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Published in:
Lancet

DOI:
10.1016/S0140-6736(97)05487-1

Citation for published version (APA):

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Randomised trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy

P J Hajenius, S Engelsbel, B W J Mol, F Van der Veen, W M Ankum, P M M Bossuyt, D J Hemrika, F B Lammes

Summary

Background Laparoscopic salpingostomy is a well-established treatment for patients with tubal pregnancy who desire to retain fertility. Another approach that preserves the fallopian tube is medical treatment. We compared systemic methotrexate and laparoscopic salpingostomy in the treatment of tubal pregnancy. Outcome measures were treatment success, tubal preservation, and homolateral tubal patency.

Methods Between January, 1994, and September, 1996, haemodynamically stable patients with laparoscopically confirmed unruptured tubal pregnancy and no signs of active bleeding were randomly assigned systemic methotrexate (four 1·0 mg/kg doses of intramuscular methotrexate alternated with 0·1 mg/kg oral folinic acid) or laparoscopic salpingostomy. Treatment success was defined as complete elimination of the tubal pregnancy (serum human chorionic gonadotropin <2 IU/L) and preservation of the tube. Homolateral tubal patency was assessed by hysterosalpingography. Analysis was by intention to treat.

Findings 100 patients were included in the trial. Of 51 patients allocated systemic methotrexate, 42 (82%) were successfully treated with one course; two (4%) patients needed a second course for persistent trophoblast. Surgical intervention was needed in seven (14%) patients; salpingectomy was necessary in five of these patients for tubal rupture. Of the 49 patients allocated laparoscopic salpingostomy, 35 (72%) were successfully treated by laparoscopic salpingostomy alone; salpingectomy was needed in four (8%) patients, and ten (20%) needed methotrexate for persistent trophoblast. The tube was preserved in 46 (90%) patients in the methotrexate group versus 45 (92%) in the salpingostomy group (rate ratio 0·98 [95% CI 0·87–1·1]). Homolateral tubal patency could be assessed in 81 patients: the tube was patent in 23 (55%) of 42 patients treated by laparoscopic salpingostomy alone, and in 23 (50%) of 45 patients in the salpingostomy group (rate ratio 0·93 [0·64–1·4]).

Interpretation In haemodynamically stable patients with unruptured tubal pregnancy, systemic methotrexate and laparoscopic salpingostomy were successful in treating the majority of cases. We found no significant difference between the treatments in the homolateral patency rate. Subsequent fertility outcome has to be awaited to show which treatment yields better fertility prospects.

Lancet 1997; 350: 774–79

Introduction

Laparoscopic salpingostomy is a well-established treatment in patients with tubal pregnancy who desire to retain fertility. This procedure preserves the fallopian tube, thereby maintaining reproductive capacity, but, in comparison with salpingectomy, carries an increased risk of persistent trophoblast and, possibly, of repeat ectopic pregnancy in the operated tube.

Another approach that preserves tubal integrity is medical treatment, in particular the systemic administration of methotrexate. Since laparoscopy is no longer essential for diagnosis in patients with suspected ectopic pregnancy, methotrexate offers the option of completely non-surgical management. Reviews summarising uncontrolled studies have reported outcomes of systemic methotrexate treatment similar to those of laparoscopic salpingostomy with respect to success rate, homolateral tubal patency, and reproductive outcome. No reports of randomised clinical trials have been published as yet.

We initiated a randomised clinical trial comparing systemic methotrexate and laparoscopic salpingostomy in the treatment of tubal pregnancy. Outcome measures were treatment success, tubal preservation, and homolateral tubal patency. Our hypothesis was that systemic methotrexate, because it is non-invasive, would offer better fertility prospects.

Methods

The trial took place between Jan 1, 1994 and Sept 1, 1996 in six Dutch hospitals: the Academic Medical Centre, the Onze Lieve Vrouwe Gasthuis, and the University Hospital Free University in Amsterdam, and the University Hospitals of Groningen, Nijmegen, and Utrecht. The study was approved by the ethics committees of all the centres.

