The METEX study

*METHOTREXATE*

VERSUS

*EXPECTANT MANAGEMENT*

IN WOMEN WITH ECTOPIC PREGNANCY

Study protocol
June, 2006
PARTICIPATING CENTERS

Academic Medical Center, University of Amsterdam
PO Box 22700
1100 DE Amsterdam
The Netherlands
Telephone: +31-20-5663654
Telefax: +31-20-6963489
Coordinators: P.J. Hajenius, MD, PhD
W.M. Ankum, MD, PhD
B.W. Mol, MD, PhD
F. van der Veen, MD, PhD
E-mail: p.hajenius@amc.uva.nl

Onze Lieve Vrouwe Gasthuis
PO Box 95500
1090 HM Amsterdam
The Netherlands
Telephone: +31-20-5993478
Telefax: +31-20-5993494
Coordinator: H.R. Verhoeve, MD
E-mail: h.r.verhoeve@olvg.nl

BovenIJ Hospital
PO Box 37610
1030 BD Amsterdam
The Netherlands
Telephone: +31-20-6346346
Telefax: +31-20-6346730
Coordinator: A.B. Dijkman, MD
E-mail: bdijkman@bovenij.nl

Maxima Medical Center
PO Box 7777
5500 MB Veldhoven
The Netherlands
Telephone: +31-40-8888000
Telefax: +31-40-8888387
Coordinator: B.W. Mol, MD, PhD
E-mail: b.mol1@chello.nl
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1. INTRODUCTION

In industrialized countries the incidence of ectopic pregnancy is approximately 1-2% of all pregnancies (1-4). The diagnosis of ectopic pregnancy is usually made by non-invasive methods, i.e. sensitive pregnancy tests (in urine and serum) and high resolution transvaginal sonography (TVS), which have been integrated in reliable diagnostic algorithms. These algorithms, in combination with the increased awareness and knowledge of risk factors among both clinicians and patients, have enabled an early and accurate diagnosis of ectopic pregnancy (5-7).

As a consequence, the clinical presentation of ectopic pregnancy has changed from a life threatening disease, necessitating emergency surgery, to a more benign condition in sometimes even asymptomatic patients for which non-surgical treatment options are available, i.e. medical treatment with systemic methotrexate or expectant management. In contrast to surgical treatment, the ectopic pregnancy is not removed and as a consequence there is a remaining risk of tubal rupture. Close serum human chorionic gonadotrophin (hCG) monitoring is therefore mandatory to detect impending treatment failure and/or inadequately declining serum hCG concentrations (8,9). The risk of tubal rupture combined with the need for scrupulous follow-up is likely to cause distress in the patient because of uncertainty about treatment outcome (10). Non-surgical treatment modalities may therefore have a negative impact on the patients’ health related quality of life.

Methotrexate is a folic acid antagonist which inhibits de novo synthesis of purines and pyrimidines, thereby interfering with DNA synthesis and cell proliferation. Secondary to its effect on highly proliferative tissues, e.g. trophoblast, methotrexate has a strong dose related potential for toxicity. Side effects include stomatitis, conjunctivitis, gastritis-enteritis, impaired liver function, bone marrow depression, and photosensitivity. Methotrexate has been shown to be safe with virtually no adverse effects reported on reproductive outcome (11).
Methotrexate can be administered systemically in a *multiple dose* regimen or in a *single dose* regimen. The multiple dose regimen involves the administration of a total of four intramuscular methotrexate injections every other day at a dose of 1.0 mg/kg body weight alternated with folinic acid 0.1 mg/kg body weight on the day following each methotrexate injection (12). The administration of folinic acid decreases the side effects of the drug. A *single dose* regimen – one single intramuscular injection of methotrexate 1.0 mg/kg body weight or 50 mg/m² body surface area- was introduced to minimize side effects and to improve patients’ compliance and to reduce overall costs (13).

Data provided by randomised controlled trials indicate that systemic methotrexate treatment should only be used in selected patients with ectopic pregnancy. Important selection criteria are the ectopic pregnancy size, absence of fetal cardiac activity on TVS, and maximum hCG concentrations (14, 15).

Expectant management has been practiced based on the acknowledgement that the natural course of many early ectopic pregnancies is a self limiting process, ultimately resulting in tubal abortion or reabsorption. Selection criteria in uncontrolled studies are the ectopic pregnancy size, absence of fetal cardiac activity on TVS and various upper limits of serum hCG concentrations that continue to decline, and/or a low serum progesterone concentration. Success rates vary between 42 and 100% (16). Data provided by randomised controlled trials is scarce.

