Transvaginal intratubal methotrexate treatment of ectopic pregnancy. Report of 100 cases


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Between November 1988 and December 1993, 100 patients with a common, unruptured ectopic pregnancy were treated with 1 mg/kg injection of intratubal methotrexate under transvaginal sonographic control. Patients were not excluded from this series on the basis of the size of the adnexal mass, the term of ectopic pregnancy or initial β-human chorionic gonadotrophin (HCG) concentrations. Patients were excluded following uncertain diagnosis, signs of a ruptured ectopic pregnancy, or a significant haemoperitoneum on ultrasound scans. The mean age of the patients was 29.5 years (range 20–41). The mean gestational age and initial HCG concentration were 7.5 weeks (5–11) and 11 614 mIU/ml (192–105 000 respectively). Of the 100 patients, 22 (22%) had an ectopic pregnancy with active cardiac activity. Complete resolution was obtained in 78 out of these 100 ectopic pregnancies. Of these, 66 patients (85%) needed only one intratubal methotrexate injection, and 12 patients (15%) required a second i.m. methotrexate injection of 1 mg/kg. In this study, local treatment with one single intratubal methotrexate injection was successful in only 66% of patients. The mean resolution time for reduction of β-HCG concentrations was 23.5 days (range 7–40). There was no statistically significant correlation between initial β-HCG concentrations and outcomes after methotrexate treatment of ectopic pregnancy in our study. Where embryonal heart beats were observed, the success rate of the procedure was 40.9% (nine out of 22 cases). In the absence of cardiac activity, or when ultrasound examination showed no embryo, the success rate achieved was 84.6% (66 out of 78 cases) (P < 0.01). In all, 34 patients were considered to be incompletely cured after only one intratubal methotrexate injection: 12 patients required a second i.m. injection, a stagnation of β-HCG concentrations was observed in 15 patients, abdominal pain occurred in six patients, and one patient suffered tubal rupture with haemoperitoneum. A total of 22 patients required secondary surgical management (salpingectomy). No biochemical or clinical side-effects of methotrexate treatment occurred. Tubal alteration ascribable to methotrexate injection occurred in one patient in our study. Out of 75 patients in this series who wished to conceive, 21 (28%) became pregnant within 1 year with the following outcomes: 11 pregnancies at term, three miscarriages, one induced abortion and six recurrent ectopic pregnancies (four occurred on the same side). Our findings suggest that treatment of common unruptured ectopic pregnancy without prior selection of patients, by a single intratubal methotrexate administration was associated with a 66% success rate. This was dependent only on the presence of embryonal heart beats and there was no correlation between the success rate and initial β-HCG concentrations. Successful outcome after methotrexate administration for ectopic pregnancy could be perfected by way of an improved selection of patients based on inactive embryonal hearts and absence of a visualized embryo.

Key words: ectopic pregnancy/methotrexate/subsequent fertility/transvaginal intratubal injection

Introduction

Ectopic pregnancy is currently observed in one out of 80 pregnancies (Creinen and Washinton, 1993), with ensuing consequences in terms of conjugal fertility and cost. Conservative medical treatment of unruptured ectopic pregnancy is possible as a consequence of the improvement of diagnostic serial serum assays (radioimmunological, immunoradiometric, and immunoenzyme methods using monoclonal antibodies) for human chorionic gonadotrophin (HCG) combined with the availability of high-resolution transvaginal sonography. Following the report of the successful management of an interstitial pregnancy by systemic administration of chemotherapeutic agents (Tanaka et al., 1982), the resolution of ectopic pregnancy after in-situ injection of methotrexate under echoguidance was described (Feichtinger and Kemet, 1987). Subsequent studies (Menard et al., 1990; Fernandez et al., 1991c; Tulandi et al., 1992; Pérez et al., 1993), involving a small number of patients have shown the value of local methotrexate treatment of ectopic pregnancy. This report describes our experience with a larger non-selected group of patients with unruptured tubal pregnancies, who were treated with transvaginal methotrexate injection.

Materials and methods

Between November 1988 and December 1993, 100 patients showing clear evidence of an unruptured ectopic pregnancy as visualized by sonography (Aloka SSD 650; Biomedic; 95610 Eragny sur Oise, France), were treated by transvaginal injection of methotrexate under sonographic control. Diagnosis of ectopic pregnancy was based on clinical examination, quantitative β-HCG concentrations and ultrasonographic findings. In admitting patients to this study, no
criteria were imposed regarding the size of the adnexal mass, the
term of the ectopic pregnancy, or initial β-HCG concentration.
However, patients were excluded from the study on the following
grounds: uncertain diagnosis, signs of a ruptured ectopic pregnancy,
or a significant haemoperitoneum (> 500 ml) on ultrasound scans.

