Medical treatment of ectopic pregnancies: a randomized clinical trial comparing methotrexate–mifepristone and methotrexate–placebo

Patrick Rozenberg1,11, Sylvie Chevret2, Eric Camus1, Renaud de Tayrac3, Olivier Garbin4, Loïc de Poncheville5, Jerry Coiffic6, Jean Philippe Lucot7, Françoise Le Goueff8, Didier Tardif9, Claude Allouche10, Hervé Fernandez3 and for the GROG*

1Department of Obstetrics and Gynecology, Poissy–Saint Germain Hospital, University Versailles–St Quentin, 2Department of Biostatistics, Saint Louis Hospital, University Paris VII, Assistance Publique—Hôpitaux de Paris, 3Department of Obstetrics and Gynecology, Antoine Béclère Hospital, Clamart, 4Department of Obstetrics and Gynecology, C.M.C.O. Schiltigheim, 5Department of Obstetrics and Gynecology, C.H.R.U. Tours, 6Department of Obstetrics and Gynecology, Hôtel Dieu Hospital, Rennes, 7Department of Obstetrics and Gynecology, Jeanne de Flandre Hospital, Lille, 8Department of Obstetrics and Gynecology, C.H.R.U. Tours, 9Department of Obstetrics and Gynecology, Annecy Hospital, and 10Department of Obstetrics and Gynecology, Evreux Hospital, France

11To whom correspondence should be addressed at: Centre hospitalier Poissy–Saint Germain, Rue du Champ Gaillard, 78303 Poissy Cedex, France. E-mail: prozenberg@chi-poissy-st-germain.fr

BACKGROUND: Medical treatment of ectopic pregnancies is common. To increase the efficacy of methotrexate, the association of mifepristone has been proposed. METHODS: We performed a large prospective multicentre double-blind sequential randomized trial in order to compare the efficacy of methotrexate and mifepristone (600 mg given orally) versus methotrexate and placebo. RESULTS: A total of 212 ectopic pregnancies was randomized. There was no significant difference in the initial characteristics between the two groups. There was no significant difference in the success rate of medical treatment between the methotrexate–mifepristone (n = 113) and the methotrexate–placebo group (n = 99): 79.6% (90/113) versus 74.2% (72/97) respectively, RR (95% CI): 1.07 (0.92–1.25), P = 0.41, non-significant. However, there was a quantitative interaction between progesterone level and effect of treatment: when progesterone level was >10 ng/l, the efficacy of the combination of mifepristone and methotrexate was significantly higher than the combination of methotrexate and placebo, with an 83.3% success rate (15/18) versus 38.5% (5/13) respectively. CONCLUSIONS: Our study failed to demonstrate any benefit of the addition of mifepristone to methotrexate. By contrast, the quantitative interaction between treatment effect and baseline serum progesterone suggested that this combination could be limited to ectopic pregnancies associated with high serum progesterone concentrations.

Key words: ectopic pregnancy/medical treatment/methotrexate/mifepristone/randomized controlled trial

Introduction

The incidence of ectopic pregnancy has almost doubled in the western world since the 1960s and the prevalence is up to 2% of all pregnancies in the USA (Centers for Disease Control and Prevention, 1995) and in France (Coste et al., 1994). Medical treatment of ectopic pregnancies has developed as an alternative to surgery. The most widely used protocol is a single dose of methotrexate given i.m., with subsequent single doses given if needed (Stovall et al., 1991; 1993; Glock et al., 1994; Henry et al., 1994; Stika et al., 1996; Lipscomb et al., 1998; 1999). However, failure rates as high as 22–26% have been reported (Ransom et al., 1994; Corsan et al., 1995; Stika et al., 1996; Perdu et al., 1998). Improving the efficacy of medical management can prevent potentially serious events such as tubal rupture with massive haemoperitoneum that can result from failed outpatient treatment. This could be achieved through two different strategies: restricting medical treatment to the least developed ectopic pregnancies as reflected by low serum β-hCG and progesterone levels <5000–10 000 mIU/ml (Kooi et al., 1992; Stika et al., 1996) and 7.0–10 ng/ml (Ransom et al., 1994; Corsan et al., 1995) respectively, a small size of the ectopic sac by ultrasound (≤35 mm) (Stika et al., 1996), and no gestational cardiac motion detected (ACOG Practice Bulletin, 1999). Indication for surgery, hospitalization, and their related costs might thus be reduced (Alexander

