ClinicalEvidence

Tubal ectopic pregnancy

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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 can lead to rupture of the tube. Risks are higher in women who smoke or have damage to the fallopian tubes due to pelvic infections, surgery, or previous ectopic pregnancy. METHODS AND OUTCOMES: We conducted a systematic overview aiming to answer the following clinical question: What are the effects of treatments for unruptured tubal ectopic pregnancy on subsequent fertility? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved nine studies. After deduplication and removal of conference abstracts, nine records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of six studies and the further review of three full publications. Of the three full articles evaluated, no systematic reviews and one RCT were added at this update. We performed a GRADE evaluation for three PICO combinations. CONCLUSIONS: In this systematic overview we present information relating to the effectiveness and safety of the following interventions for unruptured tubal ectopic pregnancy on subsequent fertility: expectant management, methotrexate, salpingotomy, and salpingectomy.

QUESTIONS

INTERVENTIONS

Key points

- Approximately 1 in 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 can 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 intrauterine device (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.

- With earlier diagnosis and better access to care, mortality linked to an ectopic pregnancy has reduced significantly in developed countries. The concern has now shifted to the issues of preserving future fertility prospects. However, there is uncertainty over which treatment option is superior.

- For this overview, we have focused on the outcomes of subsequent fertility/pregnancy for haemodynamically stable women with unruptured tubal ectopic pregnancy.

- About 15% to 40% of ectopic pregnancies may be suitable for non-surgical management (expectant management or methotrexate treatment).

- Observational studies suggest that expectant management of unruptured ectopic pregnancies in selected women who are clinically stable may lead to similar subsequent intrauterine pregnancy rates as those seen in studies of surgical interventions, but few studies have been done.

  For this overview, we evaluated evidence from RCTs and systematic reviews of RCTs only.

  We found no RCTs comparing expectant management with methotrexate, salpingotomy, or salpingectomy for women with unruptured tubal ectopic pregnancies.

- Methotrexate seems equally effective as salpingotomy in terms of subsequent intrauterine or ectopic pregnancy rates in women with small unruptured tubal pregnancies.

  We found no clinically important results from RCTs about methotrexate compared with salpingectomy.

- It is unknown whether one surgical intervention (salpingotomy or salpingectomy) is superior over the other with respect to future fertility prospects.

  We found one RCT comparing salpingectomy and salpingotomy that found similar rates of subsequent intrauterine pregnancy in women with ectopic pregnancy desiring future fertility and with a healthy contralateral fallopian tube.

Either salpingotomy or salpingectomy may be offered to a woman with an unruptured ectopic pregnancy where there is a healthy contralateral fallopian tube. In practice, the choice of surgical option is influenced by surgical experience and the woman's own preferences.

Also, in practice, salpingotomy is generally preferred to salpingectomy if the contralateral fallopian tube is diseased, because the cumulative intrauterine pregnancy rate is higher than after salpingectomy in this group of patients.

- Salpingotomy by laparoscopy or by laparotomy seem equally effective in terms of subsequent intrauterine pregnancy rates.

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

Clinical context

GENERAL BACKGROUND

With improvements in diagnosis and better access to care, mortality linked to an ectopic pregnancy has reduced significantly in developed countries. The preservation of the woman's subsequent fertility has become one of the key objectives in the treatment of unruptured ectopic pregnancy. It has remained unclear which interventions, specifically expectant management, methotrexate, salpingotomy, and salpingectomy, provide better future fertility prospects.

FOCUS OF THE REVIEW

The focus of this overview is to compare the existing treatments for unruptured ectopic pregnancy with respect to their impact on natural fertility and future pregnancy rates.

COMMENTS ON EVIDENCE

There are limited high-quality data investigating all of the existing treatments for unruptured ectopic pregnancy with respect to their impact on natural fertility and future pregnancy rates. Very few RCTs have compared individual medical and surgical treatments for ectopic pregnancy with respect to future fertility prospects. However, the limited evidence supports the view that salpingotomy and salpingectomy are equally beneficial in women desiring future fertility.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, July 2011, to September 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved nine studies. After deduplication and removal of conference abstracts, nine records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of six studies and the further review of three full publications. Of the three full articles evaluated, no systematic reviews and one RCT were added at this update.