Under transvaginal sonographic control, an 18 gauge needle was
inserted into the needle guide and into the ectopic sac. The contents
were first aspirated to decrease the risk of rupture and this was
followed by slow injection of 1 mg/kg of methotrexate (Lederterxate®
Lederle Labs., Oullins, France). This transvaginal procedure was
conducted either without anaesthesia or using an injection of 1%
lidocaine (Xylocaine®; Bellon Laboratory, Neuilly, France) in the
vaginal fornix.

Following methotrexate treatment, the patients were nearly all hospitalised for 24 h in agreement with French Health Services
regulations. Their β-HCG concentrations were monitored by β-HCG
assay (Baxter; 78311 Maurepas, France) on days 0, 1, 2, 5, 10 and
weekly thereafter until a return to normal (< 2 mIU/ml). All patients
were informed of the possibility of the failure of the treatment;
the diagnosis of such failure being based on the persistence of a high
β-HCG concentration and/or by the onset of abdominal pain and
haemodynamic instability. If methotrexate treatment failed, manage-
ment was based on primary laparoscopic surgery. Folinic acid
(Speciafoldine® Rhone-Poulenc Labs., Paris, France) was adminis-
terated orally for 1 week after local methotrexate injection, at a dose
of 20 mg per day, to prevent systemic toxicity of methotrexate. Red
and white blood cell counts and liver function tests were performed
on days 0 and 5 of treatment, in all patients.

Two months after resolution of the ectopic pregnancy, hystero-
salpingography (HSG) was performed in 26 patients. Of the 100
patients, 94 (94%) were followed-up regularly to determine their
fertility and obstetric future.

Statistical analysis
Statistical evaluation of findings was made by the χ² test and the
Yates-corrected χ² test.

Results
Of 386 cases of ectopic pregnancy seen during this study, 100
(25.9%) were treated by transvaginal methotrexate injection,
administered under sonographic control. The mean age of the
patients in the study was 29.5 years (range 20–41 years). Six
patients (6%) had been carrying an intrauterine device, and 26
patients (26%) had a past history of pelvic inflammatory
disease. Six patients (6%) had experienced a previous ectopic
pregnancy. The mean β-HCG concentration was 11 614 mIU/
ml (range 192–105 000 mIU/ml), and the mean gestational
age was 7.5 weeks (range 5–11 weeks). The mean initial size
of the adnexal mass, defined as its largest diameter on
sonograms, was 23.2 mm (range 10–60 mm). Other population
characteristics and echographic findings are presented in
Table I.

Complete resolution was observed in 78 of the 100 ectopic
pregnancies studied. Of these, 66 patients (85%) received a
single intratubal injection of methotrexate and 12 patients
(15%) required a second i.m. injection of methotrexate (1 mg/
kg). Thus, in this study, local treatment with a single intratubal
methotrexate injection was successful in only 66 out of 100
patients (66%). The mean time taken for β-HCG concentrations
to fall to normal in successfully-treated patients was 23.5 days
(range 7–40 days). Of the 22 cases (22%) in our study in which
methotrexate treatment was not effective, 13 (59%) had an initial β-HCG concentration <10 000 mIU/ml, and
nine (41.0%) of >10 000 mIU/ml. Success rates are presented
in Table II, together with initial β-HCG concentrations and
embryonal cardiac activity. In cases with initial β-HCG concen-
trations of <10 000 mIU/ml, the overall success rate was
82.4% and this dropped to 6.4% in cases with >10 000 mIU/
ml. There was no statistically significant correlation between
the initial β-HCG concentrations and the outcome of metho-
trexate treatment of ectopic pregnancy in our study. When
embryonal heart beats were observed, the success rate of the
methotrexate procedure was 41% (nine out of 22 cases). In
the absence of embryonal cardiac activity or when ultrasound
examination showed no embryo, the success rate achieved was
84.6% (66 out of 78 cases) (Table II). This difference is
statistically significant (P < 0.01).