*See Appendix for members of the GROG
et al., 1996; Yao et al., 1996; Morlock et al., 2000; Sowter et al., 2001). A second approach should be to increase the efficacy of methotrexate by medical treatment with another drug. One potential candidate is mifepristone (Mifégyne®; Excelgyne, France). In a non-randomized phase II study (Perdu et al., 1998), the failure rate was significantly more reduced in patients treated with mifepristone and methotrexate than in patients previously treated by methotrexate alone. In a randomized controlled trial (Gazvani et al., 1998), unruptured ectopic pregnancy appeared to resolve significantly faster with the combination of methotrexate and mifepristone when compared to methotrexate alone, as assessed by the interval to resolution of β-hCG levels.

However, these studies were based on small sample sizes, and the only randomized trial was not double-blind. Therefore, we underwent a prospective multicentre, double-blind, randomized trial with an appropriate number of patients in order to compare the efficacy and tolerance of the combined methotrexate–mifepristone to those of methotrexate–placebo for the medical treatment of ectopic pregnancy.

**Materials and methods**

Between October 1999 and April 2001, all women with an ectopic pregnancy meeting the criteria for medical management were counselled to participate in this multicentre, randomized, double-blind, placebo-controlled, sequential clinical trial. This study was approved by the Ethics committee of Poissy–Saint Germain hospital.

The diagnosis of ectopic pregnancy was made by using a non-laparoscopic algorithm combining quantitative β-hCG serum level, transvaginal ultrasonogram showing no intrauterine gestational sac, and any adnexal mass, and curettage failing to retrieve trophoblastic villi. Patients with serum β-hCG level >1500 mIU/ml and no intrauterine sac seen by ultrasonography were not subjected to curettage, nor were those with gestational cardiac activity by ultrasonography in the ectopic pregnancy. Patients with serum β-hCG level <1500 mIU/ml and <50% increase over 48 h underwent a curettage. Patients with serum β-hCG level <1500 mIU/ml which decreased after 48 h did not receive any treatment and were followed up until β-hCG levels were undetectable.

Inclusion criteria were: stable haemodynamics without active bleeding or evidence of haemoperitoneum, an unruptured mass, an ectopic pregnancy with gestational cardiac activity, serum β-hCG level >1500 mIU/ml and no intrauterine sac seen by ultrasonography, serum β-hCG level <1500 mIU/ml and a persistent abnormal increase in this level (<50% increase over 48 h) and no trophoblastic villi found in curettage, living within 1 h drive from the hospital (maximal route of 1 h), not living alone, patient agreeing to serial follow-up, no contraindications to methotrexate or mifepristone and signed written informed consent.

Exclusion criteria were: age <18 years, a decrease in serum β-hCG level or presence of trophoblastic villi following curettage; initial β-hCG level <1500 mIU/ml which decreased further after 48 h; hepatic (serum aminotransferase concentrations >2-fold the normal level), renal (serum creatinine concentration >1.5 mg/dl), or haematological dysfunction (leukopenia <2000/ml, thrombocytopenia <100 000/ml), suprarenal gland dysfunction, active pulmonary disease, peptic ulcer disease, overt or biological evidence of immunodeficiency, known sensitivity to methotrexate or mifepristone.

Blood type, Rh, and antibody screening were performed on all patients. Those who were Rh negative were given Rh immunoglobulin (300 μg) at inclusion. Finally, a serum progesterone level was measured at inclusion.