DEFINITION

Ectopic pregnancy is defined as a conceptus implanting outside the uterine endometrium. The most common implantation site is within the fallopian tube (96%), followed by ovarian (3%) and abdominal (1%) sites. The sites of tubal implantation in descending order of frequency are ampulla (73%), isthmus (13%), fimbrial (12%), and interstitial (3%). [1] **Population** In this systematic overview, we consider haemodynamically stable women with unruptured tubal ectopic pregnancy, diagnosed by either non-invasive or invasive techniques.

INCIDENCE/ PREVALENCE

About 10,000 ectopic pregnancies are diagnosed annually in the UK. The incidence of ectopic pregnancy in the UK is 11.1/1000 pregnancies. [2] Differing rates are reported in other countries such as Norway (14.9/1000), Australia (16.2/1000), and the US (6.4/1000). [3] [4] [5] Since 1994, the overall rates of ectopic pregnancy and resulting mortality (0.35/1000 ectopic pregnancies from 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). [6] [7] 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%. [7] Increasing rates of chlamydia infection, smoking, and assisted reproductive technology use may have contributed to the disproportionate increase in the reproductive-failure ectopic pregnancies. 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. [8] [9]

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. [6] [7] [10] [11] [12] The main risk factors for reproductive-failure ectopic pregnancy are: previous ectopic pregnancy, previous pelvic inflammatory disease, previous pelvic and tubal surgery, infertility, smoking, and use of assisted conception. [6] [13] [14] The main risk factor for contraceptive-failure ectopic pregnancy is intrauterine device (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. [15]

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 hCG or serum progesterone) that can predict rupture of tubal ectopic pregnancy. [16] [17] Maternal mortality following ectopic pregnancy is an uncommon short-term outcome in resource-rich countries. The 2006–2008 UK Confidential Enquiry into Maternal Deaths cited ectopic pregnancy as a cause of six maternal deaths (0.26/100,000 pregnancies). [18] Short-term maternal morbidity relates to pain, transfusion requirement, and operative complications. Primary treatment success (i.e., elimination of tubal pregnancy) 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, history of infertility, age of the woman) and the type of medical or surgical 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. [10] 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 hCG levels are above the discriminatory zone (1000–1500 IU/L). One 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. [19] **Subsequent fertility and intrauterine pregnancy** There is uncertainty about whether conservative or surgical treatment for ectopic pregnancy offers a potentially better fertility outcome. The focus of this overview is to compare all of the existing treatments for unruptured ectopic pregnancy with respect to their impact on natural fertility and pregnancy rate.

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

Subsequent pregnancy (future fertility/spontaneous intrauterine pregnancy; live birth rate); **adverse effects** (ectopic pregnancy recurrence, failure to conceive spontaneously, assisted conception [IVF] rate following treatment).

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal September 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to September 2014, Embase 1980 to September 2014, The Cochrane Database of Systematic Reviews, 2014, issue 9 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this overview were systematic reviews and RCTs published in English, open or blinded studies acceptable, and containing 20 or more individuals. There was no minimum length of follow-up. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed a priori with our expert contributors. In consultation with the expert contributors,

studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our predefined criteria for inclusion in the benefits and harms section, may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant: ectopic pregnancy recurrence; failure to conceive spontaneously; assisted conception (IVF) rate following treatment. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported question: What treatments improve outcomes in women with unruptured tubal ectopic pregnancy? We have added the following question: What are the effects of treatments for unruptured tubal ectopic pregnancy on subsequent fertility? **Data and quality** 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). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue which may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 15). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatments for unruptured tubal ectopic pregnancy on subsequent fertility?**

OPTION **EXPECTANT MANAGEMENT**

- For GRADE evaluation of interventions for Tubal ectopic pregnancy, see table, p 15 .
- We found no direct information from RCTs about expectant management compared with methotrexate, salpingotomy, or salpingectomy in the treatment of women with unruptured tubal ectopic pregnancies.

Benefits and harms

Expectant management versus salpingectomy or salpingotomy:

We found no systematic review or RCTs.

Expectant management versus methotrexate:

We found no systematic review or RCTs.