Patients in whom methotrexate treatment failed underwent
an initial laparoscopic procedure; in 15 cases (68.2%) β-HCG
concentrations failed to decrease, six patients (27.3%) experi-
cenced subacute tubal rupture (fissural syndrome) and one case
(4.5%) developed a significant haemoperitoneum (>500 ml)
which originated from an ectopic pregnancy on the other side
which had been overlooked. Of these latter seven cases, the
mean time between treatment by methotrexate injection and
tubal rupture was 4.3 days (range 1–12 days). The treatment
of these 22 cases was performed by laparoscopy in 14 cases
(63.6%) and by laparotomy after initial laparoscopy in eight
cases (36.4%). The surgical treatment consisted of salpingo-
ectomy in all 22 patients, due to significant tubal alteration.

No severe side-effects of methotrexate treatment, such as
bone marrow suppression or alteration of liver function tests,
were observed in this study. One patient had a residual
pelvic mass (β-HCG negative), which was visualized by
hysterosalpingography. This patient required a secondary
salpingectomy by laparoscopy 6 months later. Pathological
findings showed the destruction of the tubal mucosa and the
persistence of necrotic chorionic villi. Tubal patency was
studied either by hysterosalpingography or by secondary
laparoscopy in 26 cases of infertility. Of these, 11 patients

<table>
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<tr>
<th>Table I. Population characteristics of 100 cases. Figures in parentheses are percentages, unless otherwise indicated</th>
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<td>Past history</td>
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<tr>
<td>Nullipare</td>
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<tr>
<td>Carrying an intrauterine device</td>
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<td>Salpingitis</td>
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<td>Chlamydia infection</td>
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<td>Previous ectopic pregnancy</td>
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<tr>
<td>Previous induced abortion</td>
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<tr>
<td>Live birth</td>
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<tr>
<td>Gestational age (weeks)</td>
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<tr>
<td>Mean β-HCG concentrations before treatment (mIU/ml)</td>
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<tr>
<td>Ovular sac mean diameter (mm)</td>
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<tr>
<td>Presence of cardiac activity</td>
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<tr>
<td>Haemoperitoneum (&lt; 100 ml)</td>
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et al., pregnancy (Fernandez 1991a, 1993; Stovall 1991; et al., with a high failure rate of methotrexate treatment of ectopic pregnancy. Fernandez et al., 1993; Stovall and Pansky, 1992). As reported by Tulandi (1992) in our study, there was no statistically significant difference between the initial β-HCG concentrations, and the size of the adnexal mass. For example, the findings of previous similar studies (Atri et al., 1992) showed that methotrexate distribution was similar following i.m. methotrexate injection in our study, appears higher than that reported in recent series (Fernandez et al., 1991b, 1993; Stovall and Ling, 1993). In the absence of a randomized trial to compare the two methotrexate administration procedures, it cannot be proved which route of administration results in the best outcome, as suggested by Goldenberg et al. (1993) and Balasch et al. (1994).

However, the failure rate of 34% after a single local methotrexate injection in our study, appears higher than that reported in recent series (Fernandez et al., 1991b, 1993; Stovall and Ling, 1993). This can be explained by the absence in our trial of restrictive criteria, such as the term, initial β-HCG concentrations, and the size of the adnexal mass. For example, the mean initial β-HCG concentration of patients in previous studies was ~5000 mIU/ml while in our study it was as high as 11 614 mIU/ml. The successful outcome of methotrexate administration for ectopic pregnancy could be ensured by way of an improved selection of patients. With proper selection of patients, a success rate of 90% has been achieved, as reported by Goldenberg et al. (1993) in a recent review of literature.

Side-effects, such as nausea or stomatitis, were only reported in studies involving high doses or repeated (more than two) injections of methotrexate (Stovall et al., 1991;Prevost et al., 1992; Schoenfeld et al., 1992). No side-effects were observed in our study, because no patient received more than two local methotrexate injections. The systemic distribution of methotrexate is reduced after local injection (Bourget et al., 1991; Schiff et al., 1992) accounting for the reduction in side-effects. However, the study reported by Schiff et al. (1992), showed that methotrexate distribution was similar following i.m. methotrexate and intratubal methotrexate injections. The

(42.3%) had a past history of pelvic inflammatory disease, and 13 patients (50%) had tubal abnormalities as a result of local methotrexate treatment. Fertility after local methotrexate treatment could be evaluated in 94 patients (94%) from our study (Table III). Of these, 75 patients (79.8%) wished to conceive; and 11 patients (15%) required subsequent in-vitro fertilization (IVF) treatment. Twenty-one patients (28%) became pregnant within 1 year following IVF in four cases with the following outcomes: 11 term pregnancies, three miscarriages, and one induced abortion. Six patients (8%) had recurrent ectopic pregnancies, of which four occurred in the same tube.

