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Tubal ectopic pregnancy

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Rajesh Varma and Janesh Gupta

ABSTRACT

INTRODUCTION: Approximately 1/100 pregnancies are ectopic, with the conceptus usually implanting in the fallopian tube. Some ectopic pregnancies resolve spontaneously, but others continue to grow and lead to rupture of the tube. Risks are higher in women with damage to the fallopian tubes due to pelvic infections, surgery, or previous ectopic pregnancy. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What treatments improve outcomes in women with unruptured tubal ectopic pregnancy? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2008 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). The authors also separately searched Medline and Pubmed up to May 2008 in addition to the Clinical Evidence systematic search to support the comments and clinical guide sections. RESULTS: We found 47 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: salpingotomy, salpingectomy, systemic methotrexate, systemic methotrexate following salpingotomy, and expectant management.

QUESTIONS

INTERVENTIONS

Key points

- Approximately 1/100 pregnancies are ectopic, with the conceptus usually implanting in the fallopian tube. Some tubal ectopic pregnancies resolve spontaneously, but others continue to grow and lead to rupture of the tube.

  Risks for ectopic pregnancy are higher in women with damage to the fallopian tubes because of pelvic infections, pelvic surgery, or previous ectopic pregnancy, and in smokers.

  The IUD does not increase the absolute risk of ectopic pregnancy, but pregnancy that does occur with IUD use is more likely to be ectopic than intrauterine.

- The likelihood of subsequent intrauterine pregnancy seems to be similar after salpingectomy or salpingotomy.

  Salpingotomy by laparoscopy may lead to fewer complications and shorter recovery times compared with laparotomy, but may also be less likely to remove all the trophoblast.

- Single- or multiple-dose methotrexate seems as likely as salpingotomy to eliminate trophoblast material and leave a patent fallopian tube in women with non-invasively diagnosed small ectopic pregnancies with no tubal rupture or bleeding, no sign of fetal cardiac activity, and low beta human chorionic gonadotrophin (beta hCG) levels.

  About 15–40% of ectopic pregnancies may be suitable for such non-surgical management.

  Adding mifepristone to systemic methotrexate seems unlikely to increase treatment success compared with methotrexate alone, other than in women with higher progesterone levels.

  Expectant management of unruptured ectopic pregnancies may lead to similar subsequent intrauterine pregnancy rates compared with surgery, but few studies have been done.

DEFINITION Ectopic pregnancy is defined as a conceptus implanting outside the uterine endometrium. The most common implantation site is within the fallopian tube (95.5%), followed by ovarian (3.2%) and abdominal (1.3%) sites. The sites of tubal implantation in descending order of frequency are am-

pulla (73.3%), isthmus (12.5%), fimbrial (11.6%), and interstitial (2.6%). [1] **Population:** In this systematic review, we consider haemodynamically stable women with unruptured tubal ectopic pregnancy, diagnosed by non-invasive or invasive techniques.

INCIDENCE/ PREVALENCE

Around 10,000 ectopic pregnancies are diagnosed annually in the UK. The incidence of ectopic pregnancy in the UK (11.1/1000 pregnancies) is similar to that in other countries, such as Norway (14.9/1000) and Australia (16.2/1000). [2] [3] [4] Since 1994, the overall rate of ectopic pregnancy and resulting mortality (0.35/1000 ectopic pregnancies in 2003–2005) have been static in the UK. [4] Until recently, most epidemiological studies failed to distinguish between ectopic pregnancies occurring in women who did not use contraception (reproductive failure) and women who used contraception (contraceptive failure). [5] [6] A French population study undertaken from 1992 to 2002 found that, over the duration of the study, the rate of reproductive-failure ectopic pregnancies increased by 17%, whereas the rate of contraceptive-failure ectopic pregnancies decreased by 29%. [6] Increasing rates of chlamydia infection, smoking, and assisted reproductive-technology usage may have contributed to the disproportionate increase in reproductive-failure ectopic pregnancy rate over contraceptive-failure ectopic pregnancy rate. Widespread use of dedicated early pregnancy-assessment units and non-invasive diagnostic algorithms are likely to have contributed to increasing rates of ectopic pregnancy diagnosis. [7] [8]

AETIOLOGY/ RISK FACTORS

The aetiology of ectopic pregnancy is unclear. Ectopic pregnancy arising from reproductive or contraceptive failure should be considered as separate entities with differing aetiology, risk factors, and reproductive outcomes. [5] [6] [9] [10] [11] The main risk factors for reproductive failure are: previous ectopic pregnancy; previous pelvic inflammatory disease; previous pelvic and tubal surgery; infertility; smoking; and use of assisted conception. [5] [12] The main risk factor for contraceptive-failure ectopic pregnancy is IUD failure. IUDs do not increase the absolute risk of ectopic pregnancy, but a pregnancy occurring with an IUD is more likely to be ectopic than intrauterine. Other risk factors for ectopic pregnancy include prior spontaneous miscarriage, endometriosis, uterotubal anomalies, and prior in utero exposure to diethylstilbestrol. However, less than half of diagnosed ectopic pregnancies are associated with risk factors. [13]

PROGNOSIS

Ectopic pregnancies: As the pregnancy advances, tubal pregnancies may either diminish in size and spontaneously resolve, or increase in size and eventually lead to tubal rupture, with consequent maternal morbidity and mortality. There are no reliable clinical, sonographic, or biological markers (e.g. serum beta human chorionic gonadotrophin or serum progesterone) that can predict rupture of tubal ectopic pregnancy. [14] [15] Maternal mortality following ectopic pregnancy is an uncommon short-term outcome in resource-rich countries. The 2003–2005 UK Confidential Enquiry into Maternal Deaths cited ectopic pregnancy as a cause of 10 maternal deaths (0.35/1000 ectopic pregnancies). [4] Short-term maternal morbidity relates to pain, transfusion requirement, and operative complications. Primary treatment success and long-term fertility outcomes depend on the clinical characteristics of the ectopic pregnancy (e.g. whether the ectopic pregnancy occurred in a woman using contraception or not, tubal rupture or not, contralateral tubal disease) and the type of surgical or medical treatment chosen. A 10-year follow-up of ectopic pregnancies showed that the rate of repeat ectopic pregnancy was much higher in women with an IUD in place at the time of the index ectopic pregnancy, compared with women whose ectopic pregnancy was not associated with IUD use. By contrast, the rate of intrauterine pregnancy was 1.7 times higher (fecundity rate ratio [FRR] 1.7, 95% CI 1.3 to 2.3) in women who had an IUD in place at the time of the index ectopic pregnancy compared with women whose index ectopic pregnancy was not associated with IUD use. [9] Short- and long-term consequences on health-related quality of life and psychological issues (e.g. bereavement) are also important, but are rarely quantified. **Pregnancies of unknown location (PUL):** PUL is the absence of pregnancy localisation (either intrauterine or extrauterine) by transvaginal sonography when serum beta human chorionic gonadotrophin (beta hCG) levels are below the discriminatory zone (1000–1500 IU/L). An observational study of pregnancies of unknown location has shown that 55% spontaneously resolve, 34% are subsequently diagnosed as viable, and 11% are subsequently diagnosed as ectopic pregnancies. [16]

AIMS OF INTERVENTION

Short term: Primary treatment success; to reduce maternal morbidity and mortality related to ectopic pregnancy (tubal rupture and haemorrhage), or the treatment method used (e.g. surgical complications, medical drug toxicity), or both. **Long term (all women):** To reduce risk of recurrent ectopic pregnancy. **Long term (for subgroup of women desiring subsequent pregnancy):** To maximise the chance of future intrauterine pregnancy and live birth rate from unassisted spontaneous conception, or following use of assisted reproductive-technology techniques (e.g. in vitro fertilisation).

