Current evidence on surgery, systemic methotrexate and expectant management in the treatment of tubal ectopic pregnancy: a systematic review and meta-analysis

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BACKGROUND: To evaluate the effectiveness of surgery, medical treatment and expectant management of tubal ectopic pregnancy (EP) in terms of treatment success (i.e. complete elimination of trophoblast tissue), financial costs and future fertility. METHODS: We searched for randomized controlled trials which described treatment interventions that have been widely adopted in clinical practice. A systemic literature search identified 15 trials. RESULTS: Laparoscopic salpingostomy was significantly less successful than the open surgical approach (relative risk, RR 0.9, 95% CI 0.82–0.99) due to a higher persistent trophoblast rate, but was significantly less costly. A prophylactic single shot methotrexate (MTX), given intramuscularly (i.m.) immediately post-operatively, significantly reduced persistent trophoblast after laparoscopic salpingostomy (RR 0.89, 95% CI 0.82–0.98, number needed to treat of 10). With systemic MTX in a fixed multiple dose regimen treated patients, the likelihood of treatment success was higher than with laparoscopic salpingostomy (RR 1.15, 95% CI 0.93–1.43), but the difference was not significant. Systemic MTX in a fixed multiple dose regimen was only cost–effective if serum human chorionic gonadotrophin (hCG) concentrations were <3000 IU/l. If serum hCG concentrations were <1500 IU/l, then the single-dose MTX i.m. regimen—if necessary with additional MTX injections—was also cost–effective. Expectant management could not be evaluated yet. Subsequent fertility did not differ between the interventions studied. CONCLUSIONS: This meta-analysis shows that laparoscopic surgery is the most cost–effective treatment for tubal EP. Systemic MTX is a good alternative in selected patients with low serum hCG concentrations.

Keywords: ectopic pregnancy; laparoscopy; cost effectiveness; trophoblast

Introduction

Ectopic pregnancy (EP) occurs in ~1% of pregnant women, and may seriously compromise women’s health and future fertility. Currently, EPs can often be diagnosed before the patient’s condition has deteriorated, which has changed the former clinical picture of a life-threatening disease into a more benign condition in frequently asymptomatic patients.

The cornerstone of a timely diagnosis is the use of non-invasive diagnostic algorithms integrating transvaginal ultrasound and serum human chorionic gonadotrophin (hCG) measurement (Ankum et al., 1995; Mol et al., 1998a), which have been integrated into probabilistic models (Mol et al., 1999a; Condous et al., 2004).

Timely diagnosis allows the clinician to consider the full range of treatment options. This is important since the focus of contemporary therapeutic management exceeds the narrow aim of immediate treatment success (i.e. elimination of the EP) and includes retaining optimal fertility for those women desiring future pregnancy.

To date, therapeutic options for women with tubal EP are surgery, medical treatment or expectant management. In surgery, laparoscopy is now the accepted approach to perform salpingostomy or salpingectomy. Concerning medical treatment, systemic administration of methotrexate (MTX), has gained acceptance in selected patients. It is given intramuscularly (i.m.), either in a fixed multiple dose regimen alternated with folinic acid or in a single-dose regimen without folinic acid. Expectant management has been advocated based on the knowledge that the natural course of many early EPs is a self-limiting process, ultimately resulting in tubal abortion or re-absorption.

A well recognized hazard after salpingostomy, systemic MTX treatment and expectant management is persistent trophoblast. Persistent trophoblast may lead to recurrence of clinical symptoms and is an indication for additional treatment. Serum hCG...
monitoring enables the timely detection of inadequately declining serum hCG concentrations after treatment.

In this review we summarize the present knowledge of the management of tubal EP, focusing on clinically relevant interventions. We evaluated treatment success (i.e. complete elimination of trophoblast tissue), financial costs and subsequent fertility.

Materials and Methods

Search strategy
We searched the Cochrane Menstrual Disorders & Subfertility Group trials register, the Cochrane Central Register of Controlled Trials (both searched up to October 2006), MEDLINE (January 1966 to September 2007), and the website for registration of controlled trials (www.controlled-trials.com). In addition, all electronic databases were searched using the keywords ‘ectopic pregnancy’ and ‘tubal ectopic pregnancy’. We hand searched the reference lists of selected studies and of recent reviews on the subject and the abstract books of the annual ESHRE and ASRM meetings from 1991–2007.