Patients with a diagnosis of ectopic pregnancy were invited to participate in the trial. Ectopic pregnancy was diagnosed on the basis of a non-invasive strategy combining transvaginal sonography and measurement of serum human chorionic gonadotropin (HCG). Expectant management was used for patients with self-limiting forms of ectopic pregnancy (ie, serum HCG concentrations <1500 IU/L and declining—trophoblast in regression).
267 eligible patients with diagnosis of ectopic pregnancy in AMC and OLVG

147 not randomised in AMC and OLVG
104 excluded
43 no consent

120 randomised in AMC and OLVG
20 randomised in other centres

140 randomised in total

73 allocated systemic methotrexate
22 secondary exclusions

67 allocated laparoscopic salpingostomy
18 secondary exclusions

Completed trial;
Treatment success 51
Tubal preservation 51
Tubal patency 42

Completed trial;
Treatment success 49
Tubal preservation 49
Tubal patency 39

Figure 1: Trial profile

AMC=Academic Medical Centre, Amsterdam; OLVG=Onze Lieve Vrouwe Gasthuis, Amsterdam.

Exclusion criteria were unstable vital signs, fetal cardiac activity, sonographically detected interstitial, cervical, ovarian, or heterotopic pregnancy, contraindications to systemic methotrexate (leucopenia, thrombocytopenia, or high concentrations of liver enzymes or serum creatinine), and contraindications to laparoscopic surgery (documented extensive pelvic adhesions, large fibroid uterus, or severe ovarian hyperstimulation syndrome).

All eligible patients were informed about the possible complications and risk of failure of both treatments by the trial investigators (PJH, SE). Patients who gave written informed consent were randomly assigned one of the two treatment modalities before a confirmatory laparoscopy. Randomisation was done by means of a computer program with block randomisation, and with stratification for pre-existing tubal pathology and initial serum HCG concentration. Pre-existing tubal pathology was defined as previous ectopic pregnancy, previous tubal surgery, previous pelvic inflammatory disease, or proven tubal pathology by hysterosalpingography or laparoscopy.

Laparoscopy was done under general anaesthesia with a 10 mm laparoscope introduced through the umbilicus and a 5 mm suprapubic trocar. Reasons for exclusion at this stage were: tubal rupture, active bleeding, non-tubal pregnancy, and impossibility of laparoscopic salpingostomy. Although randomisation at laparoscopy could have overcome these secondary exclusions, the ethics committees judged a design in which patients did not know the randomisation outcome before surgery to be unethical. The secondary exclusion criteria were assessed by a surgeon unaware of the randomisation outcome so that adequate concealment of the treatment allocation could be achieved, thereby preventing potential selection bias. All patients with laparoscopically confirmed unruptured tubal pregnancy and no active bleeding were included in the trial. Since folic acid might negatively influence the effect of systemic methotrexate, all patients were instructed to discontinue any prenatal vitamins.

In patients allocated systemic methotrexate, treatment was started immediately after laparoscopy and completed on an outpatient basis. One full therapeutic course consisted of four doses of methotrexate given intramuscularly (1-0 mg/kg, on days 0, 2, 4, 6; Lederexate, Lederle Pharmaceutical Division, Cyanamid, Etten-Leur, Netherlands), and four doses of folic acid administered orally (0-1 mg/kg, days 1, 3, 5, and 7; hospital preparation; calcium folinate 5H2O, Bupha Chemie, Uitgeest, Netherlands), followed by 7 days without medication. During the methotrexate course patients were instructed not to use alcohol or aspirin, to refrain from sexual intercourse, to avoid exposure to sunlight, to drink at least 1·5 L fluid daily, and to use 0·9% saline mouthwashes or, in case of stomatitis, chlorhexidine 0·12% mouthwashes.

In patients allocated laparoscopic salpingostomy, the intervention immediately followed laparoscopy. The 5 mm suprapubic trocar was replaced with a 10 mm disposable trocar, and one or two additional 5 mm ports were inserted in the right and left hypochondrium for introduction of grasping forces, a microdissector needle, and a suction/irrigation unit. A monopolar linear incision was made over the bulging antimesenteric portion of the tube. The ectopic mass was removed by use of an irrigation probe for hydrodissection and grasping forces. After haemostasis had been achieved the tubal incision was left open to allow secondary healing. The pelvis was then irrigated. Surgery was done by trained laparoscopic surgeons or by other consultants and senior registrars under supervision of the experienced surgeons. All patients were discharged, if possible, on the following day.