Comment: We excluded one cohort study, [20] which suggested that expectant management of unruptured ectopic pregnancies might lead to similar subsequent intrauterine pregnancy rates compared with surgery (51% pregnancy rate with expectant management *v* 63% with salpingectomy or salpingo-

tomy). Another cohort study [21] also reported intrauterine pregnancy rates of 41/49 (84%) with expectant management and 62/97 (64%) with salpingectomy (OR 2.89, 95% CI 1.22 to 6.86). Overall, there is conflicting evidence from observational studies on how expectant management affects primary treatment success and future fertility outcomes compared with surgically treated ectopic pregnancy. [22]

Expectant management is confined to a selected subgroup of unruptured ectopic pregnancies. Data for expectant management have sometimes derived from retrospective studies with different inclusion criteria (e.g., ectopic size, serum beta hCG level, presence of fetal cardiac activity) that contribute to bias in the methods used and preclude effective statistical comparison. A multi-centre RCT comparing expectant management with systemic methotrexate for women with unruptured ectopic pregnancy or pregnancy of unknown location with low but plateauing serum hCG concentrations demonstrated no difference in primary treatment success rate (59% with expectant management *v* 76% with single-dose methotrexate, RR 1.3, CI 0.9 to 1.8). This trial did not report on fertility outcomes. [23]

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. [24] 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. [25] 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. [26] The review reported that 2.5% of women had a tubal rupture in one of the cohort studies. [24] The two cohort studies gave no information on adverse effects. [25] [26]

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 less than 1000 IU/L (when the success rate increases to 80%), [24] 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. [27] These factors have been verified as favourable prognostic signs in observational studies. [24] Prospective and retrospective observational studies have suggested that low serum progesterone (<20 nanomol/L) and an increased rate of decline of beta hCG level are important predictors of successful expectant management in pregnancies of unknown location. [19] [28] [29] [30] [31] 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 less than 50 IU/L. [32] [33]

OPTION METHOTREXATE

- For GRADE evaluation of interventions for Tubal ectopic pregnancy, see table, p 15 .
- Methotrexate (single or multiple dose) seems to be equally effective as salpingotomy in terms of subsequent intrauterine or ectopic pregnancy rates in women with small unruptured tubal pregnancies.
- We found no clinically important results from RCTs about methotrexate compared with salpingectomy or with expectant management in women with ectopic pregnancies.

Benefits and harms

Methotrexate (single or multiple dose) versus salpingotomy:

We found two systematic reviews (search dates 2006; [34] and 2007, [35] 6 RCTs) comparing systemic methotrexate with salpingotomy. The second review included the same RCTs as the first review, performed a similar analysis, and came to similar conclusions. We have, therefore, reported the later review in detail. [35] We have reported the earlier review only where it reported additional data not reported by the later review. We found one subsequent RCT. [36]
For general comments on adverse effects, see Comment, p 5 .

Subsequent pregnancy

Methotrexate (single or multiple dose) compared with salpingotomy Methotrexate seems equally as effective as salpingotomy at increasing subsequent intrauterine pregnancy rates in women with small unruptured tubal pregnancies (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Subsequent intrauterine pregnancy					
[35] Systematic review	Haemodynamically stable women, each with small unruptured tubal pregnancy 3 RCTs in this analysis	**Subsequent intrauterine pregnancy rates** 18/40 (45%) with single-dose methotrexate (intramuscular) 29/58 (50%) with salpingotomy (by laparoscopy)	RR 1.01 95% CI 0.66 to 1.54	⟷	Not significant
[35] Systematic review	74 haemodynamically stable women, each with a laparoscopically confirmed unruptured tubal pregnancy Data from 1 RCT	**Subsequent intrauterine pregnancy rates** 12/34 (35%) with multiple-dose methotrexate (intramuscular) 16/40 (40%) with salpingotomy (by laparoscopy)	RR 0.88 95% CI 0.49 to 1.60	⟷	Not significant
[36] RCT	106 women with ectopic pregnancy	**Cumulative rates of spontaneous intrauterine pregnancy** with single-dose methotrexate with laparoscopic salpingotomy Absolute results reported graphically	HR 1.41 95% CI 0.88 to 2.26 P = 0.15 Study was underpowered; see Further information on studies	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Repeat ectopic pregnancy					
[34] Systematic review	Haemodynamically stable women, each with small unruptured tubal pregnancy 3 RCTs in this analysis	**Repeat ectopic pregnancy rates** 2/40 (5%) with single-dose methotrexate (intramuscular) 7/58 (12%) with salpingotomy (by laparoscopy)	OR 0.54 95% CI 0.12 to 2.44	⟷	Not significant
[34] Systematic review	74 haemodynamically stable women, each with a laparoscopically confirmed unruptured tubal pregnancy Data from 1 RCT	**Repeat ectopic pregnancy rates** 3/34 (9%) with multiple-dose methotrexate (intramuscular) 4/40 (10%) with salpingotomy (by laparoscopy)	OR 0.87 95% CI 0.19 to 4.12	⟷	Not significant

No data from the following reference on this outcome. [35] [36]

Methotrexate versus salpingectomy:

We found no RCTs or systematic reviews.