OUTCOMES

Primary outcomes: Primary treatment success (eradication of ectopic pregnancy without the need for secondary treatment arising from: persisting trophoblast; tubal rupture; and worsening clinical symptoms and signs); persistent trophoblast. **Secondary outcomes:** Future fertility/spontaneous

intrauterine pregnancy; live birth rate; and repeat ectopic pregnancy in women desiring subsequent pregnancy (this should ideally be expressed as FRRs over specific time intervals corrected for known confounders [e.g. history of infertility and contraception usage at time of index ectopic pregnancy]). **Other outcome measures:** Tubal rupture; ipsilateral tubal patency following tubal-preserving treatment (salpingotomy, methotrexate, or expectant management); maternal morbidity and mortality (prior to ectopic treatment [natural history of ectopic pregnancy] and following treatment alternatives); harms of treatment alternatives; complications of surgery (injury, infection, thromboembolism); drug toxicity; and health-related quality-of-life assessments.

METHODS

Clinical Evidence search and appraisal May 2008. The following databases were used to identify studies for this review: Medline 1966 to May 2008; Embase 1980 to May 2008; and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2008, Issue 2. Additional searches were carried out using the following websites: NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE guidance. Abstracts of the studies retrieved were assessed independently by information specialists using predetermined criteria to identify relevant studies. Study design criteria for inclusion were: published systematic reviews, meta-analyses, RCTs, controlled clinical trials, cohort studies with a control or comparison group, or case-control studies in any language; open label or blinded studies, which included 20 or more participants. There was no maximum loss to, or minimum length of, follow-up. Cohort studies were reported when there were insufficient data from RCTs. FRRs have been calculated by the *Clinical Evidence* contributor, except where indicated. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). The contributors of the review also carried out their own systematic search to enhance the clinical guide statements and comments section of the review. They searched Medline and Pubmed databases from 1996 to May 2008, using the following search terms: pregnancy, ectopic; pregnancy, tubal; laparoscopy or salpingectomy; fallopian-tube diseases; methotrexate; mifepristone; salpingostomy or salpingotomy; pregnancy outcome; methotrexate and mifepristone in combination with subheadings of: complications; diagnosis; drug therapy; mortality; surgery; and therapy. They included systematic reviews, non-systematic reviews with meta-analysis, RCTs, cohort, and case-control studies.

QUESTION What treatments improve outcomes in women with unruptured tubal ectopic pregnancy?

OPTION SALPINGECTOMY

Treatment failure (persistent trophoblast)

Compared with salpingotomy Salpingectomy may be more effective at reducing initial treatment-failure rates (very low-quality evidence).

Compared with methotrexate Salpingectomy may be more effective at reducing initial treatment failure rates (very low-quality evidence).

Subsequent pregnancy rates

Compared with salpingotomy We don't know whether salpingectomy may result in lower rates of subsequent intrauterine pregnancies or recurrent ectopic pregnancy rates (very low-quality evidence).

Compared with expectant management Salpingectomy may be no more effective at increasing subsequent pregnancy rates in women with ectopic pregnancies (very low-quality evidence).

For GRADE evaluation of interventions in tubal ectopic pregnancy, see table, p 15 .

Benefits:

Salpingectomy versus salpingotomy:

We found no systematic reviews or RCTs. We found one non-systematic review [17] and four cohort studies (and related single follow-up publication) [9] [18] [19] [20] [21] comparing salpingectomy versus salpingotomy (see table 1, p 13).

One retrospective cohort study found that the 7-year cumulative intrauterine pregnancy rate was lower in women who had undergone salpingectomy than salpingotomy (see table 1, p 13). [18] One non-systematic review [17] and four cohort studies [9] [18] [19] [20] [21] found limited evidence that subsequent spontaneous intrauterine pregnancy rates were lower in women who had undergone salpingectomy compared with salpingotomy in women with contralateral tube disease (see table 1, p 13).

Salpingectomy versus salpingotomy or methotrexate (systemic):
We found no RCTs of sufficient quality. One cohort study and its follow-up publication compared three interventions: salpingotomy, salpingectomy, and methotrexate. [9] [19] It found that the rate of treatment failure with salpingectomy was less than salpingotomy, and less than with methotrexate (see table 1, p 13). It found similar rates of subsequent intrauterine pregnancy and subsequent ectopic pregnancy between salpingectomy and salpingotomy (see table 1, p 13).

Salpingectomy versus expectant management:
See benefits of expectant management, p 9 .

Harms:

Salpingectomy versus salpingotomy:
The non-systematic review [17] and cohort studies (see table 1, p 13) [9] [18] [19] [20] [21] did not report on harms.

Salpingectomy versus salpingotomy or methotrexate (systemic):
The cohort study gave no information on adverse effects. [9] [19] One cost-effectiveness meta-analysis found rates of 0–22% (mean 10%) for minor complications (e.g. drug adverse effects), and 0–11% (mean 7%) for serious complications (e.g. ruptured ectopic, or other symptoms of persistent trophoblast) in women who had methotrexate. [22] It also found intraoperative complications of 0–8% (mean 2%) and postoperative complications of 0–15% (mean 9%) for laparoscopy (either salpingectomy or salpingotomy).

Salpingectomy versus expectant management:
See harms of expectant management, p 9 .

Comment:

Clinical guide:
All comparisons included here were based on retrospective or prospective observational cohort studies in women with unruptured tubal ectopic pregnancies (see table 1, p 13). Few studies have considered the impact of infertility factors (known infertility, contralateral tubal disease) on treatment choice (conservative salpingotomy or radical salpingectomy) and future fertility outcome. Differences in such prognostic factors may not be adequately clear when comparing salpingotomy with salpingectomy, even when adopting multivariate analysis techniques. However, further information may be provided by a currently ongoing RCT comparing salpingotomy with salpingectomy. This is the European Surgery in Ectopic Pregnancy study, which represents an international, multicentre, Dutch–Swedish–British collaboration. [23] Importantly, any potential benefits of improved intrauterine pregnancy rate with salpingotomy compared with salpingectomy appear to be small, and possibly restricted to subgroups with contralateral tubal disease. This effect and its magnitude should be verified by RCTs comparing salpingotomy with salpingectomy.

