td>
<td>19 (38.8)</td>
</tr>
<tr>
<td>History of ectopic pregnancy (%)</td>
<td>12 (23.5)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>History of tubal surgery (%)</td>
<td>5 (9.8)</td>
<td>7 (14.3)</td>
</tr>
<tr>
<td>History of PID (%)</td>
<td>5 (9.8)</td>
<td>7 (14.3)</td>
</tr>
<tr>
<td>CT serology &gt;1/64 (%)</td>
<td>23 (45)</td>
<td>15 (30.6)</td>
</tr>
<tr>
<td>Induction of ovulation (%)</td>
<td>6 (11.7)</td>
<td>10 (20.4)</td>
</tr>
<tr>
<td>Contraception failure (%)</td>
<td>7 (13.7)</td>
<td>3 (6.1)</td>
</tr>
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*Significant difference between groups (P < 0.05).

CT = Chlamydia trachomatis; PID = pelvic inflammatory disease.
pregnancy. Her initial HCG concentration was 880 mIU/ml. Another women with HCG at 5480 mIU/ml and a score of 12 was managed similarly 10 days after initial laparoscopy. No patient had a second laparoscopy.

The postoperative stay was shorter ($P < 0.05$) in the methotrexate group, and the HCG median resolution time was shorter ($P < 0.001$) in the salpingotomy group. Treatment failure could be diagnosed early, from the rate of decrease in HCG concentrations. In the methotrexate group, the mean number of blood samples for HCG measurements until return to normal (i.e. HCG concentration $<10$ mIU/ml) was $5 \pm 1$, and, in the conservative surgery group, $3 \pm 0.7$. Five ectopic pregnancies with cardiac activity and score $<13$ were treated successfully (one in group 1 and four in group 2). The postoperative course was uneventful, with no side-effects or septic complications in either group. Seven patients in the methotrexate group required a second dose by i.m. administration because HCG did not decrease at the normal rate. Four had abdominal pain between 3 and 5 days after methotrexate administration. Ultrasound had shown no fissuration syndrome, and the pain resolved spontaneously. Therefore, of 51 patients allocated to methotrexate treatment, 38 (75%) were successfully treated with a single injection, seven (13.7%) needed a second injection, and six (11.8%) required surgical intervention, with no salpingectomies. Of the 49 patients allocated to the salpingotomy group, 47 (95.9%) were successfully treated by surgery alone and two (4.1%) needed methotrexate for persistent trophoblast.

To date, 100 patients have had a follow-up period of at least 1 year. Eighteen of them have been lost to follow-up, 10 and eight respectively in group 1 and 2, and 26 patients did not desire a subsequent pregnancy, 14 and 12 respectively. We compared the women with whom we kept contact and those lost to follow-up, according to their main characteristics and their management. There was no difference for any of the factors studied.

Subsequent reproductive performance is presented in Table III.

Of the 27 women in the methotrexate group and 29 in the salpingotomy group who had attempted to become pregnant, 26 (96.3%) and 18 (62%) respectively had an intrauterine pregnancy ($P < 0.05$). In this series, we analysed only the first conception. In the methotrexate group, 22 occurred spontaneously, and four after IVF. In the salpingotomy group, 16 occurred spontaneously, and two after IVF. One spontaneous pregnancy in each group ended in miscarriage. Ectopic pregnancy recurred in one methotrexate patient and five salpingotomy patients. The mean time to pregnancy among women who became pregnant was similar in both groups.

Discussion

Our findings suggest that, among patients with an unruptured tubal pregnancy, treatment with local single dose of methotrexate and with laparoscopic linear salpingotomy have similar rates of success, defined as return to HCG $<10$ mIU/ml. In our experience, with strict inclusion criteria, 30–40% of patients with ectopic pregnancy could be treated by this medical approach.

Currently, most cases of tubal pregnancy are diagnosed by ultrasound examination: methotrexate can be administered at the same time that transvaginal ultrasound locates the ectopic sac if the puncture appears easy. If not, methotrexate can be injected i.m. This procedure can be done on an outpatient basis.