Serial serum HCG measurements (by microparticle enzyme immunoassay; IMX analyser, Abbott kit β-total, Abbott Diagnostics Division, Chicago, IL, USA) were made to assess treatment response. The variation within and between assays was less than 5%. Results were expressed in IU/L according to the WHO Third International Standard 75/537. An initial value for each patient was read from a sample taken on day 0. Serum HCG concentrations were measured until the hormone was undetectable (<2 IU/L).

In patients treated with systemic methotrexate, persistent trophoblast was defined as a serum HCG concentration above 40% of the initial value on day 14 and was treated with a second course of methotrexate. In patients treated by salpingostomy, persistent trophoblast was defined as rising or stable HCG concentrations postoperatively and was treated with a course of systemic methotrexate.

Transvaginal sonography (Hitachi EUB 415/515, Hitachi Medical Corporation, Tokyo, Japan) was done in both treatment groups routinely within 1 week after the start of treatment or whenever complications were suspected. Patients

<table>
<thead>
<tr>
<th>Methotrexate (n=51)</th>
<th>Salpingostomy (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics of patients</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age in years</td>
<td>31·3 (5·9)</td>
</tr>
<tr>
<td>Median (range) parity</td>
<td>0 (0-6)</td>
</tr>
<tr>
<td>Mean (SD) duration of gestation in days</td>
<td>46·6 (18·5)</td>
</tr>
<tr>
<td>Clinical symptoms*</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain only</td>
<td>7</td>
</tr>
<tr>
<td>Vaginal bleeding only</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal pain and vaginal bleeding</td>
<td>24</td>
</tr>
<tr>
<td>Pre-existing tubal pathology*</td>
<td>21</td>
</tr>
<tr>
<td>Pregnancy*</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>45</td>
</tr>
<tr>
<td>Insemination</td>
<td>4</td>
</tr>
<tr>
<td>IVF-ET</td>
<td>2</td>
</tr>
<tr>
<td>Median (range) periperoitic serum HCG (IU/L)</td>
<td>1950 (110-19 500)</td>
</tr>
<tr>
<td>Mean (SD) preoperative haemoglobin (mmol/L)</td>
<td>7·9 (0·8)</td>
</tr>
<tr>
<td>Localisation of tubal pregnancy*</td>
<td></td>
</tr>
<tr>
<td>Isthmic</td>
<td>6</td>
</tr>
<tr>
<td>Ampullary</td>
<td>37</td>
</tr>
<tr>
<td>Fimbrial</td>
<td>8</td>
</tr>
<tr>
<td>Mean (SD) diameter tubal pregnancy (mm)</td>
<td>23 (9·6)</td>
</tr>
<tr>
<td>Median (range) haemoperitoneum (mL)</td>
<td>50 (0-800)</td>
</tr>
</tbody>
</table>

*Number of patients. TtO convert to mg/dL, multiply by 6·25.
The progress of the patients invited to participate is shown in figure 1. 100 patients were included in the trial, 86 from the Academic Medical Centre and Onze Lieve Vrouwe Gasthuis and 14 from the four other participating hospitals. In the first two centres the exact number of exclusions was known because the two trial investigators (PJH, SE) were present continuously. Of 267 patients with the diagnosis ectopic pregnancy, 104 (39%) were primarily excluded, 43 (16%) refused to give informed consent, and 34 (13%) were excluded at laparoscopy. Only 86 patients (32%) were eligible for inclusion in the trial. In the other four hospitals, six of 20 patients (30%) were excluded at laparoscopy.

Baseline characteristics of the final treatment groups are shown in table 1. There were slightly more patients with pre-existing tubal pathology and slightly fewer patients with pregnancy resulting from in-vitro fertilisation and embryo transfer (IVF-ET) in the systemic methotrexate group.