Study selection and data extraction
Studies were selected if the target population contained women with tubal EP. We only included randomized controlled trials (RCTs) comparing treatment strategies for the management of tubal EP. The primary outcome measure was treatment success defined as the complete elimination of trophoblast tissue with an uneventful decline of serum hCG to undetectable levels after the index treatment. Re-interventions (surgical or medical) for either clinical symptoms or inadequately declining serum hCG levels, i.e. persistent trophoblast, were thus considered treatment failures. Secondary outcomes were persistent trophoblast, patients’ health-related quality of life (HRQL), financial costs and subsequent fertility in patients desiring future pregnancy. For subsequent fertility we looked at the occurrence of spontaneous pregnancy and its outcome [intrauterine pregnancy (IUP), repeat EP].

Two reviewers judged all citations identified by the search strategies independently (F.M. and P.J.H.). Abstracts of all citations were obtained to identify eligible studies. Full reports of all eligible studies were obtained to assess whether these studies met the pre-defined inclusion criteria. Differences of opinion were registered and resolved by consensus with all authors.

For eligible studies, information was collected regarding the location and methods of the study using a quality assessment checklist, EP characteristics (size of the EP, mean serum hCG concentration, presence or absence of fetal cardiac activity), the nature of the interventions and data relating to the outcomes specified above. Whenever required, we made an attempt to retrieve missing data by contacting the principal author(s).

We distinguished three treatment strategies: surgery, medical treatment and expectant management. Concerning surgery, we excluded trials describing interventions by open surgery only, since the laparoscopic intervention is nowadays standard clinical care. We also excluded trials dealing with subtle adjustments in surgical technique, e.g. tubal suturing or the additional use of a vasopressin or oxytocin injection into the mesosalpinx. Concerning medical treatment, we focused on treatment with MTX and excluded trials on prostaglandins and hyperosmolar glucose as these drugs have not been adopted in clinical practice. For the same reason, we did not include trials on local MTX, be it under laparoscopic guidance or transvaginally under ultrasound guidance. Trials reporting on complementary alternative medicine were disregarded, as the working mechanism of these herbal has never been proven. For a complete overview of all RCTs we refer to the recently updated Cochrane review (Hajenius et al., 2007).

Statistical analysis
Statistical analysis was performed according to the guidelines for reviewers for the Cochrane Menstrual Disorders and Subfertility Group. Two by two tables were generated for each study for dichotomous outcome measures. The treatment effect in each study was expressed as a relative risk (RR) with a 95% confidence interval (CI). Whenever sufficient data were available, a summary statistic for each outcome was calculated using the fixed effect model. Statistical heterogeneity between results of studies was examined by inspecting the scatter in the data points on the graphs and the overlap of CIs, and by checking the $I^2$ statistic. A value of $\geq 50\%$ was considered to indicate substantial heterogeneity. In case of statistical heterogeneity the original trials were checked for differences in patient characteristics. Review Manager-software (RevMan 4.2.7, Cochrane Collaboration, Oxford, UK) was used for the statistical analysis. We analysed the data according to the intention-to-treat principle. In case of a clinical significant effect, the number needed to treat (NNT) was calculated by taking the reciprocal of the absolute risk reduction.

Data on patients’ HRQL and financial costs are reported as published in the original trials.

The cost analysis studies alongside some trials, made a distinction between costs of medical interventions (direct costs) and costs resulting from productivity losses (indirect costs). Reported costs were calculated in Euros (€), using an exchange rate of 0.11 for Swedish Kronor, 0.51 for New Zealand dollars and 0.74 for US dollars.

Results of the search
Sixty-nine reports were identified by the search strategy. Of these, eight studies were excluded because treatments were non-randomly allocated (Lund, 1955; Konincx et al., 1991; Murphy et al., 1992; Laatikainen et al., 1993; Shea et al., 1994; Porpora et al., 1996; Colacurci et al., 1998; Kaya et al., 2002), one study because of an irrelevant comparison between two different MTX regimens with the addition of mifepristone in one study arm (Hu and Han, 2003), five studies because these were still ongoing (ISRCTN948210491, ISRCTN95698259, ISRCTN37002267, NCT00137982 describing two trials) and seven studies from which results had been published in earlier reports (Lundorff, 1993, 1997; Fernandez et al., 1991, 1996; Lundorff et al., 1993; Lindblom et al., 1997; Garbin et al., 2004). We excluded one study describing mini laparotomy without using packs or retractors versus conventional laparotomy (Sharma et al., 2003). Four studies were excluded because these focused on subtle adjustments in surgical technique (Tulandi and Guralnick, 1991; Ugur et al., 1996; Fedele et al., 1998; Fujishita et al., 2004). Nineeen studies were excluded because these described less accepted medical therapies: one on prostaglandins (Egger et al., 1991), five on hyperosmolar glucose (Lang et al., 1990; Gjelland et al., 1995; Hordnes, 1997; Landstrom et al., 1998; Sadan et al., 2001), five on local MTX under laparoscopic guidance (Motla et al., 1992; Shulman et al., 1992; Tzafettas et al., 1994; Fujishita et al., 1995; Zilber et al., 1996), four on local MTX administered transvaginally under ultrasound guidance (Fernandez and Baton, 1990; Fernandez et al., 1994, 1995; Cohen et al., 1996) and four on complementary alternative medicine (Peng, 1997; Wang et al., 1998; Su et al., 2002; Wei and Chen, 2003).
In total, 15 original RCTs were evaluated from which the results were published in 24 reports. These nine additional reports described the secondary outcomes and/or follow-up data of the 15 original trials. The 15 original RCTs described eight different comparisons (Fig. 1).