### Table II. Clinical, laboratory and sonographic findings in 100 patients with ectopic pregnancy. Values are mean ± SD

<table>
<thead>
<tr>
<th></th>
<th>Methotrexate (n = 51)</th>
<th>Salpingotomy (n = 49)</th>
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<tr>
<td></td>
<td>Local injection (n = 29)</td>
<td>i.m. injection (n = 22)</td>
</tr>
<tr>
<td>Successful (return to HCG $&lt;10$ mIU/ml)</td>
<td>27 (93.1)</td>
<td>18 (81.8)</td>
</tr>
<tr>
<td>Gestational age (day)</td>
<td>47.9 ± 9.4 (33–62)</td>
<td>48.6 ± 11.1 (36–70)</td>
</tr>
<tr>
<td>Score</td>
<td>10.7 ± 1.5 (7–13)</td>
<td>10 ± 1.3 (7–13)</td>
</tr>
<tr>
<td>Preoperative HCG (mIU/ml)</td>
<td>3805 ± 5710 (250–22 600)</td>
<td>3120 ± 5280 (100–13 500)</td>
</tr>
<tr>
<td>Preoperative progesterone (ng/ml)</td>
<td>11.2 ± 23.9 (1.8–38.6)</td>
<td>9.4 ± 21.3 (0.5–28)</td>
</tr>
<tr>
<td>Haematosalpinx (mm)</td>
<td>19.3 ± 11.2 (8–52)</td>
<td>19.3 ± 10.1 (6–49)</td>
</tr>
<tr>
<td>Resolution time (day)$^a$</td>
<td>28.6 ± 18.6 (7–110)</td>
<td>29.9 ± 18.9 (9–120)</td>
</tr>
<tr>
<td>Postoperative stay (h)</td>
<td>24 ± 8.7</td>
<td>24 ± 1.2</td>
</tr>
<tr>
<td>Second injection of methotrexate</td>
<td>4</td>
<td>3</td>
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</tbody>
</table>

There were no significant differences between the two methotrexate (MTX) groups. Significant difference between salpingectomy and methotrexate groups: $^aP < 0.05$, $^bP < 0.001$.

$^a$Failure excluded.

Day 0, day of MTX injection or laparoscopy.

HCG: conversion factor to SI units, 1.00.

Progesterone: conversion factor to SI units, 3.18.

### Table III. First reproductive performance after ectopic pregnancy (EP) (follow-up >1 year: n = 100)

<table>
<thead>
<tr>
<th></th>
<th>Methotrexate (n = 51)</th>
<th>Salpingotomy (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy not desired</td>
<td>14 (27.4)</td>
<td>12 (24.5)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>10 (19.6)</td>
<td>8 (16.3)</td>
</tr>
<tr>
<td>Spontaneous ongoing or term pregnancy$^a$</td>
<td>21 (56.7)</td>
<td>15 (40.5)</td>
</tr>
<tr>
<td>Miscarriage$^a$</td>
<td>1 (2.7)</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td>Recurrent Ep$^a$</td>
<td>1 (2.7)</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>Ongoing/or a term pregnancy after IVF$^a$</td>
<td>4 (10.8)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Mean time to pregnancy (months)</td>
<td>6.22 ± 3.34</td>
<td>7.25 ± 6.34</td>
</tr>
</tbody>
</table>

$^a$Excludes those who did not desire a pregnancy.

Values in parentheses are percentages.

Laparoscopy and methotrexate in ectopic pregnancy
without anaesthesia or surgery. In this series, the diagnostic sensitivity of ultrasound was 100%. Good results have been obtained with a single dose of methotrexate (Feichtinger and Kemeter, 1987; Pastner and Kenigsberg, 1988; Pansky et al., 1989; Kooi and Kock, 1990; Menard et al., 1990; Fernandez et al., 1993; Stovall and Ling, 1993). In such cases the site of injection (locally or i.m.) may be important. Our observations about the kinetics of methotrexate indicate that local injection is preferable (Fernandez et al., 1994). In that study, the area under the curve (Auc→∞) decreased more rapidly after injection into the gestational sac than after i.m. injection. This finding may be related to a decrease in the bioavailability of methotrexate that is absorbed by trophoblastic cells (Schiff et al., 1992). Only a prospective randomized study could provide a clear rationale for local or i.m. injection. Although this was not one of the aims of the present study, we did observe a 93.1% success rate (27 of 29) after local injection and 81.8% (18 of 22) after i.m. injection. More recently, however, we compared i.m. administration and local injection of methotrexate in a randomized trial: their respective success rates were 77 and 92% (P < 0.05) (unpublished data).

Some local inflammatory response and tubal epithelial desquamation have been reported as well (Schiff et al., 1992; Maymon and Shulman, 1996).

Finally, in our experience, local injection should be proposed when the sac is visualized and the direct puncture is easy to perform. I.m. injection should be confined to cases where the ectopic pregnancy cannot be safely or easily punctured under ultrasound guidance.

The failure rate observed in this series after laparoscopic salpingotomy is similar to the best rates reported earlier (Pouly et al., 1986; Yao and Tulandi, 1997).