Of the 51 patients assigned and treated with systemic methotrexate, one course was successful in 42 (82%). Two (4%) were successfully treated but needed a second course for persistent trophoblast. Seven (14%) patients needed surgical intervention (table 2). Surgical intervention was necessary during or after the first methotrexate course in six of these patients, and after a second course in the other patient. Conservative surgery was possible in two patients. Patient 1 had laparoscopic salpingostomy for active bleeding, and patient 2 underwent nettoyage by laparotomy for tubal rupture. In the remaining five patients salpingectomy was necessary for tubal rupture, either by laparoscopy (patients 4 and 5) or by laparotomy. Patient 4, treated first by systemic methotrexate, was then treated with additional methotrexate.

### Table 3: Side-effects and complications

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Methotrexate (n=51)</th>
<th>Salpingostomy† (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>20 (39%)</td>
<td>38 (78%)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>13 (25%)</td>
<td>1 (36%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (12%)</td>
<td>0 (2%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>12 (24%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>18 (35%)</td>
<td>3 (36%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>19 (37%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Other major complications</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Bone-marrow depression</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Raised liver enzymes</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

†First number=after salpingostomy alone, second number=after salpingostomy and additional methotrexate.
The serum HCG clearance curves of all patients successfully treated by one course of methotrexate or by laparoscopic salpingostomy alone are shown in figure 2. Median serum HCG clearance time was 19 days (range 2–53) after systemic methotrexate treatment and 14 days (2–50) after laparoscopic salpingostomy (p=0.64). In the systemic methotrexate group transvaginal sonography was normal in all patients after a median of 34 days (1–191).

In the systemic methotrexate group, hysterosalpingography was not done in the five patients who underwent secondary salpingectomy. Of the remaining 46 patients eligible for hysterosalpingography, four became pregnant while awaiting this diagnostic procedure. Five patients refused to give informed consent or were lost to follow-up. Thus 37 patients underwent hysterosalpingography, a mean 122 days (SD 36) after completion of treatment. Homolateral tubal patency was found in 23 (62%). Overall homolateral tubal patency, including the five patients who underwent salpingectomy, was 55% (23/42).

In the salpingostomy group, hysterosalpingography was not done in the four patients who needed salpingectomy. Of the remaining 45 patients eligible for hysterosalpingography, three became pregnant while awaiting this diagnostic procedure. Seven patients refused to give informed consent or were lost to follow-up. Thus 35 patients underwent hysterosalpingography, a mean 114 days (43) after completion of treatment. Homolateral tubal patency was found in 23 (66%). Overall homolateral tubal patency, including the four patients who underwent salpingectomy, was 59% (23/39).

The results with the two treatment modalities are summarised in table 4. Adjustment for pre-existing tubal pathology and initial serum HCG concentration in logistic regression analysis also showed a lower, but not significant, overall homolateral tubal patency rate in the systemic methotrexate group (odds ratio 0.74 [95% CI 0.27–2.1]).

At completion of the study in September, 1996, nine patients in the systemic methotrexate group had become pregnant: seven were intrauterine pregnancies (one by IVF-ET), one was a repeat ectopic pregnancy, and one patient had trophoblast in regression. In the salpingostomy group, 12 patients had become pregnant: ten were intrauterine pregnancies (one by IVF-ET), and two were repeat ectopic pregnancies.

**Discussion**

In this multicentre randomised clinical trial of systemic methotrexate versus laparoscopic salpingostomy in patients with laparoscopically confirmed unruptured tubal pregnancy without active bleeding, both treatment modalities were successful in treating the majority of cases. Persistent trophoblast occurred more commonly in the salpingostomy group, whereas more surgical reinterventions were needed in the systemic methotrexate group

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**Table 4: Outcome measures**

<table>
<thead>
<tr>
<th>Methotrexate</th>
<th>Salpingostomy</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary treatment success</td>
<td>42/51 (82%)</td>
<td>35/49 (72%)</td>
</tr>
<tr>
<td>Tubal preservation</td>
<td>46/51 (90%)</td>
<td>45/49 (92%)</td>
</tr>
<tr>
<td>Homolateral tubal patency on hysterosalpingogram</td>
<td>23/37 (62%)</td>
<td>23/35 (66%)</td>
</tr>
<tr>
<td>Overall homolateral tubal patency</td>
<td>23/42 (55%)</td>
<td>23/39 (59%)</td>
</tr>
</tbody>
</table>

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Figure 2: Serum HCG clearance curves of all patients successfully treated with one course of systemic methotrexate or laparoscopic salpingostomy alone

laparoscopic salpingectomy, needed a reintervention by laparotomy for secondary haemorrhage.