Methotrexate versus expectant management:

We found no RCTs or systematic reviews.

Further information on studies

[34] 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). [37] 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 <0.05 for all these comparisons). [38]

[36] The RCT reported that inclusion was stopped after 3.5 years because of recruitment problems, and that the study was underpowered.

Comment:

Adverse effects

The frequency of methotrexate complications is similar to that with laparoscopy. [39] However, the nature of the complications differs, 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. [40] 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; [41] anaphylaxis; [42] haematosalpinx and pelvic haematocoele; [43] and death due to multi-organ failure). [44] 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. [45]

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%), [39] 84%, [45] and 89%. [40] The risk of persistent trophoblast has been reported as 18% (range 6%–31%). [34] 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 14% of women receiving single-dose methotrexate. [40] One retrospective study (93 women) reported 2-year subsequent cumulative intrauterine pregnancy rates of 67% and repeat ectopic pregnancy rates of 24%. [46]

Prospective studies suggest that around 25% to 40% of non-invasively diagnosed ectopic pregnancies are suitable for non-surgical (methotrexate or expectant) management. [37] [47] [48] [25] The criteria necessary for methotrexate treatment have been agreed by the Royal College of Obstetricians and Gynaecologists, 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 use; and assurance from the woman to attend frequent outpatient follow-up visits. [27] 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, <1000 IU/L). [37] [49] [50] [51] [52] [53] [54] [55] 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. [56] One population-based study found that previous use of combined oral contraception and initial hCG levels (>1300 IU/L) were associated with treatment failure of methotrexate. [57] One prospective cohort study found that success rates were significantly associated with size of gestational mass and recommended that women with gestational mass greater than 3 cm should be followed up more carefully. [58] Another prospective cohort

study found that pre-treatment hCG ratio was significantly associated with failure rate. [59] Other factors reported to be associated with methotrexate success include ectopic pregnancies that have absent fetal embryo, [60] absent fetal cardiac activity, [51] [61] absent yolk sac identified by sonography, [62] [63] no prior history of treated ectopic pregnancy, [61] women with no pelvic pain, [53] and no previous history of infertility. [46] Therefore, outcomes of methotrexate should be compared against other tube-conserving methods (salpingotomy and expectant management). See also Comment under Expectant management, p 4 .

OPTION SALPINGECTOMY

- For GRADE evaluation of interventions for Tubal ectopic pregnancy, see table, p 15 .
- Salpingectomy and salpingotomy show similar rates of subsequent intrauterine pregnancy in women with ectopic pregnancy desiring future pregnancy; however, we only found one RCT and this only included women with a healthy contralateral fallopian tube.
- We found no clinically important results from RCTs or systematic reviews comparing salpingectomy with methotrexate, or with expectant management.

Benefits and harms

Salpingectomy versus salpingotomy:

We found one RCT (446 women) comparing salpingectomy with salpingotomy in women with tubal pregnancy scheduled for surgery (all women had healthy contralateral fallopian tubes). [64] See the Further information on studies and Comment, p 8 sections.

Subsequent pregnancy

Salpingectomy compared with salpingotomy Salpingectomy and salpingotomy seem to be associated with similar rates of subsequent intrauterine pregnancy by natural conception after surgery (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Ongoing pregnancy rate by natural conception					
[64] RCT	446 women with tubal pregnancy scheduled for surgery (tubal pregnancy confirmed during surgery; all women had healthy contralateral fallopian tube)	**Cumulative ongoing pregnancy rate by natural conception , 36 months** 61% with salpingotomy 56% with salpingectomy Absolute results reported graphically	Fecundity rate ratio (FRR) 1.06 95% CI 0.81 to 1.38 P = 0.678	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Repeat ectopic pregnancy					
[64] RCT	446 women with tubal pregnancy scheduled for surgery (tubal pregnancy confirmed during surgery; all women had healthy contralateral fallopian tube)	**Repeat ectopic pregnancy** 18/215 (8%) with salpingotomy 12/231 (5%) with salpingectomy	RR 1.6 95% CI 0.8 to 3.3 P = 0.19	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Assisted conception (IVF) rate following treatment					
[64] RCT	446 women with tubal pregnancy scheduled for surgery (tubal pregnancy confirmed during surgery; all women had healthy contralateral fallopian tube)	**IVF rate , following treatment** 7/215 (3%) with salpingotomy 2/231 (1%) with salpingectomy	RR 3.8 95% CI 0.8 to 17.9 P = 0.10	⟷	Not significant

Salpingectomy versus methotrexate:

We found no RCTs or systematic reviews. See Comment section, p 8 .