OPTION SALPINGOTOMY

Treatment failure (persistent trophoblast)
Salpingotomy by laparoscopy compared with salpingotomy by laparotomy Salpingotomy by laparoscopy is less effective at increasing primary treatment-success rates (high-quality evidence).

Compared with salpingectomy Salpingotomy may be less effective at reducing initial treatment-failure rates (very low-quality evidence).

Compared with methotrexate Salpingotomy may be more effective at reducing initial treatment-failure rates (very low-quality evidence).

Compared with single-dose methotrexate Salpingotomy is more effective at increasing primary treatment-success rates in women with small unruptured tubal pregnancies (high-quality evidence).

Compared with multiple-dose methotrexate Salpingotomy by laparoscopy and multiple-dose methotrexate are equally effective at increasing primary treatment-success rates in women with confirmed unruptured tubal pregnancy (moderate-quality evidence).

Subsequent pregnancy rates
Salpingotomy by laparoscopy compared with salpingotomy by laparotomy Salpingotomy by laparoscopy and salpingotomy by laparotomy are equally effective at increasing tubal patencies and subsequent intrauterine pregnancy rates, and at decreasing subsequent ectopic pregnancies (high-quality evidence).

Compared with salpingectomy We don't know whether salpingotomy may result in lower rates of subsequent intrauterine pregnancies or recurrent ectopic pregnancies (very low-quality evidence).

Compared with expectant management Salpingotomy may be no more effective at increasing subsequent pregnancy rates in women with ectopic pregnancies (very low-quality evidence).

Compared with single-dose methotrexate Salpingotomy by laparoscopy and single-dose methotrexate are equally effective at increasing tubal patency, subsequent intrauterine pregnancy rates, and at reducing ectopic pregnancy rates in women with small unruptured tubal pregnancies (high-quality evidence).

Compared with multiple-dose methotrexate Salpingotomy by laparoscopy and multiple-dose methotrexate are equally effective at increasing tubal patency rates in women with a confirmed unruptured tubal pregnancy (moderate-quality evidence).

For GRADE evaluation of interventions in tubal ectopic pregnancy, see table, p 15 .

Benefits:

Salpingotomy by laparoscopy versus salpingotomy by laparotomy:
We found one systematic review (search date 2006, 4 RCTs, 292 haemodynamically stable women with a small unruptured tubal pregnancy) comparing salpingotomy by laparoscopy versus salpingotomy by laparotomy (see table 2, p 14). [25] It found that primary treatment success was achieved in significantly fewer women receiving salpingotomy by laparoscopy compared with by laparotomy (2 RCTs, 165 women) (see table 2, p 14). The review found no significant difference between laparoscopy and laparotomy in tubal patency (2 RCTs, 165 women), subsequent pregnancy, or repeat ectopic pregnancy (2 RCTs, 127 women) (see table 2, p 14). [25]

Salpingotomy versus salpingectomy:
See benefits of salpingectomy, p 3 .

Salpingotomy versus expectant management:
See benefits of expectant management, p 9 .

Salpingotomy versus systemic methotrexate (single- or multiple-dose):
See benefits of systemic methotrexate (single- or multiple-dose), p 4 .

Harms:

Salpingotomy by laparoscopy versus salpingotomy by laparotomy:
The systematic review gave no information on adverse effects. [25]

Salpingotomy versus salpingectomy:
See harms of salpingectomy, p 3 .

Salpingotomy versus expectant management:
We found no RCTs or observational studies of sufficient quality.

Salpingotomy versus systemic methotrexate (single- or multiple-dose):
See harms of systemic methotrexate (single- or multiple-dose), p 4 .

Comment:

Clinical guide:
The surgeon's preference and operative experience, as well as patient-related factors (e.g. obesity, previous abdominal surgery, known pelvic adhesions, haemodynamic instability), dictate whether laparoscopy or laparotomy is preferred. These confounding factors may lead to an overestimation of laparotomy-related complications in high operative-risk groups. [26] See comment on salpingectomy, p 3 .

Laparoscopy or laparotomy surgical treatment of ectopic pregnancy:
It has been suggested that laparoscopy incurs less blood loss and analgesic requirement, and has a shorter duration of operation time, hospital stay, and convalescence time compared with laparotomy. [25] Fewer pelvic adhesions seem to affect the higher future fertility rate observed with laparoscopy compared with laparotomy. [27] [28] One multicentre observational study reported major surgical complication rates of 2.7/1000 for diagnostic laparoscopic procedures and 17.9/1000 for operative laparoscopy. [29] The major complications arise following laparoscopic bowel (0.4–0.7/1000 cases) and major vessel (0.2/1000 cases) injury. [30] .

OPTION METHOTREXATE (SYSTEMIC PROPHYLACTIC) FOLLOWING SALPINGOTOMY

Treatment failure (persistent trophoblast)
Compared with salpingotomy alone A single prophylactic dose of methotrexate after salpingotomy is more effective at reducing persistent trophoblast (moderate-quality evidence).

For GRADE evaluation of interventions in tubal ectopic pregnancy, see table, p 15 .

Benefits: **Systemic single-dose methotrexate plus salpingotomy versus salpingotomy alone:**
One RCT found that adding a single prophylactic dose of systemic methotrexate (1 mg/kg im) after salpingotomy (by laparoscopy or laparotomy) significantly reduced the incidence of persistent trophoblast compared with salpingotomy alone (1/54 [2%] with methotrexate plus salpingotomy *v* 9/62 [15%] with salpingotomy alone; RR 0.13, 95% CI 0.02 to 0.74; NNT 8, 95% CI 4 to 33). [31]

Harms: **Systemic single-dose methotrexate plus salpingotomy versus salpingotomy alone:**
The RCT reported no "clinically significant" adverse effects in women who had received methotrexate. It also reported no significant difference in laboratory values (white blood cell count, haemoglobin, haematocrit, serum creatinine, and transaminase) between groups 7 days after surgery (reported as non-significant; P value not reported). [31]

Comment: See comment of methotrexate, p 6 .

OPTION METHOTREXATE (SYSTEMIC)

Treatment failure
Single-dose methotrexate compared with multiple-dose regimens We don't know whether single-dose methotrexate is more effective in improving treatment success in women with ectopic pregnancy (low-quality evidence).

Compared with salpingectomy Methotrexate may be less effective at reducing initial treatment-failure rates (low-quality evidence).

Primary treatment-success rates
Single-dose methotrexate compared with salpingotomy by laparoscopy Single-dose methotrexate is less effective at increasing primary treatment-success rates in women with small unruptured tubal pregnancies (high-quality evidence).

Multiple-dose methotrexate compared with salpingotomy by laparoscopy Multiple-dose methotrexate is equally effective at increasing primary treatment-success rates in women with confirmed unruptured tubal pregnancy (moderate-quality evidence).

