Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

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THE MANAGEMENT OF TUBAL PREGNANCY

This guideline replaces *The management of tubal pregnancies*, produced in October 1999.

1. Purpose and scope

There were 13 maternal deaths resulting from ectopic pregnancy in the UK during the period 1997–99. The incidence of ectopic pregnancy has remained static in recent years (11.1/1000 pregnancies) and nearly 32000 ectopic pregnancies are diagnosed in the UK within a three year period.[1]

Tubal pregnancy can be managed by laparotomy, operative laparoscopy, medically and occasionally by observation alone. Management must be tailored to the clinical condition and future fertility requirements of the woman.

One concern raised in the Confidential Enquiry into Maternal Deaths was the difficulty encountered in diagnosing ectopic pregnancy.[1] The remit of this guideline is not to discuss the methods available for the diagnosis of ectopic pregnancy but to discuss the methods and techniques that may be used once a diagnosis has been made. However, it is acknowledged that, when discussing the expectant and medical management of tubal pregnancy, in some women the site of pregnancy implantation will be uncertain.

2. Identification and assessment of evidence

Previous guidelines within this subject area were sought using the sites and gateways laid out in the RCOG clinical governance advice document *Searching for evidence*.[2] The Cochrane Library (including the Database of Systematic Reviews, DARE and the trials registry) and Medline were searched using a combination of MeSH terms and keywords. The keywords used were 'ectopic pregnancy', 'tubal pregnancy', 'laparoscopy', 'laparoscopic', 'salpingectomy', 'salpingotomy', 'methotrexate', 'persistent trophoblast' and 'beta human chorionic gonadotrophin (βhCG).' Reference lists of the articles identified were hand searched for additional articles, and some experts within the field were contacted.

The levels of evidence and the grades of recommendations used in this guideline for effectiveness originate from the US Agency for Healthcare Research and Quality. Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as 'good practice points'.

3. Surgical management of tubal pregnancy

A laparoscopic approach to the surgical management of tubal pregnancy, in the haemodynamically stable patient, is preferable to an open approach. **A**

Laparoscopic surgery has been compared with open surgery in 228 women in three randomised controlled trials (RCTs). Laparoscopic procedures were associated with shorter operation times, less intraoperative blood loss, shorter hospital stays and lower analgesic requirements.[3–7] There was no difference in overall tubal patency rates (RR 0.89, 95% CI 0.74–1.1) between the two approaches. In women who desired future fertility (n = 145), the subsequent intrauterine pregnancy rates were similar (RR 1.2, 95% CI 0.88–1.15) and there was a trend toward lower repeat ectopic pregnancy rates if a laparoscopic approach was used (RR 0.43, 95% CI 0.15–1.2). However, laparoscopic salpingotomy was less successful than an open approach in elimination of the tubal pregnancy (RR 0.90, 95% CI 0.83–0.97), reflected in a trend towards higher rates of persistent trophoblast (RR 3.6, 95% CI 0.63–21.0).

Evidence level Ia

It is important to note that these three trials only include 228 women, which is insufficient to look at small differences between the two interventions with respect to many of the outcomes examined.

Management of tubal pregnancy in the presence of haemodynamic instability should be by the most expedient method. In most cases this will be laparotomy. **C**

There is no role for medical management in the treatment of tubal pregnancy or suspected tubal pregnancy when a patient shows signs of hypovolaemic shock. Transvaginal ultrasonography can rapidly confirm the presence of haemoperitoneum if there is any diagnostic uncertainty[8] but expedient resuscitation and surgery should be undertaken. Experienced operators may be able to manage laparoscopically women with even a large haemoperitoneum safely[9] but the surgical procedure which prevents further blood loss most quickly should be used. In most centres this will be laparotomy.

Evidence level IV

In the presence of a healthy contralateral tube there is no clear evidence that salpingotomy should be used in preference to salpingectomy. **B**

A number of systematic reviews have examined reproductive outcomes following the management of tubal pregnancy with either salpingotomy or salpingectomy. However, there are no RCTs that specifically compare laparoscopic (or open) salpingectomy and salpingotomy. The reviews published on this subject include data from observational studies, often a mixture of both cohort studies and case series, as well as a mixture of open and laparoscopic comparisons. These reviews show that there is not an increased chance of subsequent intrauterine pregnancy after salpingotomy compared with salpingectomy. However, these data must be interpreted with caution. Included studies are subject to a wide range of biases relating to patient selection, surgical procedures used, length of follow-up and the proportion of patients lost to follow-up.[10–16]