**Results**

The main characteristics and quality features of the 15 included trials are presented in Table I. All patients were haemodynamically stable and, if applicable, had no contra indications for MTX treatment. In most trials the size of the tubal EP was <3–4 cm, the upper limits of serum hCG concentrations varied between 5000 and 15 000 IU/l and fetal cardiac activity was absent.

Ten trials described their method of randomization. In five trials the exact method of randomization was not reported, although three of these mentioned the use of sealed envelopes. Eight trials described an adequate concealed treatment allocation. In six trials the allocation was unclear, whereas in one trial the allocation was inadequate by drawing cards. Three trials employed double blinding, two of which were placebo controlled. Blinding of treatment, however, was not applicable for most comparisons.

A power calculation was performed beforehand in six trials. Trial size varied from 47 to 212 women. Seven trials included 100 patients or more. Meta-analysis was possible for five comparisons.

Twelve trials were published as a full paper, whereas the other three were published as a conference abstract only. Five trials were performed in the USA, two in Egypt and France and the others in Finland, Iran, New Zealand, Sweden, The Netherlands and The UK.

Eight trials reported on subsequent fertility. The rate of patients lost to follow-up varied between 0.9 and 44%.

Forest plots of the outcome measures, i.e. primary treatment success, subsequent IUP and repeat EP are presented in Figs 2, 3 and 4, respectively. No heterogeneity ($I^2$) was found.

**Surgery**

**Laparoscopy versus open surgery**

Pooled results from two trials, with a total of 165 haemodynamically stable women with a small unruptured tubal EP (Vermesh et al., 1989; Lundorff et al., 1991), showed laparoscopic salpingostomy to be significantly less successful than the open surgical approach in the elimination of the tubal EP (RR 0.90, 95% CI 0.82–0.99), predominantly due to a higher persistent trophoblast rate in laparoscopic surgery.

Costs of laparoscopic surgery were reduced when compared with the open surgical approach. In one trial average savings of €1110 was reported for each patient undergoing laparoscopy as a result of a shorter hospital stay than after laparotomy (1.4 versus 3.3 days, $P < 0.001$) (Vermesh et al., 1989).

A cost effectiveness study alongside the other trial reported mean costs (±SEM) of laparoscopic surgery to be €2986 (189) versus €3480 (115) for the open surgical approach ($P = 0.03$) (Gray et al., 1995). These cost savings after laparoscopic surgery resulted from a significantly shorter operation time (73 versus 88 min, $P < 0.001$), less peri-operative blood loss (79 versus 195 ml, $P < 0.01$), shorter duration of hospital stay (1 and 2 versus 3 and 5 days, $P < 0.01$) and shorter convalescence time (11 versus 24 days, $P < 0.001$).
**Table I.** Main characteristics of included trials.