Salpingectomy versus expectant management:

We found no RCTs or systematic reviews.

Salpingectomy by laparoscopy versus salpingectomy by laparotomy:

We found no RCTs or systematic reviews.

Further information on studies

[64] In this RCT, 231 women were allocated to salpingectomy and 215 to salpingotomy. Of the 215 women allocated to salpingotomy, 164 (76%) women underwent the assigned treatment, with the remainder (51 women) receiving salpingectomy. In most cases (43 women), conversion to salpingectomy was deemed necessary because of persistent tubal bleeding, three women had suspected bleeding, and five had persistent trophoblast.

Comment:

We identified one multi-centre RCT, which was not included in this overview as it fell outside our inclusion criteria because of the combination of interventions used. [65] However, we have included it in this Comment section for interest.

The RCT compared fertility rates in women 2 years after treatment for ectopic pregnancy. Women were divided into two arms according to the characteristics of the ectopic pregnancy. In the first arm, women with stable ectopic pregnancy were randomly allocated either to salpingectomy plus an intramuscular methotrexate injection (n = 97) or to an intramuscular methotrexate injection alone (n = 110). In the second arm, the trial studied women with unstable ectopic pregnancies, which did not meet our criteria for inclusion for this overview. The cumulative intrauterine pregnancy rates after 2 years of follow-up in the first arm were 67% after medical treatment with methotrexate alone and 71% after salpingectomy plus methotrexate. These rates were not statistically different, with the log-rank test equal to 0.83 (P = 0.36) and a HR 0.85 (CI 0.59 to 1.22). There was no difference in ectopic pregnancy recurrences between groups (P = 0.58).

We have excluded several retrospective and prospective observational cohort studies that have compared the effects of salpingectomy with salpingotomy [10] [66] [67] [68] [69] or with methotrexate [10] [67] on rates of subsequent spontaneous intrauterine pregnancy in women with unruptured tubal ectopic pregnancy and desiring future fertility. The findings of these studies suggested no difference in subsequent intrauterine pregnancy rates following salpingectomy compared with salpingotomy, or salpingectomy compared with methotrexate.

Clinical guide
In practice, the choice of surgical option is influenced by surgical experience, the woman's own preferences, and the condition of the contralateral fallopian tube.

OPTION SALPINGOTOMY

- For GRADE evaluation of interventions for Tubal ectopic pregnancy, see table, p 15 .
- Salpingotomy and salpingectomy show similar rates of subsequent intrauterine pregnancy in women with ectopic pregnancy desiring future pregnancy; however, we only found one RCT and this only included women with a healthy contralateral fallopian tube.
- Salpingotomy by laparoscopy and salpingotomy by laparotomy seem equally effective at increasing subsequent intrauterine pregnancy rates.
- Salpingotomy by laparoscopy may lead to fewer complications and shorter recovery times compared with salpingotomy by laparotomy but may also be less likely to remove all the trophoblast.
- Salpingotomy seems equally as effective as methotrexate (single or multiple dose) at increasing subsequent intrauterine or ectopic pregnancy rates in women with small unruptured tubal pregnancies.
- We found no direct information from RCTs about salpingotomy compared with expectant management in women with unruptured tubal ectopic pregnancies.

Benefits and harms

Salpingotomy by laparoscopy versus salpingotomy by laparotomy:

We found two systematic reviews (search dates 2006; [34] and 2007, [35] 2 RCTs, 165 haemodynamically stable women with a small unruptured tubal pregnancy) comparing salpingotomy by laparoscopy with salpingotomy by laparotomy. The second review included the same RCTs as the first review, performed a similar analysis, and came to similar conclusions. We have, therefore, reported the later review in detail. [35] See Comment, p 10 for more information.