Evidence level IIa

There are four recent cohort studies that specifically compare laparoscopic conservative and radical treatments of ectopic pregnancy[17–20] Silva *et al.*[17] examined reproductive outcomes prospectively in 143 women undergoing laparoscopic salpingectomy (55.9%) or laparoscopic salpingotomy (36.4%). The intrauterine pregnancy rates were similar when comparing the two groups but there was a trend towards higher subsequent ectopic pregnancy in the salpingotomy arm (intrauterine pregnancy 60% versus 54%, RR 1.11, 95% CI 0.74–1.68; recurrent ectopic pregnancy 18% versus 8%, RR 2.38, 95% CI 0.57–10.01).[17]

Job-Spira *et al.*,[18] in a study of 155 women, performed a multivariate analysis on reproductive outcomes following ectopic pregnancy. They demonstrated a trend towards improved subsequent intrauterine pregnancy rates with conservative surgery (hazard ratio 1.22, 95% CI 0.68–2.20). The cumulative pregnancy rates at one year were 72.4% after conservative and 56.3% after radical surgery.[18]

In study by Mol *et al.*[19] of a cohort of 135 women, the fecundity rate ratio (FRR) when comparing laparoscopic salpingotomy to salpingectomy during the 18-month follow-up period was 1.4 (95% CI 0.68–2.7) for women with a healthy contralateral tube and 3.1 (95% CI 0.76–12.0) for women with contralateral tubal disease. The three-year cumulative pregnancy rate was 62% after salpingotomy and 38% after salpingectomy.[19]

In a study by Bangsgaard *et al.*[20] reviewing a cohort of 276 women undergoing salpingotomy or salpingectomy, the subsequent cumulative pregnancy rate at seven years was 89% following salpingotomy and 66% following salpingectomy (log rank $P<0.05$). The hazard ratio for intrauterine pregnancy following salpingectomy was 0.630 (95% CI 0.421–0.940) when compared with salpingotomy.[20]

Evidence level IIa

These results suggest that there may be a higher subsequent intrauterine pregnancy rate associated with salpingotomy but the magnitude of this benefit may be small. Data from future RCTs examining this question are needed. The use of conservative surgical techniques exposes women to a small risk of tubal bleeding in the immediate postoperative period and the potential need for further treatment for persistent trophoblast. Both these risks and the possibility of further ectopic pregnancies in the conserved tube should be discussed if salpingotomy is being considered by the surgeon or requested by the patient.

Laparoscopic salpingotomy should be considered as the primary treatment when managing tubal pregnancy in the presence of contralateral tubal disease and the desire for future fertility. **B**

Four cohort studies have examined reproductive outcomes in women with contralateral tubal disease and show a trend toward a greater subsequent intrauterine pregnancy following laparoscopic salpingotomy compared with laparoscopic salpingectomy (Silva *et al.*,[17] intrauterine pregnancy rate 49% versus 27%; Mol *et al.*,[19] FRR 3.1, 95% CI 0.76–12; Job-Spira *et al.*,[18] OR 4.0, 95% CI 0.96–16.7); Bangsgaard *et al.*,[20] hazard ratio 0.463 (95% CI 0.262–0.820).

In women with a damaged or absent contralateral tube *in vitro* fertilisation is likely to be required if salpingectomy is performed. Because of the requirement for postoperative follow-up and the treatment of persistent trophoblast, the short-term costs of salpingotomy are greater than salpingectomy.[21] However, if the subsequent need for assisted conception is taken into account, an increase in intrauterine pregnancy rate of only 3% would make salpingotomy more cost effective than salpingectomy.[19] In the presence of contralateral tubal disease the use of more conservative surgery is appropriate. Women must be made aware of the risk of a further ectopic pregnancy.

Evidence level IIa

4. Medical management of tubal pregnancy

Medical therapy should be offered to suitable women, and units should have treatment and follow-up protocols for the use of methotrexate in the treatment of ectopic pregnancy. **B**

Many ectopic pregnancies will follow a relatively chronic course and transvaginal ultrasonography combined with serum hCG measurement permits the confident diagnosis of ectopic pregnancy in many women without resort to laparoscopy.[22–24] The use of laparoscopy for the diagnosis of ectopic pregnancy is often the main reason for the use of surgical interventions.