<table>
<thead>
<tr>
<th>Number of randomized patients (n), country</th>
<th>Participants*</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Main outcomes</th>
<th>Quality features</th>
</tr>
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<tbody>
<tr>
<td><strong>Alleyasin et al. (2006), n = 108, Iran</strong>&lt;br&gt;Randomized by computer generated random table; Adequate allocation with sealed envelopes; No blinding; Power calculation performed; Single centre; Full paper</td>
<td>&lt;3.5 cm on TVS; No fetal cardiac activity; Serum hCG &lt; 15 000 IU/l</td>
<td>Single-dose MTX (50 mg/m² i.m.)</td>
<td>Multiple dose MTX (1.0 mg/kg i.m. on Days 0, 2, 4, 6; alternated folinic acid 0.1 mg/kg oral on Days 1, 3, 5, 7)</td>
<td>Treatment success</td>
<td>(Block) randomization by computer generated random table; Adequate allocation with sealed envelopes; No blinding; Power calculation performed; Single centre; Full paper</td>
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<td><strong>El-Sherbini et al. (2003), n = 55, Egypt</strong>&lt;br&gt;Randomization by computer; Allocation unclear; No power calculation; Multi centre; Full paper</td>
<td>&lt;4 cm No fetal cardiac activity; Serum hCG &lt; 10 000 IU/l</td>
<td>Single-dose MTX (50 mg/m² i.m.)</td>
<td>Laparoscopic salpingostomy</td>
<td>Treatment success; Fertility outcome</td>
<td>Randomization by computer; Allocation unclear; No power calculation; Multi centre; Full paper</td>
</tr>
<tr>
<td><strong>Elmoghazy and Nour-Ei-Dine (2000), n = 47, Egypt</strong>&lt;br&gt;Randomization method nr; Allocation unclear; No power calculation; Single centre; Abstract</td>
<td>Size nr; Fetal cardiac activity nr; Upper limit serum hCG nr</td>
<td>Salpingostomy</td>
<td>Salpingostomy and single-dose MTX (1 mg/kg i.m.) &lt;24 h</td>
<td>Treatment success</td>
<td>Randomization with a random number table; Allocation unclear; No power calculation; Single centre; Full paper</td>
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<tr>
<td><strong>Fernandez et al. (1998), n = 100, France</strong>&lt;br&gt;Randomization by drawing cards; Allocation inadequate; No power calculation; Single centre; Intention-to-treat analysis; Full paper</td>
<td>EP by TVS/TAS; Pre-therapeutic score &lt;13; Size nr; Fetal cardiac activity nr; Upper limit serum hCG nr</td>
<td>Single-dose MTX (1 mg/kg i.m.)</td>
<td>Laparoscopic salpingostomy</td>
<td>Treatment success; Fertility outcome</td>
<td>Randomization by computer-generated sequence; Allocation adequate with consecutively numbered envelopes; No power calculation; Single centre; Intention-to-treat analysis; Full paper</td>
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<td><strong>Gazvani et al. (1998), n = 50, UK</strong>&lt;br&gt;Randomization by drawing cards; Allocation inadequate; No power calculation; Single centre; Full paper</td>
<td>&lt;4 cm on TVS; Laparoscopically confirmed Fetal cardiac activity nr; Upper limit serum hCG nr</td>
<td>Single-dose MTX (50 mg/m² i.m.)</td>
<td>Single-dose MTX (50 mg/m² i.m. and mifepristone (600 mg orally)</td>
<td>Treatment success</td>
<td>Randomization by computer-generated sequence; Allocation adequate with consecutively numbered envelopes; No power calculation; Single centre; Intention-to-treat analysis; Full paper</td>
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<tr>
<td><strong>Graczykowski and Mishell (1997), n = 129, USA</strong>&lt;br&gt;Randomization method nr; Allocation unclear; No power calculation; Single centre; Full paper</td>
<td>Size nr; Fetal cardiac activity nr; Upper limit serum hCG nr</td>
<td>Salpingostomy</td>
<td>Salpingostomy and single-dose MTX (1 mg/kg i.m.) &lt;24 h</td>
<td>Treatment success</td>
<td>Randomization by drawing cards; Allocation inadequate; No power calculation; Single centre; Full paper</td>
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<tr>
<td><strong>Hajenius et al. (1997), n = 100, The Netherlands</strong>&lt;br&gt;(Block) randomization by a computer program; Allocation adequate; Power calculation performed; Intention-to-treat analysis; Multi centre; Full paper</td>
<td>Laparoscopically confirmed; No fetal cardiac activity; No limit in EP size; No upper limit serum hCG</td>
<td>Multiple dose MTX (1.0 mg/kg im on Days 0, 2, 4, 6; alternated folinic acid 0.1 mg/kg oral on Days 1, 3, 5, 7)</td>
<td>Laparoscopic salpingostomy</td>
<td>Treatment success; HQRL (Nieuwkerk et al., 1998a, b); Costs (Mol et al., 1998a, b); Fertility outcome (Dias Pereira et al., 1999)</td>
<td>(Block) randomization by a computer program; Allocation adequate; Power calculation performed; Intention-to-treat analysis; Multi centre; Full paper</td>
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<td><strong>Klausen et al. (2005), n = 51, USA</strong>&lt;br&gt;Randomization method nr; Allocation unclear, although sealed envelopes; No power calculation; Single centre</td>
<td>Size nr; Fetal cardiac activity nr; Serum hCG &lt; 10 000 IU/l</td>
<td>Single-dose MTX (50 mg/m² i.m.)</td>
<td>Multiple dose MTX (1.0 mg/kg on Day 1,3,5</td>
<td>Treatment success</td>
<td>Randomization method nr; Allocation unclear, although sealed envelopes; No power calculation; Single centre</td>
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<tr>
<td><strong>Korhonen et al. (1996), n = 60, Finland</strong>&lt;br&gt;Randomization method nr; Allocation unclear, although sealed envelopes; No power calculation; Single centre</td>
<td>&lt;4 cm; Fetal cardiac activity nr; Serum hCG &lt;5000 IU/l</td>
<td>Expectant management</td>
<td>MTX 2.5 mg/day orally for 5 days</td>
<td>Treatment success</td>
<td>Randomization method nr; Allocation unclear, although sealed envelopes; No power calculation; Single centre</td>
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<td><strong>Lundorro et al. (1991), n = 109, Sweden</strong>&lt;br&gt;Randomization by computer-generated list; Allocation adequate by sealed opaque envelopes, stored in the pharmacy of each hospital; double blind, placebo controlled; Power calculation performed; Single centre; Full paper</td>
<td>Laparoscopically confirmed; &lt;4 cm; Fetal cardiac activity nr; Serum hCG &lt;10 000 IU/l</td>
<td>Laparoscopic salpingostomy</td>
<td>Salpingostomy by open surgery</td>
<td>Treatment success; Costs (Gray et al., 1995); Fertility outcome (Lundorff et al., 1992)</td>
<td>(Block) randomization by computer-generated list; Allocation adequate by sealed opaque envelopes, stored in the pharmacy of each hospital; double blind, placebo controlled; Power calculation performed; Intention to treat analysis; Multi centre; Full paper</td>
</tr>
<tr>
<td><strong>Rozenberg et al. (2003), n = 212, France</strong>&lt;br&gt;Randomization by drawing cards; Allocation inadequate; No power calculation; Single centre</td>
<td>Non-laparoscopic algorithm; Fetal cardiac activity allowed; Upper limit serum hCG nr</td>
<td>Single-dose MTX (50 mg/m² i.m.)</td>
<td>Single-dose MTX (50 mg/m² i.m. alone and mifepristone (600 mg orally)</td>
<td>Treatment success</td>
<td>Randomization by drawing cards; Allocation inadequate; No power calculation; Single centre</td>
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Table I. Continued