Subsequent pregnancy rates
Single-dose methotrexate compared with salpingotomy Single-dose methotrexate is equally effective at increasing tubal patency, subsequent intrauterine, or ectopic pregnancy rates in women with small unruptured tubal pregnancies (high-quality evidence).

Multiple-dose methotrexate compared with salpingotomy by laparoscopy Multiple-dose methotrexate is equally effective at increasing tubal patency rates in women with a confirmed unruptured tubal pregnancy (moderate-quality evidence).

Adverse effects
Methotrexate may cause more vaginal bleeding compared with salpingotomy.

Note
We found no clinically important results from RCTs or cohort studies about methotrexate compared with expectant management in women with ectopic pregnancies.

For GRADE evaluation of interventions in tubal ectopic pregnancy, see table, p 15 .

Benefits: **Systemic single- versus multiple-dose methotrexate regimens:**
We found one systematic review (search date 2001, 3 RCTs, 23 observational studies [no further information reported], 1327 women with ectopic pregnancy). [32] The systematic review found that single-dose methotrexate was associated with significantly higher primary treatment failure compared with multiple-dose methotrexate (absolute numbers not reported; OR 1.71, 95% CI 1.04 to 2.82). The results remained significant when meta-analysing only studies considered to be high quality (according to the review authors' own rating system; absolute numbers not reported; OR 1.96, 95% CI 1.07 to 3.60) and when assessing only studies that controlled for confounding factors (beta human chorionic gonadotrophin [beta hCG] and fetal cardiac activity: OR 4.74, 95% CI 1.77 to 12.62). One subsequent RCT (108 women with ectopic pregnancy) found no significant difference between single-dose and multiple-dose methotrexate in rates of success of medical management (48/54 [89%] with single dose *v* 50/54 [93%] with multiple dose; OR 0.64, 95% CI 0.17 to 2.40; P = 0.7). [33]

Systemic single- or multiple-dose methotrexate versus salpingotomy:
We found one systematic review (search date 2006, 6 RCTs) comparing systemic methotrexate versus salpingotomy. [25] The review found that single-dose methotrexate was significantly less effective than salpingotomy (by laparoscopy) in primary treatment success (elimination of tubal

pregnancy: 4 RCTs, 265 haemodynamically stable women with small unruptured tubal pregnancy). It found no significant difference in tubal patency, subsequent intrauterine pregnancy, and repeat ectopic pregnancy rates (3 RCTs, 115 haemodynamically stable women with small unruptured tubal pregnancy) (see table 2, p 14). [25] The review also found no significant difference between multiple-dose methotrexate compared with salpingotomy (by laparoscopy) in primary treatment success, tubal patency (1 RCT, 100 haemodynamically stable women with a laparoscopically confirmed unruptured tubal pregnancy), subsequent pregnancy, or repeat ectopic pregnancy (1 RCT, 74 haemodynamically stable women with a laparoscopically confirmed unruptured tubal pregnancy) (see table 2 , p 14). [25] One RCT identified by the review found that physical functioning (measured by Short-Form-36 [SF-36] Health Survey: 0 = worst, 100 = best) was significantly better with single-dose methotrexate compared with salpingotomy at 4 and 10 days (4 days: 73 with methotrexate *v* 43 with salpingotomy; P = 0.001; 10 days: 93 with methotrexate *v* 70 with salpingotomy; P = 0.006). [34] Another RCT identified by the review found that a variety of quality-of-life scores were significantly lower with multiple-dose methotrexate compared with salpingotomy at 2 weeks (Medical Outcomes Study: 0 = worst, 100 = best; role function: 29 with methotrexate *v* 51 with salpingotomy; social function: 45 with methotrexate *v* 68 with salpingotomy; health perceptions: 52 with methotrexate *v* 63 with salpingotomy; P greater than 0.05 for all comparisons). [35]

Systemic methotrexate versus salpingectomy or salpingotomy:
See benefits of salpingectomy, p 3 .

Systemic methotrexate versus expectant management:
We found no RCTs or observational studies of sufficient quality.

Harms:

Systemic single- versus multiple-dose methotrexate regimens:
One systematic review found significantly lower rates of adverse effects (including nausea, vomiting, and alopecia) in women who received single-dose compared with multiple-dose methotrexate (31% with single dose *v* 41% with multiple dose; absolute numbers not reported; OR 0.44, 95% CI 0.31 to 0.63). However, it found no significant difference between regimens when it adjusted for serum beta hCG (OR 0.79, 95% CI 0.21 to 3.01). [32] It also found no significant difference between regimens for abdominal pain or hospital admission (abdominal pain: 22% with single dose *v* 26% with multiple dose; OR 0.80, 95% CI 0.53 to 1.19; hospital admission: 12% with single dose *v* 11% with multiple dose; OR 1.11, 95% CI 0.83 to 1.47). The subsequent RCT reported no significant difference between groups for adverse effects (15/54 [28%] with single dose *v* 20/54 [37%] with multiple dose; P = 0.3), including abdominal pain, diarrhoea, elevated liver enzymes, stomatitis, dermatitis, and pruritus. [33]

Systemic single- or multiple-dose methotrexate versus salpingotomy:
The systematic review gave no information on adverse effects. [25] One RCT included in the review found that women who received single-dose methotrexate had significantly longer vaginal bleeding than those who underwent salpingotomy (7.5 days with methotrexate *v* 3 days with salpingotomy; P less than 0.001). [34] A second RCT included in the review found that pain was greater with multiple-dose methotrexate over 16 weeks compared with salpingotomy (results presented graphically; significance assessment not reported). [35]

Systemic single-dose methotrexate plus salpingotomy versus salpingotomy alone:
See harms of prophylactic methotrexate after salpingotomy, p 5 .

Systemic methotrexate versus salpingectomy or salpingotomy:
See harms of salpingectomy, p 3 .

Systemic methotrexate versus expectant management:
We found no RCTs or observational studies of sufficient quality.

Comment:

None.