Evidence level IIa

A review of uncontrolled and controlled studies has shown that in stable patients a variety of medical treatments are as effective as surgery.[25] The most widely used medical treatment at present is intramuscular methotrexate given as a single dose calculated from patient body surface area (50 mg/m^2). For most women this will be between 75 mg and 90 mg. Serum hCG levels are checked on days four and seven and a further dose is given if hCG levels have failed to fall by more than 15% between day four and day seven.[16,27,28] Large uncontrolled studies have reported that about 14% of women will require more than one dose of methotrexate and less than 10% of women treated with this regimen will require surgical intervention.[25,26] This has also been reported in randomised trials comparing methotrexate with laparoscopic surgery.[27,28]

Evidence level IIa

If medical therapy is offered, women should be given clear information (preferably written) about the possible need for further treatment and adverse effects following treatment. Women should be able to return easily for assessment at any time during follow-up.

B

Pooled data from uncontrolled studies suggests that at least 15% of medically treated women will require more than one dose of methotrexate and 7% will experience tubal rupture during follow-up.[15,16] Nearly 75% will experience abdominal pain following treatment. Occasional women will also experience conjunctivitis, stomatitis and gastrointestinal upset. Differentiating so-called 'separation pain' due to a tubal abortion from pain due to tubal rupture can be difficult and a proportion of women will need to be admitted for observation and assessment by transvaginal ultrasound following methotrexate therapy.[25,29] Women should also be advised to avoid sexual intercourse during treatment, to maintain ample fluid intake and to use reliable contraception for three months after methotrexate has been given, because of a possible teratogenic risk.

Evidence level IIa

Women most suitable for methotrexate therapy are those with a serum hCG below 3000 iu/l, and minimal symptoms.

B

Large uncontrolled studies have used methotrexate in women presenting at a wide range of serum hCG concentrations, although the great majority of women in these studies have had serum hCG concentrations below 5000 iu/l.[15,16] Duration of follow up, the need for further doses of methotrexate and the likelihood of surgical intervention all increase with serum hCG concentration at presentation.[26]

Although medical therapy can be successful at serum hCG concentrations considerably higher than 3000 iu/l, quality-of-life data suggest that methotrexate is only an attractive option for women with an hCG below 3000 iu/l.[30,31]

Evidence level IIa

Data concerning the effect of ectopic pregnancy size on outcome are less clear but women with large adnexal masses are more likely to have already ruptured.[26]

The presence of cardiac activity in an ectopic pregnancy is associated with a reduced chance of success following medical therapy and should be considered a contraindication to medical therapy.[15,16]

Outpatient medical therapy with single-dose methotrexate is associated with a saving in treatment costs.

A

One important advantage of medical therapy is the potential for considerable savings in treatment costs. Economic evaluations undertaken alongside randomised trials comparing methotrexate and laparoscopic surgery have shown direct costs for medical therapy to be less than half of those associated with laparoscopy. Indirect costs are also less with women and their carers losing less

Evidence level Ib

time from work.[30,31] However, in both these randomised trials no cost saving was seen at serum hCG levels above 1500 iu/l due to the increased need for further treatment and prolonged follow-up.

Evidence level Ib

5. Expectant management of pregnancy of unknown location

Expectant management is an option for clinically stable women with minimal symptoms and a pregnancy of unknown location.

C

In the management of suspected ectopic pregnancy there is a serum hCG level at which it is assumed that all viable intrauterine pregnancies will be visualised by transvaginal ultrasound. This is referred to as the discriminatory zone.[32] When serum hCG levels are below the discriminatory zone (<1000 iu) and there is no pregnancy (intra- or extrauterine) visible on transvaginal ultrasound scan, the pregnancy can be described as being of unknown location.[33]

The concept of a discriminatory zone has limitations. Levels of hCG of 1000 iu/l, 1500 iu/l and 2000 iu/l have been used as discriminatory levels.[23,24,33] These levels are dependent upon the quality of the ultrasound equipment, the experience of the sonographer, prior knowledge of the woman's risks and symptoms and the presence of physical factors such as uterine fibroids and multiple pregnancy. For specialised units performing high resolution vaginal ultrasound with prior knowledge of the woman's symptoms and serum hCG, a discriminatory zone of 1000 iu/l can be used. In other units offering a diagnostic transvaginal scan without prior clinical or biochemical knowledge a discriminatory zone of 1500 iu/l or 2000 iu/l is acceptable.