<table>
<thead>
<tr>
<th>Number of randomized patients (n), country</th>
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<th>Intervention</th>
<th>Comparison</th>
<th>Main outcomes</th>
<th>Quality features</th>
</tr>
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<tbody>
<tr>
<td>Sanj et al. (1998), n = 75, USA</td>
<td>&lt;3.5 cm on TVS; No fetal cardiac activity; Upper limit serum hCG nr</td>
<td>Single-dose MTX (1 mg/kg i.m.)</td>
<td>Laparoscopic salpingostomy</td>
<td>Treatment success; Fertility outcome</td>
<td>Randomization nr; Allocation unclear, although sealed envelopes; No power calculation; Multi centre; Full paper</td>
</tr>
<tr>
<td>Sowter et al. (2001a, b), n = 62, New Zealand</td>
<td>&lt;3.5 cm; No fetal cardiac activity; Serum hCG &lt;5000 IU/l</td>
<td>Single-dose MTX (50 mg/m(^2) i.m.)</td>
<td>Laparoscopic salpingostomy</td>
<td>Treatment success; Fertility outcome</td>
<td>Unblocked randomization procedure by a computer program; Allocation adequate by sequentially numbered opaque envelopes sealed by a third party; Power calculation performed; Intention-to-treat analysis; Multi centre; Full paper</td>
</tr>
<tr>
<td>Vermesh et al. (1989), n = 60, USA</td>
<td>Laparoscopically confirmed &lt;5 cm; Fetal cardiac activity nr; Upper limit serum hCG nr</td>
<td>Laparoscopic salpingostomy by open surgery</td>
<td>Laparoscopic salpingostomy</td>
<td>Treatment success; Costs; Fertility outcome (Vermesh and Presser, 1992)</td>
<td>Randomization by coded card; Allocation adequate by sequential selection of unmarked opaque envelopes; No power calculation; Single centre; Full paper</td>
</tr>
<tr>
<td>Yalcinkaya et al. (2000), n = 100, USA</td>
<td>&lt;3.5 cm on TVS; Fetal cardiac activity allowed; Rising/plateauing hCG; Upper limit serum hCG nr</td>
<td>Single-dose MTX (25 mg/m(^2) i.m.)</td>
<td>Single-dose MTX (50 mg/m(^2) i.m.)</td>
<td>Success; Fertility outcome</td>
<td>Randomization method nr; Allocation adequate by sealed envelopes at central pharmacy, double blind; Single centre; Power calculation was performed; Abstract</td>
</tr>
</tbody>
</table>

\(^a\) All women were haemodynamically stable, no signs of tubal rupture and if applicable no contraindications for methotrexate (MTX) or laparoscopic surgery.