Of the 49 patients allocated laparoscopic salpingostomy, 35 (72%) were successfully treated by this intervention alone. Conservative surgery failed in four patients (8%). In these patients, persistent bleeding (despite extensive coagulation after salpingostomy) necessitated salpingectomy, in one case by laparotomy. Ten patients (20%) were successfully treated by laparoscopic salpingostomy and additional methotrexate for persistent trophoblast. No surgical reinterventions were necessary.

Side-effects of systemic methotrexate therapy and complications in both treatment groups are shown in table 3. Only 20 (39%) patients underwent systemic methotrexate therapy without any side-effects or complications, compared with 38 (78%) patients in the salpingostomy group. Abdominal pain was the most common symptom in both treatment groups. In the systemic methotrexate group, two patients received antibiotic therapy for cystitis. Two other patients experienced major complications. One was admitted to hospital with high fever, abdominal pain, and bloody diarrhoea. After 2 weeks, although cultures from blood and faeces were negative, antibiotic therapy was started for persistent fever with good results. Sigmoidoscopy for persistent bloody diarrhoea showed colitis, probably as a result of methotrexate or antibiotic therapy, or both. The other patient was admitted to the hospital with widespread intraoral blisters and genital erosions. The clinical diagnosis of erythema exudativum multiforme (Stevens-Johnson syndrome) was made. She was treated with 15 mg folinic acid orally every 6 h for 24 h. Chlorhexidine 0·12% was sprayed intraorally every 4 h for as long as the blisters were present. Both patients recovered completely. In the salpingostomy group, virtually all complications occurred in patients treated with systemic methotrexate for persistent trophoblast.
methotrexate group. Additional interventions after primary treatment, however, had no impact on the preservation of the tube in either treatment group. Although the advantage of systemic medical therapy over surgical treatment is the avoidance of surgical trauma to the tube, we did not find a significantly improved homolateral tubal patency rate after systemic methotrexate. The absence of such an improvement could not be attributed to a higher number of treatment failures necessitating salpingectomy, nor by selective dropouts before hysterosalpingography.

Five published randomised clinical trials have compared conservative laparoscopic surgery with medical treatment. Laparoscopic salpingostomy has been compared with methotrexate injected laparoscopically,14–16 with methotrexate injected transvaginally,17 and with hyperosmolar glucose injected laparoscopically.18 However, the comparison of a complete non-surgical and non-invasive treatment by the systemic administration of methotrexate with laparoscopic salpingostomy was lacking until our randomised clinical trial.

Only a minority of patients presenting with ectopic pregnancy (32%) could be included in our trial because of the rigorous selection criteria that were used in the study protocol. These selection criteria were based on uncontrolled studies updated until 1992, the year in which the study protocol was written and approved by the ethics committee of the Academic Medical Centre in Amsterdam. Selection criteria for methotrexate treatment varied in these studies. Although all studies limited recruitment to haemodynamically stable patients with unruptured ectopic pregnancy, in some series large ectopic pregnancies (>3 cm), fetal cardiac activity, and serum HCG concentrations above 10,000 IU/L were classified as contraindications to systemic methotrexate treatment. In our study there were no limitations to the size of the ectopic pregnancy or the initial serum HCG concentration. We did exclude patients with fetal cardiac activity, since we expected this feature to have an adverse effect on clinical outcome. Successful results in patients with fetal cardiac activity have been reported since our trial was designed.19 The majority of patients (39%) were excluded before randomisation either before diagnostic work-up (unstable vital signs), or by sonographic criteria (fetal cardiac activity, non-tubal pregnancy) or because of contraindications to one of the two treatment modalities. 16% of the patients refused to give informed consent. This proportion might have been lower if the confirmatory laparoscopy had been omitted, thus avoiding surgery altogether. However, a confirmatory laparoscopy was judged necessary for safety reasons to ensure that only patients with unruptured tubal pregnancies and no active bleeding were recruited. With laparoscopy and the possibility of secondary exclusion at that stage, all eligible haemodynamically stable patients were randomised. Adequate concealment of the allocation sequence was achieved since the assessment of secondary exclusion criteria was made by a surgeon unaware of the randomisation outcome. 13% of the randomised patients were secondarily excluded at laparoscopy, almost half of them for tubal rupture or active bleeding.