Five observational studies have shown that 44–69% of pregnancies of unknown location resolve spontaneously with expectant management.[34–38] It is probable that a number of the spontaneously resolving pregnancies or trophoblast in regression[35] in these studies were small ectopic pregnancies which were spontaneously absorbed or resolved by tubal abortion. The remainder were early intrauterine pregnancies that miscarried. Ectopic pregnancy was subsequently diagnosed in 14–28% of cases of pregnancy of unknown location.[36,38]

Evidence level III

Using an initial upper level of serum hCG of 1000–1500 iu/l to diagnose pregnancy of unknown location, women with minimal or no symptoms at risk of ectopic pregnancy should be managed expectantly with 48–72 hours of follow-up and should be considered for active intervention if symptoms of ectopic pregnancy occur, serum hCG levels rise above the discriminatory level (1000 iu/l) or levels start to plateau.[36,38]

Intervention has been shown to be required in 23–29% of cases[34,36] but with more experience lower intervention levels are achievable.[37] If women are managed expectantly, serial serum hCG measurements should be performed until hCG levels are less than 20 iu/l. In addition, women selected for expectant management of pregnancy of unknown location should be given clear information (preferably written) about the importance of compliance with follow-up and should be within easy access to the hospital treating them.

Expectant management is an option for clinically stable asymptomatic women with an ultrasound diagnosis of ectopic pregnancy and a decreasing serum hCG, initially less than serum 1000 iu/l.

C

Studies examining the role of expectant management of ectopic pregnancy vary in their methods of diagnosis. Laparoscopic identification of ectopic pregnancy prior to expectant management is used in some.[39,40] In others there is no surgical proof that ectopic pregnancies managed expectantly were in fact of ectopic location. In this guideline, only studies with clear ultrasound identification of an ectopic gestation sac or predominantly solid extraovarian adnexal mass or absence of villi

Evidence level III

with endometrial sampling were considered. All reviewed studies required the patient to be clinically stable, with minimal symptoms. Most studies required an adnexal mass of less than 4 cm[41,42] or less than 5 cm[43] and less than 50 ml[43] or 100 ml[42] of free fluid. A fall in initial hCG of greater than 15% in 24 hours was required for entry into one study.[43]

Seven observational studies were reviewed and a total of 478 women were treated expectantly.[39–45] Expectant management was successful in 318 (67%) women. Lower initial hCG levels were a significant predictor of spontaneous resolution.[44] Expectant management was more successful (88%) when the initial hCG level was less than 1000 iu/l,[42] a finding confirmed in a review by Cohen *et al*.[46] In addition, a rapidly decreasing hCG level appears to predict a favourable outcome.[42,45] The lack of an identifiable extrauterine gestational sac on transvaginal ultrasound increased the odds of a spontaneous resolution by 5.6 times.[44] However, it is uncertain whether the initial size of an ectopic pregnancy is a predictor of the eventual outcome, with one study showing no effect.[44] What does appear to be significant to successful resolution is a reduction in the average diameter of the adnexal mass by day seven.[43]

Evidence level III

Expectant management is a useful form of treatment management for ectopic pregnancy in selected cases. It is however only acceptable if it involves minimal risks to the woman. Expectant management should only be used for asymptomatic women with an ultrasound diagnosis of ectopic pregnancy, with no evidence of blood in the pouch of Douglas and decreasing hCG levels that are less than hCG 1000 iu/l at initial presentation and less than 100 ml fluid in the pouch of Douglas. Women managed expectantly should be followed twice weekly with serial hCG measurements and weekly by transvaginal examinations to ensure a rapidly decreasing hCG level (ideally less than 50% of its initial level within seven days) and a reduction in the size of adnexal mass by seven days. Thereafter, weekly hCG and transvaginal ultrasound examinations are advised until serum hCG levels are less than 20 iu/l as there are case reports of tubal rupture at low levels of βhCG.[47] In addition, women selected for expectant management of pregnancy of unknown origin should be counselled about the importance of compliance with follow-up and should be within easy access to the hospital in question.

6. Persistent trophoblast

When salpingotomy is used for the management of tubal pregnancy, protocols should be in place for the identification and treatment of women with persistent trophoblast. ✓

Persistent trophoblast is detected by the failure of serum hCG levels to fall as expected after initial treatment. It is primarily a problem occurring after salpingotomy rather than following salpingectomy. Although, even in the presence of persistent trophoblast, hCG levels may return uneventfully to normal, cases of delayed haemorrhage due to persistent trophoblast have been described[48] and this provides the rationale for following women with serial hCG measurements after treatment and administering methotrexate if levels fail to fall as expected.