Randomization, based on a computer-generated list and balanced in blocks of variable size, stratified by centre, was carried out with sealed, opaque envelopes, stored in the pharmacy of each hospital. The envelope was opened immediately before the allocated treatment was administered.

All patients received a single i.m. injection of 50 mg/m² of body surface of methotrexate, and a single oral dose of mifepristone (600 mg) or placebo according to randomization.

Women were discharged home following treatment. They were reviewed at day 4 and day 7 on an outpatient basis. All women had serial serum β-hCG, hepatic and renal function tests and full blood counts on each visit. If β-hCG levels dropped by >15% between days 4 and 7, the women were then reviewed weekly until serum β-hCG concentrations fell to <10 mIU/ml. If the decrease was <15% between days 4 and 7, a second injection of methotrexate (50 mg/m²) was given i.m. In these cases, β-hCG levels were also checked on days 11 and 14. A repeated dose of methotrexate was also given if gestational cardiac activity was still present on day 7 after the first or the subsequent dose of methotrexate.

Patients were instructed to refrain from alcohol and intercourse and to avoid vitamin preparations containing folic acid until complete resolution of the ectopic pregnancy, and to use either oral contraceptive pills or barrier contraception for ≥3 months after treatment completion.

Women were asked about side-effects and complaints on each visit. These were recorded on data sheets. Repeat transvaginal scanning was performed to rule out rupture of ectopic pregnancy if the patient presented increasing abdominal pain. When gestational cardiac activity was seen at treatment initiation, transvaginal scanning was performed on alternate days until cardiac activity disappeared. Repeated clinical pelvic examinations were not performed in any patients to avoid the potential of iatrogenic tubal rupture after treatment initiation.

Patients were admitted in hospital if transient and isolated pelvic pain appeared or worsened. Laparoscopic treatment was indicated if the β-hCG level had not decreased sufficiently after day 14 and if pelvic pain was not controlled by non-opiate analgesics or if signs of internal haemorrhage developed.

The primary outcome was the success rate of the medical treatment, defined by the absence of indication for surgical intervention before serum β-hCG levels were below 10 mIU/ml irrespective of the number of injections of methotrexate.

The secondary outcomes were: (i) efficacy criteria: indications for surgical intervention, surgical modalities, need for a second dose of methotrexate, number of days in hospital, time-interval from treatment completion; (ii) safety and tolerance criteria: gastritis, stomatitis, reversible alopecia, increase in serum aminotransferase concentrations, severe neutropenia or thrombocytopenia.

**Computation of sample size, stopping rules**

Assuming a success rate of 80% in the methotrexate group, it was computed that 158 patients had to be enrolled in each group to demonstrate a benefit of ≥15% in the methotrexate–mifepristone group (i.e. a success rate of ≥95%), controlling for a type I error of 5% and a power of 90% (two-sided test). Nevertheless, owing to the uncertainties of the benefit associated with methotrexate–mifepristone treatment, the protocol had planned the schedule of inspections ahead, with computation of stopping rule based on the triangular test (Whitehead, 1992). Briefly, the triangular test consisted of drawing stopping boundaries on the plot of the difference in efficacy (Z) against
its precision ($V$), which complied with type I error and power requirements. Following inclusion of each group of 60 patients, all available data on the patient responses were gathered together, and current values of $Z$ and $V$ were computed. If the computed point lay between the boundaries, then the trial was continued until the next inspection. If it lay outside the stopping boundaries, then the trial was stopped (Figure 1).

Statistical analysis was based on the intention-to-treat principle; all patients were therefore analysed in the group allocated by randomization.

Estimation of treatment success was defined by the ratio of observed successes to the total number of randomized patients, with computation of relative risk (RR) and 95% confidence interval (95% CI). Regression logistic models allowed to search for prognostic covariates, estimating the strength of the association between covariates and outcome by odds ratio (OR) of success with 95% confidence interval (95% CI). Such a modelling approach also allowed us to: (i) explore the shape of the influence of continuous covariates on success rate, using smoothing (spline) functions, and (ii) test for treatment by centre interaction. Finally, Gail and Simon (1985) tests for quantitative interaction between randomization and either $\beta$-hCG or progesterone levels were carried out.