Moreover, use of the pre-therapeutic score allows medical treatment with a low failure rate at the same time as it defines a population that, even with fetal cardiac activity, can really benefit from this less traumatic procedure.

Three prospective randomized trials have compared laparoscopic salpingotomy with local methotrexate by laparoscopy. Mottla et al. (1992) reported a randomized trial that was discontinued because of poor results in the group treated by methotrexate. The doses of methotrexate used were unusually low (12.5 mg), however, and the criteria used to judge treatment failure were unclear. The conclusions of this preliminary study have been debated (Fernandez and Lelaidier, 1993; Kooi and Kock, 1993; Pansky et al., 1993b). O’Shea et al. (1994) reported a success rate of 89.7% for local methotrexate under laparoscopic guidance (n = 29) and 87.5% for CO2 laser laparoscopic salpingotomy (n = 24), results that are equivalent in both groups and similar to ours. Zilber et al. (1996) found a lower incidence of persistent trophoblastic activity (4.2% compared with 16.7%) in the salpingostomy group; this difference was not statistically significant.

Laatikainen et al. (1993) compared local injection of hyperosmolar glucose solution by laparoscopy (n = 20) with salpingostomy (n = 20). There were four and two failures respectively. This difference was not significant, but of course, one major difficulty of this type of study is the large number of patients needed to observe a significant difference.

A recent (Hajenius et al., 1997) prospective randomized trial compared systemic methotrexate (n = 51) and laparoscopic salpingostomy (n = 49). Both methods were successful in treating the majority of cases. The authors reported a fairly high rate of failure after salpingotomy: 8% of the patients required salpingectomy, even after treatment of persistent trophoblast by methotrexate. Moreover, all of the patients treated by i.m. methotrexate underwent a laparoscopy before medical treatment, and 14% subsequently required surgical intervention.

For practical purposes, when an ectopic sac is found at laparoscopy, either a linear salpingotomy, removing the trophoblast, or removal of the tube should be performed immediately. In these cases, i.m. methotrexate is indicated only when high serum HCG concentrations persist. For patients who meet the inclusion criteria defined in our study, local methotrexate treatment at the same time that the ectopic sac is visualized by ultrasound appears both safe and efficient. In these cases, surgical treatment is required only rarely, for cases of unusual abdominal pain, with increasing haematosalpinx observed sonographically, or when the HCG concentration continues to rise after an additional i.m. methotrexate injection. It is not uncommon for patients treated by methotrexate, either locally or i.m., to experience increased abdominal pain on day 2 or 3 without any sonographic evidence of cul de sac fluid or increasing haematosalpinx. In accordance with published recommendations, we do not perform serial ultrasound examination after medical treatment. Follow-up studies comparing the decrease in HCG concentrations and the ultrasound image have found no correlation between them. Atri et al. (1992) have observed an increase in size and vascularity of ectopic pregnancies after successful treatment. Brown et al. (1991) have also confirmed the absence of correlation between HCG concentrations and ultrasound findings.

In this series, the presence of cardiac activity was not considered a contraindication for methotrexate treatment, when the score was <13, and all such patients were successfully treated.

Finally, the power of the randomized trial should be considered. In this study, the power was 56%. We would need 260 patients in each group with a risk α = 5% and β = 5% to clarify definitively a significant difference in success rates.

Follow-up in this series lasted for at least 1 year, and showed that spontaneous reproductive performance was equivalent in the two groups, thus confirming the results of previous studies (Fernandez et al., 1993; Pansky et al., 1993; Stovall and Ling, 1993). Moreover, a prior history of infertility appears to be the most significant factor in predicting fertility potential, and the choice of surgical procedures, either radical or conservative, does not influence outcome (Ory et al., 1993).

However, the overall rate of intrauterine pregnancy, including those obtained after assisted reproductive procedures, appeared better after methotrexate treatment, although the difference in this small number of patients was not statistically significant. Moreover, the proportion of women with a recurrent ectopic pregnancy was lower after medical treatment. One hypothesis for this observation is that new surgical trauma to the tube is avoided.
Preliminary results of this prospective randomized study confirm that when the initial score is <13, this non-surgical approach is an efficient alternative to laparoscopic surgery. The potential cost-effectiveness, already reported (Creinin and Washington, 1993; Yao et al., 1996), may become a determinative factor in selecting among various treatments. Moreover, methotrexate may be superior because of its simplicity: in those situations where laparoscopic salpingotomy failure rates exceed 15%, it may be desirable to use a technique for which laparoscopic surgery skills are not required.

References


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