In a subanalysis (data not shown), a sonographically detected moderate to large amount of free fluid in the pouch of Douglas and an initial serum haemoglobin concentration below 6 mmol/L were found to be prognostic factors for secondary exclusion. However, we cannot speculate about the clinical outcome if these haemodynamically stable patients had had non-invasive diagnosis followed by non-invasive systemic methotrexate treatment.

In most series the diagnosis, localisation, and viability of the ectopic pregnancy are presumptive since no confirmatory laparoscopy is done; by contrast, our study leaves no doubt as to the correct diagnosis. This feature may explain our low success rate of systemic methotrexate compared with these series (82% vs a reported 95%).

The need for scrupulous follow-up and monitoring have been regarded by some as objections to primary methotrexate treatment. Despite the long-term persistence of the ectopic mass in the systemic methotrexate group, serum HCG clearance time did not differ between the two treatment groups. Concerns about potential toxicity and pain due to treatment may also hamper the replacement of a surgical approach to ectopic pregnancy by a medical one. The high frequency of side-effects (table 3) might be due to our methotrexate regimen (four doses). Single-dose regimens have been introduced since our trial was designed, with success rates of 71–94%.19–21 Although the first such study reported no significant side-effects,20 the latest reported side-effects in 41% of patients,21 Future studies should focus on varying methotrexate dose in view of potential toxic effects and potentially adverse long-term reproductive effects to improve compliance. To investigate whether these concerns are shared by patients with ectopic pregnancy, assessment of their health-related quality of life during different treatment modalities is necessary. Moreover, perhaps patients are willing to trade an increased burden of treatment against the benefits of a completely non-surgical management of ectopic pregnancy.

Our study does not show whether systemic methotrexate or laparoscopic salpingostomy is the treatment of choice in the conservative management of tubal pregnancy. Subsequent fertility outcome still has to be awaited to show which treatment yields better fertility prospects. Meta-analysis, pooling our results with those of future trials, may ultimately give more precise estimates of the relative value in counselling of patients and decision analysis. Moreover, the choice between the two treatment modalities will also be determined by the impact on patients’ health-related quality of life, patients’ preferences, and costs.

Contributors
All authors contributed to the writing of the paper. P J Hajenius was the principal trial investigator and was involved in all components of the study. S Engelshoel was the trial investigator in the Onze Lieve Vrouwe Gasthuis, Amsterdam. B W J Mol was co-investigator of the trial in the Academic Medical Centre, Amsterdam, and contributed to the data management and statistical analysis. P Van der Veen designed the trial and gave clinical supervision. W M Ankum designed the trial, was the principal trial coordinator, and gave clinical supervision. P M Bossuyt contributed to the design of the trial and supervised data management and statistical analysis. D J Hemrika was the trial coordinator in the Onze Lieve Vrouwe Gasthuis, Amsterdam, and gave clinical supervision.

Acknowledgments
Coordinators in the participating hospitals were P G A Hompes (University Hospital Free University Amsterdam), D J Tinga (University Hospital Groningen), W N P Willemsen (University Hospital Nijmegen), and F Broekmans (University Hospital Utrecht).

This study was funded by grant 93/007 from the Health Insurance Funds Council, Amsterdam, the Netherlands. We thank E Ender for his clinical chemist, and the technicians of the laboratory of endocrinology,
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