Statistical analysis was performed using SAS 8.2 (SAS Inc., USA) and Splus2000 (MathSoft Inc, USA) software packages. All tests were two-sided, with $P \leq 0.05$ considered statistically significant.

**Results**

**Decision to stop**

Figure 1 displays the results of the two interim analyses, performed through the use of the triangular test after 60 and 120 inclusions respectively. The crossing of the lower boundary at the second interim analysis led us to stop inclusions in the trial with the conclusion of no significant difference in terms of success rate of treatment between the randomization arms. However, data accumulated for some time after the formal stopping criterion had been reached. Indeed, there was a predictable and unavoidable delay between the assessment of response on these 120 patients and the actual date when checked data were available for analysis. Moreover, owing to the rapid rhythm of recruitment into the study, by the actual time of stopping decision based on the findings of the second interim analysis, extra information on 92 additional women was available. Since the conduct of the trial was not changed by the realization that the formal stopping criterion had been achieved, and given that the blindness of the study had been maintained, then the extra data was pooled with the old. Therefore, the following statistical analysis is based on the total of 212 inclusions (see Figure 2 for flow diagram of trial).

**Population**

A total of 597 patients was admitted for ectopic pregnancy in 18 participating centres during the study period; 212 (35.5%) of these were randomized. Non-inclusion occurred due to: refusal of participation in the study [$n = 65$ (16.9%)], presence of at least one exclusion criterion [$n = 207$ (53.8%)], or to the indication of immediate surgical treatment [$n = 113$ (29.3%)].

Among the 212 randomized women, 113 (53.3%) were included in the methotrexate–mifepristone group and 99 (46.7%) in the methotrexate–placebo group. Table I shows the initial characteristics of these 212 women according to the randomization group.

**Primary outcome**

Two patients (0.9%) (both in the methotrexate–placebo group) were lost to follow-up, and one (in the methotrexate–mifepristone group) required emergency surgery for a tubal rupture, 1 day after $\beta$-hCG resolution.

The overall success rate of medical treatment was 77.1% (162/210). There was no significant difference between the methotrexate–mifepristone and the methotrexate–placebo groups: 79.6% (90/113) versus 74.2% (72/97) respectively [RR (95% CI): 1.07 (0.92–1.25), $P = 0.41$ (non-significant) by Fisher’s exact test]; the results remained similar when assuming that the two patients lost to follow-up in the methotrexate–
placebo group could have been successfully treated [RR (95% CI): 1.065 (0.92–1.23), P = 0.42, non-significant or not (RR (95%CI): 1.095 (0.94–1.27), P = 0.26, non-significant]. No evidence of treatment by centre interaction was found (P = 0.36, non-significant).

Predictive factors for the main outcome measure (i.e. treatment success) were studied, on the basis of logistic models, overall and according to treatment group (Table II). Only serum β-hCG levels at inclusion were significantly related to the outcome (P < 0.0001), whatever the randomized group, while progesterone levels were only related to the outcome in the methotrexate–placebo group (P = 0.01). To obtained further insight in these relationships, we estimated the shape of the influence for β-hCG and progesterone levels measured at baseline on the risk of success, using smoothing functions. As displayed in Figure 3, the assumption of log linearity of the effect of serum β-hCG levels was checked: the higher the level of β-hCG, the lower the probability of success. On the other hand, Figure 3 shows a non-linear effect for progesterone levels: risk of success falls with increasing progesterone level, up to a value of ~10–15 ng/ml, and then rises after 15 ng/ml. The threshold of 10 ng/ml was chosen on the basis of a non-parametric estimate of the effect of progesterone on the risk of success, and this value roughly corresponds to the change in slope observed on the curve.