TVS, transvaginal sonography; im, intramuscularly; EP, ectopic pregnancy; nr, not reported; TAS, trans abdominal scan.

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Long-term follow-up was assessed in 127 women (Lundorff et al., 1992; Vermesh and Presser, 1992). The number of subsequent IUPs showed no evidence of a difference (RR 1.08, 95% CI 0.80–1.48) and there was a non-significant tendency to a lower repeat EP rate in laparoscopic surgery (RR 0.48, 95% CI 0.16–1.49).

Laparoscopic salpingostomy alone versus laparoscopic salpingostomy with single-dose systemic MTX

The combined results of two trials, involving 163 women, showed that salpingostomy alone was significantly less successful than when combined with a prophylactic single dose of systemic 1 mg/kg i.m. MTX (RR 0.89, 95% CI 0.82–0.98), given within 24 h post-operatively to prevent persistent trophoblast (Graczykowski and Mishell, 1997; Elmoghazy and Nour-Ei-Dine, 2000).

Medical treatment with systemic MTX

Systemic MTX in a fixed multiple dose regimen compared with laparoscopic salpingostomy

In a multi centre trial, 100 haemodynamically stable women with a laparoscopically confirmed unruptured tubal EP without fetal cardiac activity and no signs of active bleeding were randomly allocated between systemic MTX in a fixed multiple dose (MTX 1 mg/kg i.m. Day 0, 2, 4, 6 alternated with folic acid 0.1 mg/kg orally Day 1, 3, 5, 7) and laparoscopic salpingostomy (Hajenius et al., 1997). There were no limits on serum hCG concentration or size of the tubal EP. The mean serum hCG concentration in women treated with MTX was 1950 IU/l (110–19 500). There was a non-significant trend to a higher treatment success with systemic MTX treatment (RR 1.15, 95% CI 0.93–1.43).

Patients’ HRQL was more severely impaired after systemic MTX than after laparoscopic salpingostomy (P < 0.05) (Nieuwkerk et al., 1998a). Medically treated women showed more limitations in physical functioning, role functioning and social functioning, had worse health perceptions, less energy, more pain, more physical symptoms, a worse overall quality of life, and were more depressed than surgically treated women (P < 0.05).

Systemic MTX treatment was significantly more expensive than laparoscopic salpingostomy (Mol et al., 1999b). Mean total costs per patient were € 4207 (direct costs € 2426 and indirect costs € 1781) for systemic MTX and € 2990 (direct costs € 1853 and indirect costs € 1137) for laparoscopic salpingostomy with a mean difference of € 1217 (95% CI 666–1775). However, the costs of the confirmative laparoscopy in the MTX group were included, whereas in daily practice this procedure would not be performed in women receiving MTX treatment for EP.

In a scenario analysis, it was calculated that systemic MTX, if administered as part of a totally non-invasive treatment strategy, was only less costly in women with initial serum hCG concentrations <1500 IU/l (total costs € 2200) and equally costly if the initial serum hCG concentration ranged between 1500 and 3000 IU/l (€ 2858), whereas in women with initial serum hCG concentrations >3000 IU/l systemic MTX was more costly compared with laparoscopic surgery (€ 3660).

Fertility outcome was assessed in 74 patients. No significant differences were found for IUP (RR 0.88, 95% CI 0.49–1.60) as well as for repeat EP (RR 0.88, 95% CI 0.21–3.67) (Dias Pereira et al., 1999).
The combined results of four trials (Fernandez et al., 1998; Saraj et al., 1998; Sowter et al., 2001b; El-Sherbiny et al., 2003), involving 265 haemodynamically stable women with a small unruptured tubal EP, showed that a single dose of systemic MTX (50 mg/m² or 1 mg/kg i.m.) was significantly less successful than laparoscopic salpingostomy (RR 0.82, 95% CI 0.72–0.94).