Clinical guide:
The primary treatment-success rate of systemic methotrexate (single- or multiple-dose regimens) in treating ectopic pregnancies has been reported by some meta-analyses as 87% (range 75–90%), [22] 84%, [36] and 89%. [32] The risk of persistent trophoblast has been reported as 18% (range 6–31%). [25] Despite the use of the term “single-dose methotrexate regimen”, repeat doses are permitted every 7 days if there is an inadequate decrease in beta hCG levels. Furthermore, a meta-analysis found that two or more doses were required in 13.5% of women receiving single-dose methotrexate. [32] One retrospective study (93 women) reported 2-year subsequent cumulative intrauterine pregnancy rates of 67% and repeat ectopic pregnancy rates of 24%. [37]

Prospective studies suggest that around 25–40% of non-invasively diagnosed ectopic pregnancies are suitable for non-surgical (methotrexate or expectant) management. [34] [38] [39] [40] The criteria necessary for methotrexate treatment have been agreed by the Royal College of Obstetrics and Gynaecology, and include: non-invasive diagnosis of ectopic pregnancy; haemodynamic stability with no signs of tubal rupture; an ectopic mass less than 3.5 cm in diameter and no sign of fetal cardiac activity; a beta hCG level exceeding no more than 3000 IU/L; no medical contraindications to methotrexate usage; and assurance from the woman to attend frequent outpatient follow-up visits. [41] Observational (prospective and retrospective) studies have suggested higher primary treatment success of methotrexate with ectopic pregnancies that have low pre-treatment beta hCG levels (preferably less than 1000 IU/L). [34] [42] [43] [44] [45] [46] [47] [48] A meta-analysis of five observational studies reported that treatment failure with methotrexate was increased if the initial pre-treatment hCG exceeded 5000 IU/L. [49] Other factors reported to be associated with methotrexate success include: ectopic pregnancies that have absent fetal embryo; [50] absent fetal cardiac activity; [44] [51] absent yolk sac identified by sonography; [52] [53] no prior history of treated ectopic; [51] women with no pelvic pain; [46] and no previous history of infertility. [37] Therefore, outcomes of methotrexate should be compared against other tubal-conserving methods (salpingotomy and expectant management).

Adverse effects:
The frequency of methotrexate complications is similar to those with laparoscopy. [22] However, the nature of the complications differ, with serious complications of laparoscopy having greater morbidity and mortality than those related to methotrexate. Women who experienced adverse effects were more likely to have successful treatment, regardless of whether they received a single- or multiple-dose methotrexate regimen. [32] Although drug adverse effects are prevalent, they are usually self-limiting and relatively minor, and include: nausea, vomiting, gastritis, diarrhoea, abdominal pain, oral mucositis, pneumonitis, bone marrow suppression, and abnormal liver function. Case reports have described other rare but serious complications: life-threatening neutropenia and fever; [54] anaphylaxis; [55] haematosalpinx and pelvic haematocoele; [56] and death due to multiorgan failure. [57] One meta-analysis of single-dose methotrexate treatment reported adverse effects in 24% (95% CI 9% to 47%) of women, and 10% (95% CI 7% to 14%) had a ruptured ectopic pregnancy. [36]

OPTION METHOTREXATE PLUS MIFEPRISTONE (SYSTEMIC)

Treatment failure
Compared with methotrexate alone Systemic methotrexate plus mifepristone is no more effective at increasing treatment-success rates overall, but this combination may be more effective in increasing treatment-success rates in women with high levels of progesterone (high-quality evidence).

For GRADE evaluation of interventions in tubal ectopic pregnancy, see table, p 15 .

Benefits:

Systemic methotrexate plus mifepristone versus systemic methotrexate alone:
One RCT found no significant difference between systemic methotrexate plus mifepristone and methotrexate alone in the proportion of women with initial treatment success (22/25 [88%] with methotrexate plus mifepristone *v* 18/25 [72%] with methotrexate alone; OR 2.85, 95% CI 0.54 to 19.17). [58] However, the median time to resolution of the ectopic pregnancy was quicker with the combined treatment (14 days methotrexate plus mifepristone *v* 21 days with methotrexate alone; significance assessment not reported). A second RCT also found no significant difference between methotrexate plus mifepristone and methotrexate alone in the proportion of women who had initial treatment success (90/113 [80%] with methotrexate plus mifepristone *v* 72/97 [74%] with methotrexate alone; RR 1.07, 95% CI 0.92 to 1.25). [59] In women with higher levels of progesterone (10 nmol/L or greater), it found treatment success was more successful with combined treatment than with methotrexate alone (15/18 [83%] methotrexate plus mifepristone *v* 5/13 [39%] with methotrexate alone; RR 2.16, 95% CI 1.06 to 4.44). One prospective cohort study found fewer treatment failures with methotrexate plus mifepristone compared with methotrexate alone (1/30 [3%] with methotrexate plus mifepristone *v* 11/42 [26%] with methotrexate alone; significance not reported). [60]

Harms:

Systemic methotrexate plus mifepristone versus systemic methotrexate alone:
The first RCT found that two women in each group reported mild nausea. [58] The second RCT found the same rate of gastritis in both groups (34/113 [30.1%] with methotrexate plus mifepristone *v* 30/99 [30.3%] with methotrexate alone; P = 1.00). [59] The cohort study gave no information on adverse effects. [60]

Comment:

See comment on methotrexate, p 6 .

OPTION EXPECTANT MANAGEMENT

Subsequent pregnancy rates
Compared with surgery We don't know whether expectant management leads to lower subsequent pregnancy rates in women with non-viable embryos (non-invasive with declining human chorionic gonadotrophin [hCG] levels) (very low-quality evidence).

Note
We found no clinically important results from RCTs or cohort studies about expectant management compared with methotrexate in women with ectopic pregnancies.

For GRADE evaluation of interventions in tubal ectopic pregnancy, see table, p 15 .

Benefits:

We found no systematic review or RCTs. We found two retrospective cohort studies with differing results. [24] [61]

Expectant management versus salpingectomy or salpingotomy:
The first retrospective cohort study (180 women with ectopic pregnancy) found similar rates of subsequent intrauterine conception between expectant management and salpingectomy or salpingotomy in those women desiring subsequent pregnancy (19/37 [51%] with expectant management *v* 31/49 [63%] with surgery). [61] The study did not report success of treatment or data by type of surgery. [61] The second retrospective cohort study (146 women with ectopic pregnancy) found that expectant management increased the rate of subsequent pregnancy compared with salpingectomy (41/49 [84%] with expectant management *v* 62/97 [64%] with salpingectomy; OR 2.89, 95% CI 1.22 to 6.86). [24]

Expectant management versus methotrexate:
We found no RCTs or observational studies of sufficient quality.

Expectant management in studies with no control group:
We found one non-systematic review (15 prospective cohort studies, 482 women with ectopic pregnancy who were described as “stable” or “well”), which found a mean rate of 67% (range 47–82%) for successful expectant management of ectopic pregnancy. [62] The review also reported that rates of tubal patency were 57/74 (77%), subsequent intrauterine pregnancy were 42/62 (68%), and repeat ectopic pregnancy were 6/47 (13%). One prospective cohort study (107 clinically stable women with non-viable pregnancies and no signs of haematoperitoneum) found that 75/107 (70%) of ectopic pregnancies resolved spontaneously. [40] Another prospective cohort study (30 women who wanted to become pregnant again) found tubal patency in 28/30 (93%) women, subsequent intrauterine pregnancy in 21/24 (88%) women, and repeat ectopic pregnancy in 1/24 (4%) women. [63]

Harms:

Expectant management versus salpingectomy or salpingotomy:
The two retrospective cohort studies did not report on harms. [24] [61]

Expectant management versus methotrexate:
We found no RCTs or observational studies of sufficient quality.