To date, only two randomised placebo controlled trials are available comparing expectant management with other treatment options. In one trial, 30 patients with a small tubal pregnancy and no fetal cardiac activity and a serum hCG concentration < 5,000 IU/l were randomly allocated to oral methotrexate while another 30 patients were managed expectantly (17). The oral route of administration and the low dosage of methotrexate, namely 2.5 mg/day orally during five days, are uncommon and likely to fail. This trial virtually represents a comparison between two placebo treatments as demonstrated by similar success rates of 77% in both treatment
groups and is therefore not informative from a clinical viewpoint. The other trial, comparing prostaglandins versus expectant management, involving 23 women with an ectopic pregnancy and an initial serum hCG concentration < 2,500 IU/l, was stopped prematurely after the first interim analysis, showing that prostaglandin therapy was significantly better than expectant management (18). However, in view of a non-surgical management of ectopic pregnancy this trial is not informative. Prostaglandins were administered locally in the ectopic pregnancy under laparoscopic guidance combined with systemic prostaglandin injection twice daily during three days postoperatively.

In some women presenting with suspected ectopic pregnancy, the pregnancy can not be identified on TVS (19,20). These women with a so called pregnancy of unknown location (PUL) can be managed expectantly with monitoring of serum hCG to identify whether a PUL turns out to be an intra uterine pregnancy, an ectopic pregnancy, a failing PUL (with an uneventful serum hCG decline to undetectable levels) or a persisting PUL (with plateauing serum hCG concentrations) (21). Women with a persisting PUL and women with a visible ectopic pregnancy but with low and plateauing serum hCG concentrations have thus far been offered medical treatment with methotrexate (20,22). However, there is no evidence on the effects of treatment in this particular subgroup of women, which represents about 10% of women presenting with suspected ectopic pregnancy.

2. OBJECTIVE

To study whether in women with an ectopic pregnancy with low but plateauing serum hCG concentrations treatment with systemic methotrexate in a single dose intramuscular regimen is superior over expectant management in terms of tubal rupture, future pregnancy, health related quality of life and costs.
3. STUDY DESIGN

3.1 Participating centers

This study is a multicenter randomised controlled trial with four participating centers in The Netherlands:

1. Academic Medical Center Amsterdam (coordinator P.J. Hajenius, MD, PhD),
2. Onze Lieve Vrouwe Gasthuis Amsterdam (coordinator H.V. Verhoeve, MD),
3. BovenIJ Hospital Amsterdam (coordinator A.B. Dijkman, MD) and
4. Máxima Medical Center Veldhoven (coordinator B.W. Mol, MD, PhD).

Other clinics in The Netherlands, predominately those already participating in the European Surgery in Ectopic Pregnancy (ESEP) study (ISRCTN37002267), are being contacted for participation in the present study.

3.2 Inclusion criteria

All hemodynamically stable patients ≥ 18 years with either an ectopic pregnancy (a visible ectopic pregnancy or an ectopic mass on TVS) and a plateauing serum hCG concentration < 1,500 IU/L or with a PUL and a plateauing serum hCG concentration < 2,000 IU/L (persisting PUL) will be eligible for the trial. The difference in serum hCG cut-off levels for these two entities is based on our earlier work (7).

Patients with a viable ectopic pregnancy, signs of tubal rupture or active intra abdominal bleeding, and/or abnormalities in liver or renal function or in full blood count will not be included. In patients fulfilling the inclusion criteria, written informed consent will be obtained before randomisation is carried out. Those women refusing participation will be registered.

3.3 Randomisation

Randomisation will be performed by a web based randomisation program, using a computer
program with stratification for hospital, serum hCG concentration (< 1,000 IU/l versus 1,000-2,000 IU/l), TVS findings (visible ectopic pregnancy/mass or PUL). In each centre, a back-up procedure with sealed envelopes will be available in case the central randomisation procedure fails.

4. INTERVENTIONS

The following treatment options will be compared: systemic methotrexate in a single dose intramuscular regimen (1 mg/kg body weight) versus expectant management. Women who are Rhesus negative will receive 375 IE anti D intramuscularly. Pain relief, if necessary, is given with Paracetamol. Patients are advised to refrain from sexual intercourse. Treatment and follow up will be carried out in the outpatient clinic.

5. FOLLOW UP

5.1 Short term

Complications will be registered in the Case Record Form. In both groups weekly serum hCG measurements will be performed until serum hCG is no longer detectable. Serum hCG concentrations will be expressed in IU/L (conversion factor to SI unit, 1.00 according to the World Health Organization Third International Standard 75/537). Seven days after a methotrexate injection liver and renal function and full blood count will be checked as well.

In patients treated with methotrexate, a second methotrexate injection is given in case the serum hCG concentration on day 7 has declined < 15% of the initial value on day 1 (start of treatment) (11). If the serum hCG concentration fails to fall by at least 15% during any successive week of follow-up, this also results in repeat administration of methotrexate with a maximum of a total of three injections (23). In case of hemodynamic instability and/or signs of tubal rupture (i.e. increasing abdominal pain in combination with falling haemoglobin level and
signs of intra abdominal haemorrhage on TVS) or whenever more than three methotrexate injections are required, surgical treatment will be installed.