Finally, as shown in Table III, there was no heterogeneity in treatment effect according to the β-hCG level (P = 0.21, non-significant), illustrating that the observed prognostic value of β-hCG was not related to the treatment group (Table II). By contrast, we demonstrated a treatment by progesterone level quantitative interaction (P = 0.01), that is, differences in success rates between randomized groups differed according to progesterone levels at initiation of therapy, consistent with the fact that progesterone levels had prognostic value only in the methotrexate–placebo group (Table II).

### Secondary outcomes and adverse events

No significant difference was observed between groups for the secondary outcomes (Table IV). Notably, the time-interval from randomization to fall in serum β-hCG levels <10 mIU/ml and the number of second doses of methotrexate were similar. No significant difference was also observed between groups for the main adverse events (Table V). Finally, no biological evidence of hepatic, renal, or haematological dysfunction was observed.

### Discussion

This is the first randomized, double-blind, placebo-controlled trial comparing the efficacy of methotrexate–mifepristone versus methotrexate–placebo in the medical management of ectopic pregnancy. This was a multicentre trial, and this is likely to reflect a realistic approach in the management of ectopic pregnancies.
Overall, the efficacy of methotrexate was not increased by the adjunct of mifepristone. The effect of methotrexate decreased linearly when serum β-hCG levels increased. We chose as threshold the value of 1500 mIU/ml for serum β-hCG level which is near the median value of our population, to assess interaction between β-hCG levels and the effect of treatment: the addition of mifepristone did not improve the success rate of methotrexate irrespective of β-hCG concentrations (Table III).

However, there was significant quantitative interaction of mifepristone effect and serum progesterone levels, illustrating the heterogeneity in treatment effect according to baseline progesterone levels: actually, in women with progesterone level >10 ng/ml the addition of methotrexate to mifepristone improved the success rate, whereas in those with progesterone level <10 ng/ml there was no difference in outcome between randomized groups.

High serum progesterone concentrations reflect an important activity of the corpus luteum and are associated with an ectopic conceptus that is likely to be developing and growing. Indeed, in ectopic pregnancies, high baseline level of progesterone is predictive of failure of medical treatment by the methotrexate only (Ransom et al., 1994; Corsan et al., 1995). Thus, the additional therapeutic efficacy of mifepristone could be due to a luteolytic effect (Somell et al., 1990; Telleria et al., 2001) particularly useful in the case of active corpus luteum.

Furthermore, Paris et al. (1986) observed marked trophoblastic necrosis at histological examination of the tissue samples from ectopic pregnancies when mifepristone was given. Therefore, mifepristone might facilitate this necrosis by a drop in the progesterone concentration.

Finally, it is also likely that in poorly active ectopic pregnancies, i.e. when serum β-hCG level is <1500 mIU/ml, the great efficacy of methotrexate (90.6% in our study) probably masks the potential benefit due to a luteolytic effect of mifepristone even in the case of a very active corpus luteum.

Nonetheless, these conclusions must be guarded in view of the absence of initial stratification by progesterone levels which led to this post-hoc analysis. Furthermore, serum progesterone levels are not widely used clinically and were indeed omitted; these data are therefore missing from one half of the cases although it was part of the study protocol.

Table III. Tests for quantitative interactions between the effect of treatment and either serum β-hCG or progesterone levels

<table>
<thead>
<tr>
<th>Estimated success rates among patient subsets, % (no. successes/no. patients)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTX + mifepristone</td>
<td>MTX + placebo</td>
<td></td>
</tr>
</tbody>
</table>

| Whole sample | 79.6 (90/113) | 74.2 (72/97) | 1.07 (0.92–1.25) | 0.41 |
| β-hCG | 90.6 (48/53) | 93.0 (40/43) | 0.97 (0.86–1.10) | 0.21 |
| <1500 mIU/ml | 70.0 (42/60) | 59.3 (32/54) | 1.18 (0.90–1.56) | |
| ≥1500 mIU/ml | |
| Progesterone | 76.5 (26/34) | 80.0 (28/35) | 0.95 (0.74–1.23) | 0.01 |
| <10 nmol/l | 83.3 (15/18) | 38.5 (5/13) | 2.16 (1.06–4.44) | |
| ≥10 nmol/l |

*Fisher’s exact test.
*bGail and Simon’s heterogeneity test.