Subsequent pregnancy

Salpingotomy by laparoscopy compared with salpingotomy by laparotomy Salpingotomy by laparoscopy and salpingotomy by laparotomy seem equally effective at increasing subsequent intrauterine pregnancy rates (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Subsequent intrauterine pregnancy					
[35] Systematic review	Haemodynamically stable women, each with a small unruptured tubal pregnancy, who desired future fertility 2 RCTs in this analysis Subgroup analysis	**Subsequent intrauterine pregnancy rates** 35/61 (57%) with salpingotomy by laparoscopy 35/66 (53%) with salpingotomy by laparotomy	RR 1.08 95% CI 0.80 to 1.48	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Repeat ectopic pregnancy					
[35] Systematic review	Haemodynamically stable women, each with a small unruptured tubal pregnancy, who desired future fertility	**Repeat ectopic pregnancy rate** 4/61 (7%) with salpingotomy by laparoscopy 9/66 (14%) with salpingotomy by laparotomy	RR 0.48 95% CI 0.16 to 1.49	⟷	Not significant

Salpingotomy versus salpingectomy:
See option on Salpingectomy, p 8 .

Salpingotomy versus expectant management:
See option on Expectant management, p 4 .

Salpingotomy versus methotrexate:
See option on Methotrexate, p 5 .

Comment:

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. [34] Laparoscopic procedure leads to fewer pelvic adhesions compared with laparotomy, which may result in higher future fertility rate; [70] [71] however, a systematic review found no statistical difference in subsequent pregnancy rates following salpingotomy by laparoscopy or laparotomy. [35] One multi-centre observational study reported major surgical complication rates of 2.7/1000 for diagnostic laparoscopic procedures and 17.9/1000 for operative laparoscopy. [72] The major complication to arise following operative laparoscopic procedures is injury to the bowel (0.4–0.7/1000 cases) or to a major vessel (0.2/1000 cases). [73] One non-systematic review found that failure or rate of persistent ectopic pregnancy ranged from 3% to 20% in 10 cohort studies comparing laparotomy salpingotomy with laparoscopic salpingotomy. [66]

One population-based study found that the failure rate of laparoscopic salpingotomy was 6.6%. [74] It found that pre-therapeutic beta hCG levels (>1960 IU/L) were significantly associated with treatment failure of laparoscopic salpingotomy.

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. [75]

GLOSSARY

Beta hCG The pregnancy hormone beta human chorionic gonadotrophin.

Contralateral tube The opposite tube to that affected by the ectopic pregnancy.

Discriminatory zone 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.

Expectant management (ectopic pregnancy) 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, and is 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 until the start of their additional treatment. The FRR is the ratio of fecundity between the test treatment (e.g., salpingotomy) and 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 with salpingectomy. Thus, an FRR of 1.9 for intrauterine pregnancy indicates that the probability of intrauterine pregnancy is 90% higher with salpingotomy than with salpingectomy.

Fertility outcome This outcome represents the rates of subsequent intrauterine pregnancy, repeat ectopic pregnancy, and live birth rate. Such pregnancies may either be spontaneous or be 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 the 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.

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.

Persistent trophoblast 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 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 This 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 A procedure in which 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.

Short Form-36 [SF-36] Health Survey Includes one multi-item scale that assesses eight health concepts: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and wellbeing), limitations in usual role activities because of emotional problems, vitality (energy and fatigue), and general health perceptions. The survey was constructed for self-administration by people aged 14 years or older, and for administration by a trained interviewer in person or by telephone.

Tubal excision or salpingectomy The surgical removal of the tube affected by the ectopic pregnancy.

Tubal patency Freedom from obstruction; assessed by the passage of dye at hysterosalpingogram, or at second-look laparoscopy, or by 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.

SUBSTANTIVE CHANGES

Salpingectomy Condition restructured. One RCT added. [64] Categorisation unchanged (likely to be beneficial).

Expectant management Condition restructured. No new evidence. Categorisation unchanged (unknown effectiveness).

Methotrexate Condition restructured. No new evidence. Categorisation unchanged (likely to be beneficial).

Salpingotomy Condition restructured. No new evidence. Categorisation changed from 'beneficial' to 'likely to be beneficial'.

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Tubal ectopic pregnancy

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Disclaimer

GRADE **Evaluation of interventions for Tubal ectopic pregnancy.**

Important outcomes			Subsequent pregnancy						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for unruptured tubal ectopic pregnancy on subsequent fertility?									
5 (295) [35] [36]	Subsequent pregnancy	Methotrexate (single or multiple dose) versus salpingotomy	4	–1	0	0	0	Moderate	Quality point deducted for early termination of planned recruitment in 1 RCT
1 (446) [64]	Subsequent pregnancy	Salpingectomy versus salpingotomy	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (127) [35]	Subsequent pregnancy	Salpingotomy by laparoscopy versus salpingotomy by laparotomy	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.