In patients treated expectantly, treatment (systemic methotrexate or surgery) will be started whenever at any of the weekly follow up visits the serum hCG concentration has risen > 15% of the prior value. If the serum hCG concentration falls by > 15% of the prior value, expectant management is continued. In case of a persistent plateauing serum hCG concentration (i.e. < 15% fall or < 15% rise), the serum hCG concentration is assessed after 48 hours to ensure it is not increasing. If it is increasing as described above, treatment (systemic methotrexate or surgery) is installed (24). Whenever hemodynamic instability and/or clinical signs of tubal rupture (i.e. increasing abdominal pain in combination with falling haemoglobin level and signs of intra abdominal haemorrhage on TVS) occur, surgical treatment will be installed.

5.2 Long term

Women treated with methotrexate are advised not to get pregnant within three months after treatment (21). To assess fertility in both treatment arms, patients will be contacted by means of a questionnaire, every six months for a period of 24 months. Questions will focus on the desire for pregnancy, unprotected sexual intercourse with a chance of spontaneous conception, contraceptive use, infertility treatment, and the occurrence of any pregnancies and their outcome.

6. OUTCOME MEASURES

6.1 Primary outcome measure

The primary outcome measure is an uneventful decline of serum hCG to an undetectable level (< 2 IU/l) by primary treatment, i.e. single dose systemic methotrexate or expectant management.

6.2 Secondary outcome measures
Secondary outcomes are number of (re)interventions (additional methotrexate injections or surgical procedures for persistent trophoblast and/or clinical signs), treatment complications, future fertility, health related quality of life, financial costs, and patients preferences.

Future fertility is defined as time to the occurrence of a spontaneous vital intra uterine pregnancy. A vital intra uterine pregnancy is defined as a viable pregnancy visible at ultrasound at a gestational age of \( \geq 12 \) weeks, or the delivery of a child. If an intra uterine pregnancy does not occur, follow-up ends on the day of the last consultation. In addition to intra uterine pregnancies, repeat ectopic pregnancies are also assessed. The date of occurrence of an ectopic pregnancy will be determined from the first day of the last menstrual period.

Health related quality of life will be assessed by standard self administered psychometric questionnaires with established viability and reliability at different time points; before randomisation, after one week, four weeks and three months.

Costs will be assessed in direct costs with data on costs and used resources in the participating centres.

Patients’ preferences will be assessed in an interview on the basis of written descriptions of both interventions using a treatment trade-off technique and will be compared with a control group, recruited among women visiting the infertility clinics of the participating hospitals.
7. FLOWCHART

**Inclusion METEX study:**
- age ≥ 18 yrs
- EP and plateauing serum hCG < 1,500 IU/l or
- PUL and plateauing serum hCG < 2,000 IU/l

**Exclusion**
- Signs of shock
- Signs of tubal rupture/abdominal bleeding
- Vital ectopic pregnancy
- Contraindications for MTX

**Informed consent**

**No**

**Randomisation**

**Single dose MTX im**
- Serum hCG clearance time
- Additional interventions
- Tubal rupture
- Health related quality of life

**Expectant Management**

**Follow-up 6, 12, 18, 24 months after index ectopic pregnancy**
- Desire future pregnancy
- Spontaneous intra uterine pregnancy
- Repeat ectopic pregnancy
- Costs
- Health related quality of life
- Preferences

**Log registration**
8. ANALYSIS

Data analysis will be according to the *intention to treat* principle.

Short term outcome measures are compared in relative risks and their 95% confidence intervals. Future fertility is assessed by life table analysis. Kaplan-Meier curves are constructed, estimating the cumulative probability of spontaneous intra uterine pregnancy and repeat ectopic pregnancy over time. In case a spontaneous viable intra uterine pregnancy does not occur, follow up ends at the last date of consultation, or at the moment when either *in vitro* fertilisation (IVF) or tubal surgery will be performed. Spontaneous conceptions that occur after failed IVF treatment will be registered, but they will not be considered as endpoint in the analysis. The log-rank test is used to test differences between the Kaplan-Meier curves for statistical significance. The differences between both treatment modalities are expressed as a fecundity rate ratio with 95% confidence interval, calculated through Cox proportional hazard analysis.

Changes in health related quality of life over time, and differences between the two groups will be measured using analysis of variance.

Depending on differences of equivalence between the strategies, the economic evaluation will be a cost-effectiveness analysis or a cost-minimisation analysis.

Patient’s preferences will be analysed by differences in trade-off.

9. POWER CALCULATION

Assuming an uneventful decline of serum hCG of 90% in the methotrexate group and of 60% in the expectant management group, and assuming a power of 80% and a significance level of 5%, 36 patients in each group are needed (6,15,16,25,26).