### Discussion

Our experience of 100 patients treated by transvaginal methotrexate injection (1 mg/kg) under sonographic control as the primary treatment for common ectopic pregnancy demonstrated a successful outcome in 78% cases. This is consistent with the findings of previous similar studies (Atri et al., 1992; Pansky et al., 1992; Prapas et al., 1992; Tulandi et al., 1992; Fernandez et al., 1993; Stovall and Ling, 1993). As reported by Tulandi et al. (1992) in our study, there was no statistically significant difference between the initial β-HCG concentrations of patients who were successfully treated and those patients who failed to respond to treatment. Most of these authors believe that an active heart beat influences the prognosis of resolution of ectopic pregnancy after methotrexate administration. We therefore believe that an active heart beat influences the prognosis of resolution of ectopic pregnancy after methotrexate administration. In this situation, the use of a pretherapeutic score, as defined by Fernandez et al. (1991b, 1993) may help in selecting the appropriate treatment. After treatment by i.m. methotrexate injection, the success rate seems to differ from that seen after local methotrexate injection under sonographic control (Stovall et al., 1991). In the absence of a randomized trial to compare the two methotrexate administration procedures, it cannot be proved which route of administration results in the best outcome, as suggested by Goldenberg et al. (1993) and Balasch et al. (1994).

### Table II. Outcome analysis of treatment with methotrexate for unruptured ectopic pregnancy

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Success</th>
<th>Failure</th>
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<tr>
<td>Gestational age (weeks)</td>
<td>7.4 ± 1.7 (range: 5-12; n = 78)</td>
<td>7.8 ± 1.4 (range: 6-10; n = 22)</td>
</tr>
<tr>
<td>Ovular sac diameter (mm)</td>
<td>22.6 ± 10.7 (range: 10-60; n = 78)</td>
<td>26.5 ± 13.3 (range: 20-60; n = 22)</td>
</tr>
<tr>
<td>Embryonal cardiac activity</td>
<td>Active (total n = 22) 9 (41%)</td>
<td>Inactive (total n = 78) 13 (59%)</td>
</tr>
<tr>
<td>Initial β-HCG concentrations (mIU/ml)</td>
<td>&lt;10 000 (n = 74) 61 (82%)</td>
<td>≥(n = 26) 17 (63.4%)</td>
</tr>
<tr>
<td>Initial β-HCG concentrations (mIU/ml)</td>
<td>Success rate (%)</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;1000 (n = 19) 23</td>
<td>18</td>
<td>21/75 66 (85%)</td>
</tr>
<tr>
<td>1000-5000 (n = 29) 20</td>
<td>6</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>5000-10 000 (n = 26) 9</td>
<td>6</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>≥10 000 (n = 26) 7</td>
<td>9</td>
<td>4 (15%)</td>
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</table>

HCG = human chorionic gonadotrophin; NS = not significant (χ² test).

### Table III. Fertility of 94 out of 100 study cases following medical and surgical treatment of ectopic pregnancy in our series

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients wishing pregnancy</td>
<td>75</td>
<td>80</td>
</tr>
<tr>
<td>Subsequent pregnancies</td>
<td>21/75</td>
<td>28</td>
</tr>
<tr>
<td>Intrauterine pregnancy</td>
<td>15/21</td>
<td>71.4</td>
</tr>
<tr>
<td>Term deliveries</td>
<td>11/21</td>
<td>52.4</td>
</tr>
<tr>
<td>Miscarriages</td>
<td>3/21</td>
<td>14.3</td>
</tr>
<tr>
<td>Induced abortion</td>
<td>1/21</td>
<td>4.7</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>6/21</td>
<td>28.6</td>
</tr>
</tbody>
</table>

Bider et al., 1992; Karsdorp et al., 1992; Stovall and Ling, 1993). Our findings confirmed this, showing that the success rate of local methotrexate injections was significantly lower in cases with an active embryonal heart beat. We therefore believe that an active heart beat influences the prognosis of resolution of ectopic pregnancy after methotrexate administration. In this situation, the use of a pretherapeutic score, as defined by Fernandez et al. (1991b, 1993) may help in selecting the appropriate treatment. After treatment by i.m. methotrexate injection, the success rate seems to differ from that seen after local methotrexate injection under sonographic control (Stovall et al., 1991). In the absence of a randomized trial to compare the two methotrexate administration procedures, it cannot be proved which route of administration results in the best outcome, as suggested by Goldenberg et al. (1993) and Balasch et al. (1994).