MTX = methotrexate; RR = relative risk; CI = confidence interval.
In our study, the need for a second injection was not considered as a criterion of failure because the optimal dose of methotrexate is unknown. Furthermore, the absence of indication for surgical intervention is a more relevant outcome in clinical practice. Finally, this same primary outcome was also used in a prior randomized trial (Fernandez et al., 1998) comparing methotrexate treatment to laparoscopic salpingotomy for conservative management of ectopic pregnancy.

Our results are different from those first published. In Perdu et al. (1998), the combination of mifepristone and methotrexate significantly increased the risk of success in the medical treatment of ectopic pregnancy. However, the patients treated by a combination of methotrexate and mifepristone were historically compared with a group which received only methotrexate. The combination of methotrexate and mifepristone was therefore used at a time when medical management was better understood and standardized; this might have overestimated the effect of the combined treatment, since surgery (notably, for persistent pain) was likely to be offered less often in this group.

In a randomized, controlled trial (Gazvani et al., 1998), ectopic pregnancy resolved faster in women who were given the combination of methotrexate and mifepristone as compared with those who were given methotrexate alone. Several drawbacks of this trial might be kept in mind, that limit the interpretation of the study results: (i) this trial was not a double-blind study; and (ii) the small sample size (25 in each arm) was not based on pre-specified power calculations.

The overall efficacy of medical treatment is less important than that previously reported in the largest series (Stovall et al., 1993; Lipscomb et al., 1998). Several explanations are plausible. (i) Our multicentre clinical trial included both university teaching hospitals and general hospitals. Some investigators were thus possibly less trained in medical management and might have indicated surgery more often in the absence of a rapid favourable evolution whereas the previous three published studies were performed in the same single centre. However, our results are comparable with several others reporting lower success rates (Ransom et al., 1994; Corsan et al., 1995; Hajenius et al., 1997). (ii) Patients with a serum $\beta$-hCG level <1500 mIU/ml that decreased after 48 h were not included in our trial. Thus, we only treated ectopic pregnancies that were clearly developing, although other studies included ectopic pregnancies with abnormal decrease of serum $\beta$-hCG levels to <1500 mIU/ml. This definitely applies to Korhonen et al. (1996) who found that spontaneous resolution occurred in 77% of the cases when the median baseline hCG level was low. (iii) Although the combined use of sonography and serum $\beta$-hCG measurements improves the diagnosis of ectopic pregnancies, the limitations are also documented (Ankum et al., 1993; Fernandez et al., 1998).

Among patients with low $\beta$-hCG plasma levels, a spontaneous abortion can be mistaken for an ectopic pregnancy. This is less likely when $\beta$-hCG level increases abnormally than when it decreases. Thus, the lower efficacy of medical treatment in our study might be the also consequence of a reduction in the false positive rate in the diagnosis of ectopic pregnancy.

<table>
<thead>
<tr>
<th>Table IV. Comparison of secondary outcomes between randomization groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Indications for surgery</td>
</tr>
<tr>
<td>Suspicion of tubal rupture</td>
</tr>
<tr>
<td>Pelvic pain</td>
</tr>
<tr>
<td>Patient’s refusal to reinject</td>
</tr>
<tr>
<td>methotrexate</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Operative technique (1)</td>
</tr>
<tr>
<td>Laparoscopy</td>
</tr>
<tr>
<td>Laparotomy</td>
</tr>
<tr>
<td>Operative technique (2)</td>
</tr>
<tr>
<td>Salpingotomy</td>
</tr>
<tr>
<td>Salpingectomy</td>
</tr>
<tr>
<td>Peritoneal lavage only</td>
</tr>
<tr>
<td>No. of MTX injections</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>No. of days in hospital, median (first quartile–third quartile)</td>
</tr>
<tr>
<td>Median time-interval to hCG resolution* (days) (95% CI) (first quartile–third quartile)</td>
</tr>
</tbody>
</table>

*Estimation by Kaplan and Meier’s method and comparison by the log-rank test.