Expectant management in studies with no control group:
The meta-analysis reported that 2.5% of women had a tubal rupture in one of the cohort studies. [62] The two cohort studies gave no information on adverse effects. [40] [63]

Comment:

Expectant management was confined to a selected subgroup of unruptured ectopic pregnancies. We found no RCTs comparing expectant management with laparoscopic surgery or systemic methotrexate. Data for expectant management were derived from retrospective studies with different inclusion criteria (e.g. ectopic size, serum beta human chorionic gonadotrophin (hCG) level, presence of fetal cardiac activity) that contribute to bias in the methods used, and preclude effective statistical comparison. There is conflicting evidence from observational studies that expectant management effects primary treatment success and future fertility outcomes compared with surgically treated ectopic pregnancy. [64] An RCT (METEX: methotrexate versus expectant management in women with ectopic pregnancy) was begun in April 2007, and will provide further information on the efficacy and suitability criteria for expectant management or methotrexate options for women with unruptured ectopic pregnancy or pregnancy of unknown location with low but plateauing serum hCG concentrations. [65]

Clinical guide:
Cases considered to be suitable for expectant management should conform to strict criteria. Suggestions include: non-invasive diagnosis of ectopic pregnancy; unruptured ectopic pregnancy;

haemodynamic stability of the woman; less than 100 mL of fluid in the pouch of Douglas; initial beta hCG level below 1000 IU/L (when the success rate increases to 80%); [62] consecutive serial serum beta hCG levels showing spontaneous decline; no worsening of symptoms (especially abdominal pain and vaginal bleeding) during this interval; and the woman understanding the need for ongoing surveillance. [41] These factors have been verified as favourable prognostic signs in observational studies. [62] Prospective and retrospective observational studies have suggested that low serum progesterone (less than 20 nmol/L) and an increased rate of decline of beta hCG level are important predictors of successful expectant management in pregnancies of unknown location. [16] [66] [67] [68] [69] There is no quantifiable harm in expectant management because intervention is absent. However, harm would arise if primary treatment fails or tubal rupture ensues. Expectant management necessitates regular surveillance until normalisation of clinical, ultrasound, and beta hCG variables. Despite adequately declining serum beta hCG concentrations,the risks of tubal rupture and persistent trophoblast remain. Tubal rupture has been reported with serum beta hCG levels below 50 IU/L. [70] [71]

GLOSSARY

Beta hCG is the pregnancy hormone beta human chorionic gonadotrophin.
Contralateral tube denotes the opposite tube to that affected by the ectopic pregnancy.
Discriminatory zone denotes a serum beta hCG level at which it is assumed that all intrauterine pregnancies will be visualised by transvaginal ultrasound. This may vary according to sonographic expertise, but is often between 1000 and 1500 IU/L.
Persistent trophoblast is defined as suboptimal falling, increasing, or plateauing serum beta hCG concentrations following initial ectopic pregnancy treatment for which additional treatment (surgical or medical) is needed. This rarely occurs following salpingectomy, but may arise following salpingotomy, methotrexate, or expectant management.
Pregnancy of unknown location is defined as absence of pregnancy localisation (either intrauterine or extrauterine) by transvaginal sonography when serum beta hCG levels are below the discriminatory zone (1000–1500 IU/L). If there is an absence of pregnancy localisation with the serum beta hCG above the discriminatory zone, then this, along with other clinical, ultrasonographic, and serum beta hCG features, increases the likelihood of ectopic pregnancy.
Primary treatment success is defined as progressive decline of serum beta hCG to undetectable levels following initial treatment without reintervention (surgical or medical) for persistent trophoblast or supervening clinical sequelae (e.g. tubal rupture or worsening clinical symptoms).
Salpingotomy is where the ectopic conceptus is removed from the affected tube through a linear incision of the tube overlying the ectopic pregnancy. This incision is not surgically closed and is allowed to heal through secondary intention. This surgical treatment conserves the affected tube.
Treatment failure denotes the sum of the reintervention rates for persistent trophoblast and supervening clinical sequelae (e.g. tubal rupture or worsening clinical symptoms).
Tubal excision or salpingectomy is defined as the surgical removal of the tube affected by the ectopic pregnancy.
Expectant management is where ectopic pregnancy treatment involves a watch-and-wait policy in conjunction with close clinical, ultrasonographic, and serum beta hCG surveillance.
Fecundity rate ratio (FRR) The fecundity rate represents the probability of spontaneous intrauterine pregnancy (IUP) per time unit elapsed, derived from analysing the cumulative probability of pregnancy over the study duration. Only women trying to conceive are included in the calculation, and women who have conceived using additional treatments (e.g. in vitro fertilisation) are excluded up until the start of their additional treatment. The FRR is the ratio of fecundity between the test treatment (e.g. salpingotomy) against the reference treatment (e.g. salpingectomy). A significant treatment difference between salpingotomy compared with salpingectomy is indicated if 1 is not included in the 95% confidence interval (CI) for the FRR of salpingotomy compared to salpingectomy. Thus, an FRR of 1.9 for intrauterine pregnancy indicates that the probability of intrauterine pregnancy is 90% higher with salpingotomy than salpingectomy.
Fertility outcome reports the rates of subsequent intrauterine pregnancy, repeat ectopic pregnancy, and live birth rate. Such pregnancies may either be spontaneous or achieved through assisted reproductive technology, and this should be stated clearly in the fertility outcome. Furthermore, fertility outcome rates differ according to the ectopic pregnancy-associated reproductive and pathological characteristics, and treatment method chosen. The denominator will differ in those women who desire future fertility and who are trying to conceive, compared with those women taking contraceptive measures.
High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Tubal patency examines the homolateral tube for the passage of dye at hysterosalpingogram, or at second-look laparoscopy, or the passage of contrast media at transvaginal ultrasound. Only those cases that have been managed by tubal preservation, rather than salpingectomy, are eligible for tubal patency testing.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Expectant management: One retrospective cohort added comparing expectant management versus salpingectomy. [24] It found that expectant management increased the rate of subsequent pregnancy compared with salpingectomy but there remains insufficient evidence to draw conclusions about its use. Categorisation unchanged (Unknown effectiveness).

Salpingectomy: One retrospective cohort study added comparing expectant management versus salpingectomy. [24] It found that salpingectomy did not increase the rate of subsequent pregnancy compared with expectant management. Categorisation unchanged (Beneficial).

Salpingotomy: One systematic review updated, comparing salpingotomy by laparoscopy versus salpingotomy by laparotomy. [25] It found that laparoscopy was less effective in achieving primary treatment success (elimination of tubal pregnancy) than laparotomy. However, it found no significant difference between groups in tubal patency, rate of subsequent pregnancy, and repeat ectopic pregnancy. [25] Categorisation unchanged (Unknown effectiveness).