Selection criteria used in these trials were an upper limit of serum hCG (<5000–10 000 IU/l), absence of positive fetal heartbeat, small size of the tubal EP (<3.5–4 cm) or a pretherapeutic score <13 (Fernandez et al., 1998). Mean serum hCG concentrations in women treated with MTX varied between 927 and 3162 IU/l.

Twenty-seven of the 120 women treated with a single-dose MTX had inadequately declining serum hCG concentrations. Of these 27 women, four were treated surgically, whereas 23 were given...
additional MTX injections, all but three successfully. Of the 20 women successfully treated with additional MTX, 17 women received a total of 2 doses, two women a total of 3 doses and one woman a total of 4 doses. The cumulative treatment success rates after one, two, three or four single doses were 77, 92, 93 and 94%, respectively. With this ‘variable dose’ MTX strategy, overall treatment success increased, but showed no evidence of a difference with laparoscopic salpingostomy (RR 1.01, 95% CI 0.92–1.12).

Women treated with MTX had a significantly better physical functioning than those treated with laparoscopic surgery \( (P < 0.01) \). No differences were found in psychological functioning (Sowter et al., 2001b).

Systemic MTX in a single-dose regimen resulted in significant savings in direct costs compared with laparoscopic surgery: mean direct costs per patient were £756 and £1585, respectively, with a mean difference of £829 (95% CI 599–1060). These savings resulted from both reduced theatre usage and hospital stay. Furthermore, systemic MTX resulted in a significant saving in indirect costs: mean indirect costs per patient were £587 and £977, respectively, with a mean difference of £390 (95% CI 142–638). However, in women with initial serum hCG concentrations >1500 IU/l the difference in indirect costs was lost due to the prolonged follow-up and a higher rate of surgical re-interventions (Sowter et al., 2001a).

Fertility outcomes were reported in 98 women. No significant differences were found in the number of IUPs (RR 1.05, 95% CI 0.53–2.06). There was a non-significant trend towards a lower repeat EP rate in the lower dose group (RR 0.58, 95% CI 0.11–2.90).

**Single versus multiple dose MTX**

The results of two trials comparing the single dose (50 mg/m²) versus the fixed multiple dose MTX (1 mg/kg Day 1, 3, 5) regimen, involving 159 women (Klauser et al., 2005; Alleyassin et al., 2006), showed no significant difference in treatment success (RR 0.99, 95% CI 0.89–1.10). Mean serum hCG concentrations varied between 2230–2973 and 2180–2244 IU/l, respectively.

**Systemic MTX in different dosages**

A double blinded trial (Yalcinkaya et al., 2000) compared MTX 25 mg/m² to the standard 50 mg/m² administration both in a single-dose regimen. A non-significant trend towards a lower treatment success after the lower MTX dose was found (RR 0.87, 95% CI 0.65–1.17). Mean serum hCG concentrations were 2405 IU/l (±3204) and 2841 IU/l (±4132), respectively, and fetal heart activity was present in two (4.2%) and seven (13.4%) women, respectively.

Future fertility was assessed in 56 women. No significant difference was found in the number of subsequent IUPs (RR 1.05, 95% CI 0.53–2.06). There was a non-significant trend towards a lower repeat EP rate in the lower dose group (RR 0.58, 95% CI 0.11–2.90).

**Systemic MTX in combination with mifepristone**

The combined results of two trials, involving 262 haemodynamically stable women with an unruptured EP without signs of active bleeding (Gazvani et al., 1998; Rozenberg et al., 2003), showed
that single-dose MTX alone (50 mg/m²) was less successful, with borderline significance, in the elimination of the tubal EP than when 600 mg mifepristone (anti progesterone) was added (RR 0.84, 95% CI 0.71–1.00). Although all EPs in the first study were laparoscopically confirmed, mean serum hCG concentrations were low in both treatment groups, i.e. 346 IU/l (range 52–12 700) and 497 IU/l (range 30–4200), respectively (Gazvani et al., 1998). In the second study, a non-laparoscopic diagnostic algorithm was used and mean serum hCG concentrations were 1679 IU/l (range 652–3658) and 1620 IU/l (range 805–3190), respectively (Rozenberg et al., 2003).

Expectant management

A double blind placebo controlled study, involving 60 patients (Korhonen et al., 1996), comparing expectant management with systemic MTX (2.5 mg/day MTX orally for 5 days) found no significant differences in treatment success (RR 1.00, 95% CI 0.76–1.32). Mean serum hCG concentrations were low, i.e. 211 IU/l (range 20–1343) in the expectant managed group and 395 IU/l (range 61–4279) in the MTX group. In both treatment groups, for 23% of the patients surgical intervention was required for unspecified reasons.