Values are no. (%) unless otherwise stated.

MTX = methotrexate; CI = confidence interval.

| Table V. Intolerance symptoms in each randomized group |
|--------------------------|---------------|--|
|                           | MTX + mifepristone | MTX + placebo | $P$-value |
| Gastritis                 | 34 (30.1)      | 30 (30.3)     | 1.00      |
| Stomatitis                | 8 (7.1)        | 6 (6.1)       | 0.79      |
| Reversible alopecia       | 3 (2.7)        | 3 (3.0)       | 1.00      |

Values are no. (%) unless otherwise stated.

*Fisher’s exact test.

In our study, the need for a second injection was not considered as a criterion of failure because the optimal dose of methotrexate is unknown. Furthermore, the absence of indication for surgical intervention is a more relevant outcome in clinical practice. Finally, this same primary outcome was also used in a prior randomized trial (Fernandez et al., 1998) comparing methotrexate treatment to laparoscopic salpingotomy for conservative management of ectopic pregnancy.

Our results are different from those first published. In Perdu et al. (1998), the combination of mifepristone and methotrexate significantly increased the risk of success in the medical treatment of ectopic pregnancy. However, the patients treated by a combination of methotrexate and mifepristone were historically compared with a group which received only methotrexate. The combination of methotrexate and mifepristone was therefore used at a time when medical management was better understood and standardized; this might have overestimated the effect of the combined treatment, since surgery (notably, for persistent pain) was likely to be offered less often in this group.

In a randomized, controlled trial (Gazvani et al., 1998), ectopic pregnancy resolved faster in women who were given the combination of methotrexate and mifepristone as compared...
In summary, there was a lack of statistically significant advantage in response rates for the combination of mifepris-
tone and methotrexate over methotrexate-placebo, at the 5% level. By contrast, the observed treatment by serum progester-
one level interaction suggests that this combination could be
reserved to ectopic pregnancies with high levels of progester-
one. This should be assessed in a randomized clinical trial in
this particular population.

Acknowledgements
The study was sponsored by Assistance Publique – Hôpitaux de Paris,
Délégation Régionale à la Recherche Clinique. The authors would like
to thank Dr Yves Ville for his critical review, Ms Emmanuelle André
and Dr Caroline Fisch for their monitoring assistance.