However, the failure rate of 34% after a single local methotrexate injection in our study, appears higher than that reported in recent series (Fernandez et al., 1993; Stovall and Ling, 1993). This can be explained by the absence in our trial of restrictive criteria, such as the term, initial β-HCG concentrations, and the size of the adnexal mass. For example, the mean initial β-HCG concentration of patients in previous studies was ~5000 mIU/ml while in our study it was as high as 11 614 mIU/ml. The successful outcome of methotrexate administration for ectopic pregnancy could be ensured by way of an improved selection of patients. With proper selection of patients, a success rate of 90% has been achieved, as reported by Goldenberg et al. (1993) in a recent review of literature.

Side-effects, such as nausea or stomatitis, were only reported in studies involving high doses or repeated (more than two) injections of methotrexate (Stovall et al., 1991; Prevost et al., 1992; Schoenfeld et al., 1992). No side-effects were observed in our study, because no patient received more than two local methotrexate injections. The systemic distribution of methotrexate is reduced after local injection (Bourget et al., 1991; Schiff et al., 1992) accounting for the reduction in side-effects. However, the study reported by Schiff et al. (1992), showed that methotrexate distribution was similar following i.m. methotrexate and intratubal methotrexate injections. The
advantage of tubal over i.m. injections must be proved by a randomized trial, to compare success rates and side-effects.

In-vitro studies (Lecuru et al., 1992) and histopathology of human tubes after local methotrexate treatment (Kooi et al., 1992) showed an absence of tubal alteration, ascribable to methotrexate injections. Subsequent studies on the side on which the ectopic pregnancy occurred, report tubal patency after local methotrexate treatment to be 75–90% of cases (Stovall et al., 1991; Pansky et al., 1992; Prapas et al., 1992; Fernandez et al., 1993; Stovall and Ling, 1993). In our study, of the 26 patients who were explored either by hysterosalpingography or during laparoscopic control, tubal abnormalities occurred in 50% of cases. Our findings may be accounted for by the high incidence (42.3%) of past histories of pelvic inflammatory disease in our patient series. Moreover, one patient in our series developed a residual pelvic mass which required secondary salpingectomy 6 months later. This case demonstrates the possibility of persistent tubal abnormalities after local methotrexate treatment with persistence of necrotic choriocarcinoma villi. An identical case has been reported previously by Klinkert et al. (1993).

Conservative surgical treatment of tubal pregnancy is reported to increase the likelihood of subsequent fertility (Pouly et al., 1986). Further studies have reported that fertility involving term pregnancies was preserved to a similar extent following methotrexate treatment for ectopic pregnancy. The subsequent pregnancy rates and the recurrence rates of ectopic pregnancy in these studies ranged from 67–90%, and from 10.8–13% respectively (Stovall et al., 1990, 1991; Stovall and Ling, 1993; Fernandez et al., 1993; Ory et al., 1993; Pansky et al., 1993), compared with 28 and 28.6% in our series. Therefore, methotrexate administration seems to be the treatment of choice in selected patients with common unruptured ectopic pregnancy. However, in the future, only a randomized trial comparing conservative surgical management and medical treatment procedures for unruptured common ectopic pregnancy should be carried out to demonstrate the preferred procedure in terms of outcome, tubal patency, subsequent fertility, and recurrence rate (Goldenberg et al., 1993; Balasch et al., 1994). Moreover, most recently reported data on methotrexate administration showed success in uncommon ectopic gestation. Interstitial and cornual pregnancies can be managed conservatively with methotrexate administration which represents an alternative to laparotomy, the commonly employed management of such ectopic pregnancies (Fernandez et al., 1991c; Benifla et al., 1993). However, a rupture of interstitial pregnancy remains a dangerous possibility during conservative medical treatment, especially when HCG concentrations do not decrease as expected (Voigt et al., 1994). In addition, some recent reports of successful methotrexate treatment of peritoneal trophoblastic implants after primary surgical treatment of ectopic pregnancy showed the interest in this therapy (Cartwright, 1991; Poulot et al., 1994).

In conclusion, methotrexate administration can be used to induce resolution of different forms of ectopic gestation, by intratubal methotrexate administration in an unselected group of patients with a 78% overall success rate. In patients receiving one single intratubal methotrexate injection, this success rate dropped to 66%. In our study, this outcome was only dependent on the presence of embryonal heart beats, and there was no correlation between this success rate and initial β-HCG concentrations. Successful outcome of ectopic pregnancy after methotrexate administration could be achieved by means of an improved selection of patients, particularly based on absent embryonal heart beats or on a visualized embryo. Tubal alteration ascribable to methotrexate injection occurred in only one patient.

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References


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