Discussion

In this review on the effectiveness of treatment of tubal EP we focused on clinically relevant interventions for daily practice and analysed 15 trials on eight different comparisons. We grouped these comparisons into those involving surgery, medical treatment with systemic MTX or expectant management.

From the analysis of surgical trials, it is clear that laparoscopy is the treatment of choice as it was less costly than the open surgical approach, even though there was a higher persistent trophoblast rate if salpingostomy was performed. The number needed to harm with laparoscopic surgery for persistent trophoblast was 12, in other words when 12 women are treated by laparoscopy instead of laparotomy, there is one extra case of persistent trophoblast. To prevent one case of persistent trophoblast with a prophylactic single shot of systemic MTX i.m. immediately post-operatively, the NNT was 10. Therefore, in our view, serum hCG monitoring post-operatively seems a better option for timely detection and treatment of persistent trophoblast. Unfortunately, these trials did not report on financial costs. A more recent study reported cost savings of €50 per patient after a prophylactic MTX dose after salpingostomy (Gracia et al., 2001). However, these cost savings were based on a decision analysis in a hypothetical cohort of women. Furthermore, the results depend on the persistent trophoblast rate that might be lower in future trials because the learning curve of laparoscopic surgeons is completed.

Whether salpingostomy or salpingectomy should be performed has not been studied in RCTs and is therefore still subject to debate. The inherent drawbacks of salpingostomy, i.e. the risk of persistent trophoblast and repeat tubal EP which both generate
additional costs, are only justified if this would result in a higher spontaneous IUP rate, thereby saving on the costs of subsequent infertility treatment after salpingectomy. A review of cohort studies comparing fertility outcome after salpingostomy and salpingectomy for tubal EP showed no beneficial effect of conservative surgery on IUP rates, whereas the risk of repeat EPs was increased, although not significantly (Claussen, 1996; Mol et al., 1996). Methodological limitations of these cohort studies were differences in duration of follow-up, failure to report on the desire for pregnancy and how subsequent pregnancies were achieved. Retrospective comparative studies, addressing these issues and reporting on life table analysis, showed a beneficial effect of salpingectomy compared with salpingectomy for tubal EP towards fertility outcome in women with contra lateral tubal pathology (Mol et al., 1998b) and in women with previous infertility factors (Bouyer et al., 2000).

In this review, only trials on systemic MTX were included because this administration route is practical, easier to administer and less dependent from clinical skills compared with the local routes of administration. In combination with non-invasive diagnostic tools, systemic MTX offers the option of a totally non-invasive outpatient management.

From the data of trials on systemic MTX, only systemic MTX in a fixed multiple dose i.m. regimen showed a trend towards a better primary treatment success than laparoscopic salpingostomy. This MTX regimen, however, had a negative impact on patients’ HRQL and was less cost–effective. Only in women with serum hCG concentrations <3000 IU/l, could this MTX regimen be an attractive non-surgical alternative because some women were willing to trade-off the increased treatment burden of systemic MTX for the benefit of a totally non-invasive management of EP (Nieuwkerk et al., 1998b).

Single-dose MTX i.m.—if necessary with additional MTX injections—is only cost–effective compared with laparoscopic salpingostomy in women with serum hCG concentrations <1500 IU/l.

Data on the fixed multiple dose MTX regimen versus a single-dose regimen are few and do not allow a preference one above the other in view of treatment success, side effects or patients’ HRQL. Future research on these MTX regimens is therefore needed, also in view of the possible beneficial effect of the addition of mifepristone (NNT 9) with its inherent side effects. From the single trial on expectant management, no conclusions can be drawn, especially since the comparison with systemic low-dose oral MTX does not make any clinical sense. It may be that women with low serum hCG levels (<1500 IU/l) need not be treated at all, but more research needs to be done in this subgroup of women to reach firm conclusions.

In summary, laparoscopic surgery is the most effective treatment in women with tubal EP. After laparoscopic salpingostomy, post-operative serum hCG monitoring is necessary for the early detection of persistent trophoblast. Systemic MTX in a multiple dose regimen (1 mg/kg i.m. Day 0, 2, 4, and 6 alternated with folinic acid 0.1 mg/kg, Day 1, 3, 5, 7) can only be recommended for haemodynamically stable women with an unruptured tubal EP and no signs of active bleeding presenting with serum hCG concentrations <3000 IU/l. In women with serum hCG concentrations <1500 IU/l, a single-dose MTX regimen (50 mg/m² or 1 mg/kg i.m.) can be considered.

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