References
of the small unruptured ectopic pregnancy: a cost analysis of methotrexate
Transvaginal sonography and human chorionic gonadotrophin measurements
in suspected ectopic pregnancy: a detailed analysis of a
Corsan, G.H., Karacan, M., Qasim, S., Rohrer, M.K., Ransom, M.X.
systemic single-dose methotrexate therapy in ectopic pregnancy. Hum.
Reprod., 10, 2719–2722.
Coste, J., Job-Spira, N., Aublet-Cuvelier, B., Germain, E., Glowaczower, E.,
Randomized trial of conservative laparoscopic treatment and methotrexate
administration in ectopic pregnancy and subsequent fertility. Hum. Reprod.,
13, 3239–3243.
Mifepristone in combination with methotrexate for the medical treatment of
1990.
Glock, J.L., Johnson, J.V. and Brumsted, J.R. (1994) Efficacy and safety of
single-dose systemic methotrexate in the treatment of ectopic pregnancy.
Hajenius, P.J., Engelsbel, S., Mol, B.W., Van der Veen, F., Ankum, W.M.,
Bosuyt, P.M., Hemrika, D.J. and Lammes, F.B. (1997) Randomised trial of
systemic methotrexate versus laparoscopic salpingostomy in tubal
Gynecol. Surv., 88, 775–778.
Analysis of three hundred fifteen ectopic pregnancies treated with
Lipscomb, G.H., McCord, M.L., Stovall, T.G., Huf, G., Portera, S.G.
single-dose methotrexate compared with laparoscopic treatment of ectopic
Paris, F.X., Henri-Suchet, J., Tesquier, L., Loyse1, T., Pez, J., Loffredo, V.,
Roger, M. and De Brux, J. (1986) Intérêt d’un stéroïde à action
antiprogesténone dans le traitement de la grossesse extra-utérine: résultats
Perdu, M., Camus, E., Rozenberg, P., Goffinet, F., Chastang, C., Philippe, H.J.
and Nisand, I. (1998) Treating ectopic pregnancy with the combination of
mifepristone and methotrexate: a phase II nonrandomized study. Am. J.
Ransom, M.X., Garcia, A.J., Bohrer, M., Corsan, G.H. and Kemmann, E.
(1994) Serum progesterone as a predictor of methotrexate success in the
hormones during termination of early pregnancy with mifepristone.
of single dose systemic methotrexate and laparoscopic surgery for the
204–212.
methotrexate for the treatment of ectopic pregnancy: Northwestern
Memorial Hospital three-year experience. Am. J. Obstet. Gynecol.,
174, 1840–1846.
Methotrexate treatment of unruptured ectopic pregnancy: a report of 100
Telleria, C.M., Goyeneche, A.A., Cavicchia, J.C., Stati, A.O. and Deis, R.P.
(2000) Apoptosis induced by antigestagen RU486 in rat corpus luteum of
pregnancy. Endocrine, 15, 147–155.
Ellis Horwood, Chichester.
methotrexate versus laparoscopic surgery for the treatment of ectopic

Submitted on November 21, 2002; resubmitted on March 12, 2003; accepted on May 9, 2003

Appendix
The study has been also run by the following investigators in the
Obstetrics and Gynecology Departments of the following centres:
Galal Rabiey, Dreux Hospital; Christophe Poncelet,
Bichat-Claude Bernard Hospital, Paris; Aubert Agostini, La
Conception Hospital, Marseille; Philippe Barjot, Clémenceau
Hospital, Caen; François Desmons, La Tronche Hospital,
Grenoble; Joëlle Jansé-Marec, Franco-Britannic Hospital,
Levallois; François Devianne, Orsay Hospital; Fabrice
Lecuru, Boucicaut Hospital; Marc Rettel, Notre Dame du
Bon-Secours Hospital, Metz; Amélie Gervaise, Antoine
Bélèbre Hospital, Clamart; Dr George Bader, Poissy-Saint
Germain Hospital; Jean Sébastien Autocurier, Poissy-Saint
Germain Hospital, Dr Christophe Vayssiere, C.M.C.O.
Schiltigheim; Dr Frank Perrotin, C.H.R.U. Tours; Dr Gilles
Body, C.H.R.U. Tours; Patrice Poulain, Hotel Dieu Hospital,
Rennes; Ludovic Moy, Hotel Dieu Hospital, Rennes; Joseph
Delaby, Jeanne de Flandre Hospital, Lille; Damien Subtil,
Jeanne de Flandre Hospital, Lille; Claude Virtos, Evreux
Hospital; Sylvain Tribalat, Dreux Hospital; Emmanuelle
Mathieu, Paul Gelle Hospital, Roubaix; Dominique Heajiy,
Annecy Hospital; Ludovic Cravello, La Conception Hospital,
Marseille; Florence Bretelle, La Conception Hospital,
Marseille; Michel Herlicoviez, Clémenceau Hospital, Caen;
Pascale Hoffman, La Tronche Hospital, Grenoble; Sepidieh
Guiti, Boucicaut Hospital; Philippe Lemarié, Notre Dame du
Bon-Secours Hospital.