Systemic methotrexate (single- or multiple-dose): One RCT added comparing single- versus multiple-dose methotrexate. [33] It found no significant difference between groups in rates of success of medical management. One systematic review updated comparing single- or multiple-dose methotrexate versus laparoscopic salpingotomy. [25] The review found that single-dose systemic methotrexate was significantly less effective than salpingotomy in increasing primary treatment-success rates (elimination of tubal pregnancy), but found no significant difference between multiple-dose systemic methotrexate and salpingotomy in primary treatment-success rates. Categorisation unchanged (Likely to be beneficial).

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Rajesh Varma
Consultant Obstetrician and Gynaecologist
Guy's and St. Thomas' Hospital NHS Foundation Trust
London
UK

Janesh Gupta
Professor of Obstetrics and Gynaecology
Birmingham University
Birmingham
UK

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Disclaimer

TABLE 1 **Comparison of fertility outcomes of salpingotomy versus salpingectomy from non-randomised studies and meta-analyses of observational studies (see text, p 3).**

			Salpingotomy compared with salpingectomy as the reference treatment	
Ref	**Primary treatment success**	**Sample size (sum of salpingectomy and salpingotomy cases unless otherwise stated)**	**Crude spontaneous intrauterine pregnancy (IUP) rates and/or fecundity rate ratios* (FRR) (95% CI)**	**Crude repeat ectopic pregnancy (REP) rates and/or fecundity rate ratios* (FRR) (95% CI)**
Non-systematic review [17]	Failure or rate of persistent ectopic pregnancy range 3–20% in 10 cohort studies comparing laparotomy with laparoscopic salpingotomy (corresponding results for salpingectomy not reported)	1774 women (in 9 cohort studies) undergoing salpingotomy or salpingectomy for ectopic pregnancy, and desiring subsequent pregnancy	280/528 (53%) with salpingotomy *v* 614/1246 (49%) with salpingectomy at 3 months–15 years: crude FRR 1.08 (0.97 to 1.19)*	78/528 (15%) with salpingotomy *v* 123/1246 (10%) with salpingectomy at 3 months–15 years: crude FRR 1.50 (1.15 to 1.95)*
		176 women (in 18 cohort studies) with cTD after salpingotomy (corresponding results for salpingectomy not reported)	Salpingotomy in women with cTD then IUP in 96/176 (55%)	Salpingotomy in women with cTD then REP in 36/176 (21%)
Prospective cohort [21]	8/86 (9%) of women having either subsequent laparoscopic salpingectomy or methotrexate because of treatment failure of salpingotomy. Treatment failures due to salpingectomy not reported	86 women undergoing laparoscopic surgery for ectopic pregnancy and attempting conception	36/60 (60%) with salpingotomy *v* 14/26 (54%) with salpingectomy at 48 months: FRR 1.11 (0.77 to 1.76)*	11/60 (18%) with salpingotomy *v* 2/26 (8%) with salpingectomy at 48 months: FRR 2.38 (0.67 to 9.30)*
		cTD present in 33/60 (55%) of women who had salpingotomy and 15/26 (58%) of women who had salpingectomy	Irrespective of the type of surgery performed and if cTD: crude FRR (women with cTD *v* no cTD) 0.53 (0.36 to 0.75)* (based on 20/50 [40%] pregnant with cTD *v* 27/34 [79%] not pregnant with cTD; type of surgery not reported)	
Retrospective cohort [20]	Not reported	135 women undergoing laparoscopy or laparotomy for ectopic pregnancy	62% with salpingotomy *v* 38% with salpingectomy at 3 years (numbers not reported). FRR (at 18 months) 1.9 (0.91 to 3.8)	28% with salpingotomy *v* 23% with salpingectomy at 3 years (numbers not reported): FRR 2.4 (0.57 to 11)
		cTD present in 15/56 (27%) of women having salpingotomy and 38/79 (48%) having salpingectomy	In women with cTD: 2/6 (33%) with salpingotomy *v* 3/8 (38%) with salpingectomy; FRR 0.80 (0.13 to 4.9) In women with bilateral tubal pathology: 1/8 (13%) with salpingotomy *v* 3/25 (12%) with salpingectomy; FRR 1.4 (0.13 to 16)	Irrespective of the type of surgery performed and if cTD: FRR 0.79 (0.18 to 3.4) (numbers and which type of surgery the women had not reported)
Retrospective cohort [18]	Not reported	276 women undergoing salpingotomy or salpingectomy for first ectopic pregnancy	89% with salpingotomy *v* 66% with salpingectomy at 7 years (numbers not reported): FRR 1.58 (1.06 to 2.38)*	17% with salpingotomy *v* 16% with salpingectomy at 2 years (numbers not reported): FRR 1.28 (0.57 to 2.87)*
		cTD present in 30/208 (14%) of women with salpingotomy and 17/68 (25%) with salpingectomy	Irrespective of the type of surgery performed: FRR (women with cTD *v* no cTD) 0.46 (0.26 to 0.82)* (numbers and type of surgery not reported)	Irrespective of the type of surgery performed: FRR (women with cTD *v* no cTD) 2.25 (1.11 to 4.531)* (numbers and type of surgery not reported)

		Salpingotomy compared with salpingectomy as the reference treatment		
Ref	**Primary treatment success**	**Sample size (sum of salpingectomy and salpingotomy cases unless otherwise stated)**	**Crude spontaneous intrauterine pregnancy (IUP) rates and/or fecundity rate ratios* (FRR) (95% CI)**	**Crude repeat ectopic pregnancy (REP) rates and/or fecundity rate ratios* (FRR) (95% CI)**
Cohort [9] [19]	Initial treatment failure: 1/178 [1%] with salpingectomy *v* 14/262 [5%] with salpingotomy *v* 13/36 [36%] with methotrexate	476 women with tubal ectopic pregnancy who were not using contraception at conception Salpingotomy in 262 women: cTD in 236/262 (90%). Salpingectomy in 178 women, cTD in 159/178 (89%). Methotrexate in 36 women: cTD in 8/36 (22%).	73% with salpingotomy *v* 57% with salpingectomy *v* 80% with methotrexate Irrespective of the type of surgery performed and if cTD: FRR (women with cTD *v* no cTD) 0.53 (0.33 to 0.83)* In women with infertility factors: salpingotomy *v* salpingectomy FRR 1.67 (1 to 2.78);* methotrexate *v* salpingectomy FRR 2.5 (1.95 to 8.33)* In women with no infertility factors: salpingotomy *v* salpingectomy FRR 1.18 (0.63 to 2.22);* methotrexate *v* salpingectomy FRR 2.12 (0.49 to 9.78)* (numbers not reported)	25% with salpingotomy *v* 27% with salpingectomy *v* 41% with methotrexate Salpingotomy *v* salpingectomy: FRR 0.93 (0.76 to 3.5)* Methotrexate *v* salpingectomy: FRR 1.51 (0.25 to 7.08)* (numbers not reported)
		1595 women with ectopic pregnancy [9] Salpingotomy in 798 (50%); salpingectomy in 654 (41%); methotrexate in 143 (9%) Number of women with cTD for each treatment not stated	Salpingotomy *v* salpingectomy: FRR 1.25 (1 to 1.67)* Methotrexate *v* salpingectomy: FRR 1.25 (0.7 to 2.33)* Irrespective of the type of surgery performed and if cTD: FRR (women with cTD *v* no cTD) 0.83 (0.67 to 1.0)* (numbers not reported)	Salpingotomy *v* salpingectomy: FRR 1.25 (0.67 to 2)* Methotrexate *v* salpingectomy: FRR 2.25 (0.6 to 7.4)* If irrespective of the type of surgery performed and if cTD: FRR (women with cTD *v* no cTD) 1 (0.5 to 2.0)* (numbers not reported)