In reviews of controlled and uncontrolled studies, rates of persistent trophoblast from pooled data have been 8.1–8.3% after laparoscopic salpingotomy and 3.9–4.1% after open salpingotomy.[15,16,49] Factors that have been suggested as increasing the risk of developing persistent trophoblast include higher preoperative serum hCG levels (>3000 iu/l),[50] a rapid preoperative rise in serum hCG[51] and the presence of active tubal bleeding.[50]

Evidence level IV

Following the elimination of all trophoblastic tissue, serum hCG levels will fall a predictable clearance curve[49] but the proportion of women treated for persistent trophoblast will in part depend upon the frequency of postoperative measurement and the cut off used for its definition.

In one study the treatment of persistent trophoblast was initiated if the serum hCG was greater than 10% of the preoperative level ten days after surgery.[52] Another study has suggested initiating treatment if hCG levels are above 65% of their initial level at 48 hours after surgery.[53] The definition used to define persistent trophoblast within a unit will affect both the reporting of its incidence and the effectiveness of its treatment. Currently, there are insufficient data to recommend one method of diagnosing and treating persistent trophoblast over another but protocols for its early identification and treatment should be used.

Evidence level IV

Methotrexate at a dose of 50 mg/m^2 has been widely used as a single dose instead of a repeat surgical procedure, although no formal comparative studies have been performed. The use of prophylactic methotrexate at the time of laparoscopic salpingotomy has also been reported and in one randomised trial and when compared with simple salpingotomy alone there was a significant reduction in the rate of persistent trophoblast (1.9% versus 14%, RR 0.12, 95% CI 0.02–0.97).[54]

7. Service provision and training

All NHS trusts should provide an early pregnancy assessment unit with direct access for general practitioners and accident and emergency departments. Available facilities for the management of suspected ectopic pregnancy should include:

- **diagnostic and therapeutic algorithms**
- **transvaginal ultrasound**
- **serum hCG estimations.**

In line with previous recommendations from guidelines on the management of early pregnancy complications and RCOG study groups, women with suspected ectopic pregnancy should be managed in dedicated early pregnancy clinics.[55,56]

Evidence level IV

Ideally, these clinics should be sited in a dedicated area with appropriate staffing, and should be available on a daily basis, at least during the working week.

Clinicians undertaking the surgical management of ectopic pregnancy must have received appropriate training. Laparoscopic surgery requires appropriate equipment and trained theatre staff.

Clinical staff should be trained to undertake both the open and laparoscopic management of ectopic pregnancy. This should include the safe use of monopolar and bipolar diathermy. They should have attended an appropriate RCOG-approved course in basic or intermediate laparoscopic skills. They should also be supported with sufficient efficient modern equipment to facilitate safe surgery.

Evidence level IV

Retrospective studies of the laparoscopic management of ectopic pregnancy report a low rate of intraoperative and postoperative complications and demonstrate that surgery can safely be undertaken by appropriately trained registrars.[57,58]

8. Anti-D immunoglobulin

Nonsensitised women who are rhesus negative with a confirmed or suspected ectopic pregnancy should receive anti-D immunoglobulin.

In accordance with RCOG Guideline No. 22 it is recommended that anti-D immunoglobulin at a dose of 250 iu (50 microgrammes) be given to all nonsensitised women who are rhesus negative and who have an ectopic pregnancy.[59]

Evidence level IV

9. Patient involvement

Women should be carefully advised, whenever possible, of the advantages and disadvantages associated with each approach used for the treatment of ectopic pregnancy. They should participate fully in the selection of the most appropriate treatment. ✓

The psychological impact of early pregnancy loss may seriously affect a significant proportion of women, their partners and families.[55] Plans for follow-up should be clearly recorded in the discharge letter from the early pregnancy clinic. Women should be provided with written information concerning their treatment options, follow-up and the availability of local and national support services.

Evidence level IV

Evidence has shown that there may be little difference in psychological outcomes when comparing surgical and medical methods of managing ectopic pregnancy.[28,60]

10. Audit topics

- The proportion of women who are haemodynamically stable with ectopic pregnancy treated laparoscopically.
- The proportion of women managed expectantly with 'pregnancy of unknown location' who required surgical intervention.
- The proportion of women with persistent trophoblast after salpingotomy.

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

This Guideline was produced on behalf of the Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists by:
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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

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