cTD: contralateral tubal disease. This may be absent, occluded, or distorted by pathology (hydrosalpinges, adhesions). * FRRs: calculated by *Clinical Evidence* contributor. FRRs are stated for salpingotomy compared with salpingectomy as the reference, unless otherwise stated. FRRs are also stated for the presence relative to absence of confounding factors (e.g. cTD or infertility), disregarding the type of surgery (either salpingotomy or salpingectomy) that was performed. Where studies have calculated FRR using salpingotomy as the reference standard, the reciprocal of this FRR has been quoted, because this provides the FRR of salpingotomy compared with salpingectomy as the reference standard. Crude FRRs: We report an FRR based on the results reported in the meta-analysis. However, due to study heterogeneity and non-adoption of survival analysis techniques by included studies within the meta-analysis, a pooled FRR (as we have reported) is likely to be crude and subject to bias.

TABLE 2 **Meta-analyses of surgical versus surgical and surgical versus medical treatments in the management of ectopic pregnancy (see text, p 6). [25]**

		Meta-analysis of trials [25]			
Type of comparison	**No. of RCTs**	**Primary treatment success odds ratio (95% CI)**	**Tubal patency in those desiring subsequent pregnancy odds ratio (95% CI)**	**Subsequent intrauterine pregnancy rate odds ratio (95% CI)**	**Repeat ectopic pregnancy rate odds ratio (95% CI)**
Laparoscopic salpingotomy *v* laparotomy salpingotomy	4	2 RCTs, 165 women: 68/78 [87%] laparoscopy *v* 84/98 [97%] with laparotomy; OR 0.28, 95% CI 0.09 to 0.86	2 RCTs, 165 women: 38/52 [73%] with laparoscopy *v* 48/58 [83%] with laparotomy; OR 0.58, 95% CI 0.23 to 1.42	2 RCTs, 127 women: 35/61 [57%] with laparoscopy *v* 35/66 [53%] with laparotomy; OR 1.21, 95% CI 0.59 to 2.45	2 RCTs, 127 women: 4/61 [7%] with laparoscopy *v* 9/66 [14%] with laparotomy; OR 0.47, 95% CI 0.15 to 1.47
Systemic multiple-dose methotrexate (im) *v* laparoscopic salpingotomy	2	1 RCT, 100 women: 42/51 [82%] with methotrexate *v* 35/49 [71%] with surgery; OR 1.84, 95% CI 0.73 to 4.65	1 RCT, 100 women: 23/42 [55%] with methotrexate *v* 23/39 [59%] with surgery; OR 0.84, 95% CI 0.35 to 2.02	1 RCT, 74 women: 12/34 [35%] with methotrexate *v* 16/40 [40%] with surgery; OR 0.82, 95% CI 0.32 to 2.09	1 RCT, 74 women: 3/34 [12%] with methotrexate *v* 4/40 [10%] with surgery; OR 0.87, 95% CI 0.19 to 4.12
Systemic single-dose methotrexate (im) *v* laparoscopic salpingotomy	4	4 RCTs, 265 women: 85/120 [71%] with methotrexate *v* 127/145 [88%] with surgery; OR 0.38, 95% CI 0.20 to 0.71	3 RCTs, 115 women: 36/59 [61%] with methotrexate *v* 29/56 [52%] with surgery; OR 1.47, 95% CI 0.69 to 3.14	3 RCTs, 115 women: 18/49 [7%] with methotrexate *v* 29/58 [50%] with surgery; OR 1.01, 95% CI 0.43 to 2.41	3 RCTs, 115 women: 2/40 [5%] with methotrexate *v* 7/58 [12%] with surgery; OR 0.54, 95% CI 0.12 to 2.44

TABLE **GRADE evaluation of interventions for tubal ectopic pregnancy**

Important outcomes	**Treatment failure, primary treatment success, subsequent pregnancies, mortality, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What treatments improve outcomes in women with unruptured tubal ectopic pregnancy?									
2 studies (440) [9] [19]	Treatment failure	Salpingectomy *v* salpingotomy	2	–1	0	0	0	Very low	Quality point deducted for incomplete reporting of results
2 studies (214) [9] [19]	Treatment failure	Salpingectomy *v* methotrexate	2	–1	0	0	0	Very low	Quality point deducted for incomplete reporting of results
2 studies (298) [9] [19]	Treatment failure	Salpingotomy *v* methotrexate	2	–1	0	0	0	Very low	Quality point deducted for incomplete reporting of results
3 studies (1907) [9] [20] [21]	Subsequent pregnancy rates	Salpingectomy *v* salpingotomy	2	–1	–1	0	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
12 studies (2300) [9] [19] [21] [17]	Recurrent ectopic pregnancy rates	Salpingectomy *v* salpingotomy	2	–1	–1	0	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 study (116) [31]	Treatment failure	Methotrexate plus surgery *v* surgery alone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
4 RCTs and 23 studies (1435) [32] [33]	Treatment failure	Single-dose methotrexate *v* multiple-dose regimens	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and uncertainty about quality of studies
1 SR [25] included 4 RCTs (265)	Primary treatment success	Single-dose methotrexate *v* salpingotomy	4	0	0	0	0	High	
1 SR [25] included 2 RCTs (174)	Primary treatment success	Multiple-dose methotrexate *v* salpingotomy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 SR [25] and 3 RCTs (115)	Subsequent pregnancy rates	Single-dose methotrexate *v* salpingotomy	4	0	0	0	0	High	
1 SR [25] and 1 RCT (74)	Subsequent pregnancy rates	Multiple-dose methotrexate *v* salpingotomy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 studies (232) [24] [61]	Subsequent pregnancy rates	Expectant management *v* surgery	2	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for differences in inclusion criteria
1 SR [25] and 2 RCTs (165)	Treatment failure	Laparoscopy (salpingotomy) *v* laparotomy (salpingotomy)	4	0	0	0	0	High	
1 SR [25] and 2 RCTs (127)	Subsequent pregnancy rates	Laparoscopy *v* laparotomy	4	0	0	0	0	High	
2 studies (291) [58] [59]	Treatment failure	Methotrexate plus mifepristone *v* methotrexate	4	0	0	0	0	High	

Important outcomes	Treatment failure, primary treatment success, subsequent pregnancies, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**

SR, systematic review. Type of evidence: 4 = RCT; 2 = Observational. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio