

Ectopic pregnancy and miscarriage

Evidence Update December 2014

A summary of selected new evidence relevant to NICE clinical guideline 154 'Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage' (2012)

Evidence Update 71



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Introduction

Evidence Updates are intended to increase awareness of new evidence – they do not replace current NICE guidance and do not provide formal practice recommendations.

Evidence Updates reduce the need for individuals, managers and commissioners to search for new evidence. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline.

This Evidence Update provides a summary of selected new evidence published since the literature search was last conducted for the following NICE guidance:

¹  [Ectopic pregnancy and miscarriage](#). NICE clinical guideline 154 (2012)

A search was conducted for new evidence from 8 February 2012 to 8 July 2014. A total of 5326 pieces of evidence were initially identified. After removal of duplicates, a series of automated and manual sifts were conducted to produce a list of the most relevant references. The remaining 39 references underwent a rapid critical appraisal process and then were reviewed by an [Evidence Update Advisory Group](#), which advised on the final list of 10 items selected for the Evidence Update. See [Appendix A](#) for details of the evidence search and selection process.

Evidence selected for inclusion in this Evidence Update may highlight a potential impact on guidance: that is, a high-quality study, systematic review or meta-analysis with results that suggest a change in practice. Evidence that has no impact on guidance may be a key read, or may substantially strengthen the evidence base underpinning a recommendation in the NICE guidance.

The Evidence Update gives a preliminary assessment of changes in the evidence base and a final decision on whether the guidance should be updated will be made by NICE according to its published processes and methods.

This Evidence Update was developed to help inform the review proposal on whether or not to update NICE clinical guideline 154 ([NICE CG154](#)). The process of updating NICE guidance is separate from both the process of an Evidence Update and the review proposal.

See the NICE clinical guidelines [methods guides](#) for further information about updating clinical guidelines.

NICE Pathways

NICE pathways bring together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams. The following NICE Pathways cover advice and recommendations related to this Evidence Update:

- [Ectopic pregnancy and miscarriage](#). NICE Pathway

Quality standards

- [Ectopic pregnancy and miscarriage](#). NICE quality standard 69

Feedback

If you would like to comment on this Evidence Update, please email contactus@evidence.nhs.uk

¹ [NICE-accredited guidance](#)

Key points

The following table summarises the key points for this Evidence Update and indicates whether the new evidence may have a potential impact on [NICE CG154](#). Please see the full commentaries for details of the evidence informing these key points.

The section headings used in the table below are taken from [NICE CG154](#).

Evidence Updates do not replace current NICE guidance and do not provide formal practice recommendations.

Key point	Potential impact on guidance	
	Yes	No
<p>Diagnosis of viable intrauterine pregnancy and of ectopic pregnancy</p> <p><i>A scoring system for predicting viable intrauterine pregnancy</i></p> <ul style="list-style-type: none"> Among a general cohort of women, a simple scoring system combining demographic and symptom variables (maternal age and amount of bleeding) with initial ultrasound variables (mean gestation-sac diameter, mean yolk-sac diameter, and presence of a fetal heart beat) appears able to predict pregnancy viability beyond the first trimester. <p><i>Diagnostic accuracy of serum human chorionic gonadotrophin (hCG) measurement strategies</i></p> <ul style="list-style-type: none"> In women with a pregnancy of unknown location, the ratio of serum hCG levels at 0 and 48 hours (alone, or in a logistic regression model) appears to be effective in diagnosing ectopic pregnancy. <p><i>Serum progesterone measurement to determine viability in early pregnancy</i></p> <ul style="list-style-type: none"> A single progesterone measurement for women in early pregnancy with bleeding or pain appears able to distinguish between viable and non-viable pregnancy. 	✓*	✓
<p>Management of miscarriage</p> <p><i>Expectant versus surgical management of miscarriage</i></p> <ul style="list-style-type: none"> For women with miscarriage at less than 14 weeks gestation, rates of incomplete miscarriage, blood transfusion, and unplanned surgery appear to be higher with expectant management of miscarriage than with surgery. Costs of expectant management appear to be lower than for surgery, and infection rates between the strategies are similar. Existing evidence does not firmly indicate the superiority of either strategy, and women's preferences should be a key consideration. 		✓

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE. For further details of this evidence in the context of current guidance, please see the full commentary.

Key point	Potential impact on guidance	
	Yes	No
<p>Misoprostol dose for medical management of miscarriage</p> <ul style="list-style-type: none"> In outpatient management of miscarriage, a 400 microgram dose of vaginal misoprostol² appears to be as effective at inducing complete miscarriage as an 800 microgram dose, and is associated with a reduced rate of fever and rigors, and improved patient satisfaction. <p>Cost effectiveness of medical versus surgical management of miscarriage</p> <ul style="list-style-type: none"> The cost effectiveness of medical and surgical management of miscarriage appears to depend on the circumstances. For example, manual vacuum aspiration in an outpatient setting appears to be cost saving versus medical management. However, for incomplete or inevitable miscarriage, medical management appears to be cost saving versus surgery. 	✓*	✓
<p>Management of ectopic pregnancy</p> <p>Expectant management of ectopic pregnancy</p> <ul style="list-style-type: none"> Among selected women with an ectopic pregnancy or a pregnancy of unknown location, who also have low and stabilising serum hCG levels, expectant management for many women appears to be successful (that is, leads to an uneventful decline of serum hCG without the need for further intervention), with an efficacy similar to methotrexate³. <p>Fertility after medical or surgical management of ectopic pregnancy</p> <ul style="list-style-type: none"> Among women receiving medical or surgical treatment for ectopic pregnancy appropriate to their circumstances (for example, their accompanying symptoms, and the status of the contralateral fallopian tube), ongoing fertility in the 2–3 years after treatment appears to be similar between methotrexate³, salpingotomy and salpingectomy. 	✓*	✓

² Although this use is common in UK clinical practice, at the time of publication of this Evidence Update, misoprostol did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented.

³ Although this use is common in UK clinical practice, at the time of publication of this Evidence Update, methotrexate did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

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1 Commentary on new evidence

These commentaries focus on the 'key references' identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update, which are shown in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from [NICE CG154](#).

1.1 [Support and information giving](#)

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.2 [Early pregnancy assessment services](#)

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.3 [Symptoms and signs of ectopic pregnancy and initial assessment](#)

No new key evidence for this section was selected for inclusion in this Evidence Update.

1.4 [Diagnosis of viable intrauterine pregnancy and of ectopic pregnancy](#)

A scoring system for predicting viable intrauterine pregnancy

[NICE CG154](#) does not currently recommend specific tools or scoring systems to predict the viability of intrauterine pregnancy.

A prospective observational cohort study (n=1435) in the UK by [Bottomley et al. \(2013\)](#) developed and evaluated a simple scoring system to predict viable intrauterine pregnancy beyond the first trimester. Women at a single early pregnancy assessment centre, with a positive pregnancy test and undergoing transvaginal ultrasound for pregnancies of no more than 84 days' gestation, were recruited consecutively over a 9-month period. Exclusion criteria were: post-partum presentation; complications from pregnancy termination; previously diagnosed early pregnancy loss; multiple pregnancy; absence of pregnancy; and unknown first-trimester outcome. Bleeding was scored from 0 to 4 (0=no bleeding, 4=clots or 'flooding') and pain was scored from 0 to 10 (0=no pain at all, 10=the worst pain imaginable). Transvaginal ultrasound was then performed, and whether or not a yolk sac, embryo, and fetal heartbeat were seen was recorded. Mean gestation-sac diameter, yolk-sac diameter, and crown-rump length were also measured.

Depending on the outcome of the assessment, women were managed according to Royal College of Obstetricians and Gynaecologists guidelines (2006). Women with inconclusive ultrasound findings were managed expectantly. First-trimester outcomes were obtained from the early pregnancy unit or fetal medicine databases or by telephone contact. Outcomes were ongoing intrauterine pregnancy (a live fetus seen at a routine 11–14 week scan) or early pregnancy loss (miscarriage, ectopic pregnancy or failed pregnancy of unknown location). Women lost to follow-up or who terminated the pregnancy were excluded from analysis.

Data were randomly split 2:1 into a training set and a test set. Missing data were managed via multiple imputation. Logistic regression was used in the training data set to determine the influence of selected variables. Three different models were created to assess the influence of: demographics and symptoms alone; ultrasound findings alone; and a combination of demographics, symptoms and ultrasound variables. All variables were tested for significance

in a univariable logistic regression model, and variables with $p < 0.1$ were retained for multivariable logistic regression. The models were used to derive 3 scoring systems in which points were assigned to each variable individually (for example, maternal age < 35 years = 0 points, maternal age ≥ 40 years = -4 points). The systems were then assessed using data from the test set. A receiver operating characteristic (ROC) curve was created to describe the relationship between the sensitivity and the false-positive rate for the use of the models to predict ongoing viability, and area under the curve (AUC) was calculated for each scoring system.

Among the 1435 women (median gestational age at presentation = 50 days), an ongoing viable pregnancy was seen in 885 (61.7%) and early pregnancy loss was observed in 550 (38.3%). The abilities of the 3 scoring systems to predict ongoing viability were:

- Demographic and symptom variables (maternal age and amount of bleeding) alone: AUC = 0.724 (95% confidence interval [CI] 0.692 to 0.756) in the training set and AUC = 0.729 (95% CI 0.684 to 0.774) in the test set.
- Ultrasound variables (mean gestation-sac diameter, mean yolk-sac diameter, and presence of a fetal heart beat) alone: AUC = 0.873 (95% CI 0.850 to 0.897) in the training set and AUC = 0.900 (95% CI 0.871 to 0.928) in the test set
- Demographic and ultrasound variables combined: AUC = 0.901 (95% CI 0.881 to 0.920) in the training set and AUC = 0.924 (95% CI 0.900 to 0.947) in the test set.

The final scoring system (demographic, symptom and ultrasound variables combined) was then assessed further. The score range of this system was -12 to +12 points, which equated to an estimated chance of a viable pregnancy beyond the first trimester of 4.2% to 99.8%. When the combined scoring system was assessed in the test data set, the sensitivity was 0.92, specificity 0.73, positive predictive value 84.7% and negative predictive value 85.4%.

Limitations of the evidence included that:

- The Royal College of Obstetricians and Gynaecologists guidelines used in this study for diagnosing a missed miscarriage have since been revised slightly, although the authors suggested this would not have substantially affected findings.
- Medical intervention cannot prevent miscarriage therefore a prediction model cannot change pregnancy outcomes. However, it was noted by the authors that further data to help predict pregnancy viability could benefit patients' psychological outcomes.
- The study involved relatively high-risk women presenting mainly with pain or bleeding to an early pregnancy assessment unit, which may limit generalisability to other settings.
- Data on BMI and smoking were not collected, and data on bleeding or pain were missing for 18% of women.

The evidence suggests that among a general cohort of women, a simple scoring system combining demographic and symptom variables (maternal age and amount of bleeding) with initial ultrasound variables (mean gestation-sac diameter, mean yolk-sac diameter, and presence of a fetal heart beat) appears able to predict pregnancy viability beyond the first trimester. [NICE CG154](#) does not currently recommend specific tools or scoring systems to predict the viability of intrauterine pregnancy, and the availability of more information on which to base estimates of viability in early pregnancy at around 7 weeks could be useful to both healthcare professionals and patients. These data may therefore have a potential impact on the guideline. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

Although this study involved a large general cohort, further validation of these results in a variety of settings wider than this study's single centre would be useful. Assessment is also

needed of whether early warning for women who are likely to miscarry can modify the psychological morbidity associated with pregnancy loss.

Key reference

Bottomley C, Van Belle V, Kirk E et al. (2013) [Accurate prediction of pregnancy viability by means of a simple scoring system](#). *Human Reproduction* 28: 68–76

Diagnostic accuracy of serum human chorionic gonadotrophin (hCG) measurement strategies

In a woman with a pregnancy of unknown location (that is, a woman who has a positive pregnancy test but no pregnancy can be seen on an ultrasound scan), [NICE CG154](#) recommends taking 2 serum hCG measurements as near as possible to 48 hours apart (but no earlier) to determine subsequent management. The nature of subsequent management should be determined by whether serum hCG levels have increased by more than 63%, decreased by more than 50%, or have changed somewhere in between these two values. [NICE CG154](#) also states: Do not use serum hCG measurements to determine the location of the pregnancy.

A systematic review and meta-analysis by [van Mello et al. \(2012\)](#) analysed the diagnostic accuracy of various serum hCG measurement strategies in women with pregnancy of unknown location. Only studies reporting final pregnancy outcomes (intrauterine pregnancy, ectopic pregnancy, treated persistent pregnancy of unknown location, or failed pregnancy of unknown location) were included. A total of 23 cohort studies (n=9078) were identified: 10 used a single serum hCG cut-off point; 4 used a serum hCG ratio (hCG level at 48 hours versus 0 hours); and 6 used logistic regression modelling (serum hCG ratio combined with different variables: clinical symptoms, transvaginal ultrasound findings, maternal age, gestational age, risk factors for ectopic pregnancy, and progesterone levels). The other 3 studies used combinations of serum hCG, serum progesterone and uterine curettage findings.

Sensitivity and specificity were calculated for each study and results were combined in ROC space. Bivariate regression analysis was used to obtain summary estimates of sensitivity and specificity and to construct summary ROC (sROC) curves. The threshold serum hCG value to define a positive pregnancy test result differed across the studies; therefore accuracy of all reported threshold values was measured. To avoid biasing results towards studies reporting several thresholds, a stratified bootstrap approach was used to incorporate different thresholds from the same study in the model. Only data for ectopic pregnancy outcomes could be meta-analysed (other pregnancy outcome measures were too heterogeneous across the studies). Additionally, because of the heterogeneity between studies in serum hCG thresholds used to define a positive pregnancy, sROC curves were compared rather than pooled estimates of sensitivity and specificity.

The sROC curves showed that serum hCG ratios and logistic regression were better at diagnosing ectopic pregnancy than absolute single serum hCG levels (results presented graphically). From the sROC curves, serum hCG ratios appeared to have a higher sensitivity, but regression models had a better specificity. The authors noted that regression models often involve complex computer analyses, and measuring serum hCG ratio may be easier to implement in clinical practice.

Limitations of the evidence included that:

- All included studies were cohort studies – no randomised data were available.
- Study populations differed. Most US studies evaluated women presenting to emergency departments (where ultrasound may not always be used to distinguish between pregnancy of unknown location and probable ectopic pregnancy). Whereas in European

studies, women were evaluated in early pregnancy units, which may have had a more strict ultrasound definition of pregnancy of unknown location.

- All studies used the outcome of the serum hCG test to determine the type of reference test. Therefore, the reference standard was neither the same for all patients, nor was it independent of the index test. Additionally, reference standard test results were not interpreted without knowing the result of the index test.
- Diagnosis of ectopic pregnancy differed across studies. Not all cases were confirmed laparoscopically, and various alternative ultrasound or other reference tests were used.
- Ectopic pregnancy was the only outcome that could be meta-analysed, but this may not be the most patient-centred outcome.

The evidence suggests that in women with a pregnancy of unknown location, the ratio of serum hCG levels at 0 and 48 hours (alone, or in a logistic regression model) appears to be effective in diagnosing ectopic pregnancy. This is consistent with recommendations in [NICE CG154](#) to base management decisions on the percentage change in 2 serum hCG measurements taken as near as possible to 48 hours apart.

The authors noted that current literature did not provide enough data on the diagnostic criteria used to distinguish between pregnancies that will lead to a viable intrauterine pregnancy, those pregnancies not needing intervention because they are failing, and those where intervention is needed to avoid risk to health. Well-defined prospective comparative studies with standardised diagnostic criteria and outcome definitions are needed.

Key reference

van Mello NM, Mol F, Opmeer BC et al. (2012) [Diagnostic value of serum hCG on the outcome of pregnancy of unknown location: a systematic review and meta-analysis](#). *Human Reproduction Update* 18: 603–17

Serum progesterone measurement to determine viability in early pregnancy

[NICE CG154](#) states that for women with a pregnancy of unknown location, when using serial serum hCG measurements, do not use serum progesterone measurements as an adjunct to diagnose either viable intrauterine pregnancy or ectopic pregnancy.

A systematic review and meta-analysis by [Verhaegen et al. \(2012\)](#) examined the accuracy of a single progesterone measurement in early pregnancy to discriminate between viable and non-viable pregnancy. The review included cohort studies of women with spontaneous pregnancy (<14 weeks gestation) that used a single serum progesterone measurement to predict viable intrauterine pregnancy, miscarriage, or ectopic pregnancy on the basis of combinations of pregnancy test, ultrasound scan, laparoscopy, and histological examination. Exclusion criteria were: studies of women treated with ovulation induction, progesterone supplementation or in vitro fertilisation; and studies reporting results by 'high' or 'low' progesterone rather than by a cut-off value. A total of 26 studies (n=9436) were included: 7 in women with pain or bleeding plus inconclusive ultrasound diagnosis, and 19 in women with pain or bleeding alone. Sensitivity and specificity were calculated for each study, plotted on sROC space, and subsequently meta-analysed.

Among women with pain or bleeding plus inconclusive ultrasound diagnosis, a meta-analysis of 5 studies (n=1998) with similar progesterone cut-off values (3.2–6 ng/ml) indicated that a single progesterone measurement predicted non-viable pregnancy with pooled sensitivity of 74.6% (95% CI 50.6 to 89.4%), specificity of 98.4% (95% CI 90.9 to 99.7%), positive likelihood ratio of 45 (95% CI 7.1 to 289), and negative likelihood ratio of 0.26 (95% CI 0.12 to 0.57). The median prevalence of non-viable pregnancy in these 5 studies was 73.2%. For progesterone levels lower than the cut-off value (3.2–6 ng/ml), the probability of a non-viable pregnancy was raised to 99.2%. For levels higher than the cut-off, the chance of a non-viable pregnancy was reduced to 44.8%.

For women with pain or bleeding alone, a meta-analysis of 9 studies (n=4689) indicated that a progesterone threshold of 10 ng/ml had a higher specificity for ruling out a viable pregnancy than thresholds of 15 or 20 ng/ml. The 10 ng/ml cut-off predicted a non-viable pregnancy with pooled sensitivity of 66.5% (95% CI 53.6 to 77.4%), specificity of 96.3% (95% CI 91.1 to 98.5%), positive likelihood ratio of 18 (95% CI 7.2 to 45), and negative likelihood ratio of 0.35 (95% CI 0.24 to 0.50). The median prevalence of non-viable pregnancy in these 9 studies was 62.9%. For progesterone levels lower than the cut-off value (10 ng/ml), the probability of a non-viable pregnancy was raised to 96.8%. For levels higher than the cut-off, the chance of a non-viable pregnancy was reduced to 37.2%.

Limitations of the evidence included that:

- In most studies, reporting was poor for describing the reference standard (namely, the pregnancy outcome), discussing uninterpretable results, and explaining study withdrawals.
- Many studies, especially in women without an ultrasound assessment, had prevalences of pregnancy outcomes very different from more recent studies. However, the authors stated that this disparity reflected the heterogeneity of settings and populations evaluated, and may increase the generalisability of this test to different settings.
- Progesterone measurement may not have been standardised across the studies,

The evidence suggests that a single progesterone measurement for women in early pregnancy with bleeding or pain appears able to distinguish between viable and non-viable pregnancy. [NICE CG154](#) states: do not use serum progesterone measurements as an adjunct to diagnose either viable intrauterine pregnancy or ectopic pregnancy. These results may therefore have a potential impact on the guideline. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

It was additionally noted by the Evidence Update Advisory Group that diagnostic tests such as progesterone measurement are unlikely to be used in isolation, and that this study did not look at progesterone measurement as an adjunct to other tests. Further research to evaluate the place of progesterone alongside other diagnostic markers is needed.

Additional information about the study by Verhaegen et al. (2012) is available from an independent [critical appraisal report](#) produced for the Centre for Reviews and Dissemination's Database of Abstracts of Reviews of Effects.

Key reference

Verhaegen J, Gallos ID, van Mello NM et al. (2012) [Accuracy of single progesterone test to predict early pregnancy outcome in women with pain or bleeding: meta-analysis of cohort studies](#). *BMJ* 345: e6077

1.5 [Management of miscarriage](#)

[NICE CG154](#) recommends using expectant management for 7–14 days as the first-line management strategy for women with a confirmed diagnosis of miscarriage. Management options other than expectant management should be explored if the woman is at increased risk of haemorrhage, has previous adverse and/or traumatic experience associated with pregnancy, is at increased risk from the effects of haemorrhage, or there is evidence of infection.

For medical management, women with missed or incomplete miscarriage should be offered vaginal misoprostol. Oral administration is an acceptable alternative if this is the woman's

preference. For a missed miscarriage, a single dose of 800 micrograms of misoprostol⁴ should be used. For an incomplete miscarriage, a single dose of 600 micrograms of misoprostol should be used (800 micrograms can be used as an alternative to allow alignment of treatment protocols for both missed and incomplete miscarriage). Women undergoing medical management of miscarriage should be informed about what to expect throughout the process, including the length and extent of bleeding and the potential side effects of treatment including pain, diarrhoea and vomiting.

For surgical management, where clinically appropriate, women undergoing a miscarriage should be offered a choice of:

- manual vacuum aspiration under local anaesthetic in an outpatient or clinic setting or
- surgical management in a theatre under general anaesthetic.

All treatment options (continued expectant management, medical management, and surgical management) should be discussed with the woman to allow her to make an informed choice.

Expectant versus surgical management of miscarriage

A Cochrane review by [Nanda et al. \(2012\)](#) compared the safety and effectiveness of expectant and surgical management of miscarriage. Randomised controlled trials (RCTs) were included of women with miscarriage (spontaneous pregnancy loss at <14 weeks gestation), with either: ultrasound evidence of retained tissue or of a non-viable pregnancy; or a clinical diagnosis of inevitable miscarriage or incomplete miscarriage. Trials comparing expectant care (which may have included ultrasound examination and antibiotics) and surgical treatment (vacuum aspiration or dilation and curettage, with or without ultrasound examination and antibiotics) were eligible. A total of 7 RCTs (n=1521) were identified. Most trials included a short-term follow-up of up to 2 weeks, with some trials also including longer follow-up of up to 8 weeks.

Primary outcomes were: incomplete miscarriage (based on clinical findings of retained tissue); need for unplanned (or additional) surgical evacuation; complications (such as uterine perforation); localised pelvic infection; need for blood transfusion; and death. Risk ratio (RR) was used for dichotomous data, and mean difference (MD) for continuous data.

The following outcomes were significantly more likely with expectant care than with surgery:

- Incomplete miscarriage by 2 weeks (RR=3.98, 95% CI 2.94 to 5.38, p<0.00001; 4 RCTs, n=1263).
- Incomplete miscarriage by 6–8 weeks (RR=2.56, 95% CI 1.15 to 5.69, p=0.021; 3 RCTs, n=430).
- Unplanned or additional surgery (RR=7.35, 95% CI 5.04 to 10.72, p<0.00001; 5 RCTs, n=1454).
- Blood transfusion (RR=6.45, 95% CI 1.21 to 34.42, p=0.029; 3 RCTs, n=1205).

Pelvic infection was similar between groups (RR=0.63, 95% CI 0.36 to 1.12, p=0.12; 7 RCTs, n=1514). Trials did not specifically report data for the other primary outcomes of complications or death. For the secondary outcome of costs, expectant care cost less than surgery (MD=-£499.10, 95% CI -£613.04 to -£385.16, p<0.00001; 1 RCT, n=800).

⁴ Although this use is common in UK clinical practice, at the time of publication of this Evidence Update, misoprostol did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented.

Limitations of the evidence included that:

- Most trials were of limited size, several were underpowered, and some earlier studies lacked information on study design and implementation (although most trials had no obvious risk of bias, and none had high losses to follow-up).
- The quality of evidence was assessed as moderate for the primary outcomes of incomplete miscarriage and need for additional or unplanned surgery (although quality was high for the pelvic infection data).

The evidence suggests that for women with miscarriage at less than 14 weeks' gestation, rates of incomplete miscarriage, the need for blood transfusion, and unplanned surgery appear to be higher with expectant management of miscarriage than with surgery. Costs of expectant management appear to be lower than for surgery, and infection rates between the strategies are similar. Existing evidence does not firmly indicate the superiority of either strategy, and women's preferences should be a key consideration. This evidence is consistent with recommendations in [NICE CG154](#) that both expectant and surgical management should be available to women with miscarriage, and that all treatment options should be discussed with the woman.

Key reference

Nanda K, Lopez LM, Grimes DA et al. (2012) [Expectant care versus surgical treatment for miscarriage](#). Cochrane Database of Systematic Reviews issue 3: CD003518

Misoprostol dose for medical management of miscarriage

A randomised controlled, equivalence study (n=310) in Australia by [Petersen et al. \(2013\)](#) compared the safety and effectiveness of 400 and 800 microgram doses of intravaginal misoprostol⁵ for outpatient management of miscarriage. Haemodynamically stable women aged 18 years or over presenting with uncomplicated incomplete miscarriage (8.7% of women) or missed miscarriage (91.3% of women) between 6 and 12 weeks to the emergency department or early pregnancy assessment unit of 2 hospitals were eligible. Exclusion criteria were: inevitable miscarriage; suspicion of ectopic pregnancy; infection; gestational trophoblastic disease; allergy or contraindication to prostaglandins; retained products of conception after a recent termination of pregnancy; breast feeding; baseline haemoglobin less than 9.5 g/dl.

All women were provided with information about surgical, expectant or medical management. Women choosing medical management were then randomised to either 400 or 800 micrograms vaginal misoprostol. The allocated dose was repeated the next day if the products of conception had not been passed. Surgical management was offered to any participant based on transvaginal ultrasound assessment on day 7 (if a gestational sac or endometrial thickness >30 mm was reported), or based on clinical indications (such as patient request, excessive bleeding or pain).

The primary outcome was effective induction of complete miscarriage, evaluated by 2 methods: ultrasound criteria (no gestational sac and endometrial thickness ≤30 mm on day 7), and clinical criteria (resolution of bleeding and pain, return to a normal menstrual cycle, and no surgery during 6-week follow-up [further follow-up was at the discretion of the attending gynaecologist]). The 2 doses were considered equivalent if the 95% CI of the observed risk difference (ORD) for complete miscarriage was between -15% and 15%. Secondary outcomes included adverse effects and patient satisfaction (evaluated by questionnaire), and the need for a second dose of misoprostol. The study was powered to detect a difference in the rate of fever and rigors, but not other adverse effects.

⁵ Although this use is common in UK clinical practice, at the time of publication of this Evidence Update, misoprostol did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented.

The 2 doses of misoprostol were equally effective at inducing complete miscarriage, based on both ultrasound criteria (ORD=-4.6%, 95% CI -12.8 to 3.7%, p=0.313) and clinical criteria (ORD=-5.6%, 95% CI -14.8 to 3.6%, p=0.273). In the 400 microgram group, the rate of fever and rigors was lower (ORD=-15.6%, 95% CI -28.1 to -3.0%, p=0.015), and more women reported choosing medical management as a good decision (ORD=15.2%, 95% CI 2.8 to 27.7%, p=0.018). Fewer women in the 400 microgram group reported passing tissue within 24 hours (ORD=-17.1%, 95% CI -32.7 to -1.5%, p=0.038) and more women received a second dose of misoprostol (ORD=13.8%, 95% CI 2.8 to 24.9%, p=0.016), suggesting that miscarriage took longer to resolve in the lower dose group.

Limitations of the evidence included that:

- The rate of incomplete miscarriage differed between the 800 microgram group (12%) and the 400 microgram group (6%), but randomisation was not stratified for miscarriage type.
- Analysis of adverse effects and patient satisfaction was based on subjective questionnaires, of which only 63% were completed, and not all questions were answered.
- Staff who administered the misoprostol, and attending clinicians, were not blinded to dose allocation.
- The study was based at 2 Australian hospitals where medical management of miscarriage was not routinely practiced before the trial began. The study may not therefore directly reflect practice in the UK, or in settings with greater prior experience of medical management.

The evidence suggests that in outpatient management of miscarriage, a 400 microgram dose of vaginal misoprostol appears to be as effective at inducing complete miscarriage as an 800 microgram dose, and is associated with a reduced rate of fever and rigors, and improved patient satisfaction. [NICE CG154](#) currently recommends a dose of 600–800 micrograms misoprostol for medical management of miscarriage, therefore these results may have a potential impact on the guideline. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

Key reference

Petersen SG, Perkins A, Gibbons K et al. (2013) [Can we use a lower intravaginal dose of misoprostol in the medical management of miscarriage? A randomised controlled study](#). *The Australian and New Zealand Journal of Obstetrics and Gynaecology* 53: 64–73

Cost effectiveness of medical versus surgical management of miscarriage

A study by [Rausch et al. \(2012\)](#) compared the cost effectiveness of medical and surgical management of miscarriage. The analysis was based on a multicentre RCT (n=652) from the USA by [Zhang et al. \(2005\)](#). In the original RCT, women with a first-trimester pregnancy loss (anembryonic gestation, embryonic or fetal death, or incomplete or inevitable spontaneous miscarriage) were randomised to 800 micrograms vaginal misoprostol⁶ (medical treatment) or vacuum aspiration surgery in a 3:1 ratio. In the medical treatment group, a second dose of misoprostol was given on day 3 if needed, followed by vacuum aspiration on day 8 in case of misoprostol failure. Aspiration technique depended on the centre and was either manual vacuum in an outpatient setting, or electric vacuum in an operating theatre. Treatment success constituted complete uterine evacuation without the need for vacuum aspiration in the medical treatment group, or without the need for repeat aspiration in the surgical group.

Zhang et al. (2005) reported that of the 491 women assigned to misoprostol, 84% had complete uterine evacuation by day 8 (16% treatment failure). In the 161 women assigned to

⁶ Although this use is common in UK clinical practice, at the time of publication of this Evidence Update, misoprostol did not have a UK marketing authorisation for this indication. Informed consent should be obtained and documented.

surgery, 97% were treated successfully and 3% had treatment failure that required a repeat aspiration. The percentage of women who would recommend the procedure was the same in both groups (83%), and the percentage who would use the treatment again was similar in both the misoprostol group (78%) and surgical group (75%).

In Rausch et al. (2012), analyses of cost, effectiveness, and incremental cost-effectiveness ratios and utilities were conducted. Costs evaluated were: misoprostol; vacuum aspiration; operating room and anaesthesia; clinic visits; unscheduled visits; ultrasound; surgery for treatment failure; and rehospitalisations. All costs were taken from University of Pennsylvania or Medicare cost reports. Incremental cost-effectiveness ratios (based on a modified utility score with failure=0, medication success=1, and surgical success=0.95) were calculated for initial treatment (plus secondary surgery costs in case of initial treatment failure). Patient preference was also examined in a utility analysis.

In an economic analysis comparing medical treatment with either type of surgical treatment (manual or electric vacuum aspiration), medical treatment cost \$563 and surgery cost \$899; an incremental increase of \$336 (60%) for surgery. The incremental efficacy of surgery over medical treatment was 0.124 giving an incremental cost-effectiveness ratio (ICER) for surgery of \$2707. Manual and electric vacuum aspiration were then analysed individually. Inpatient electric aspiration was more effective than medical treatment (incremental efficacy=0.134) and cost \$745 more, giving an ICER of \$5580. Outpatient manual aspiration was also more effective than medical treatment (incremental efficacy=0.112) but cost \$202 less than medical treatment, therefore manual aspiration was cost saving versus medical treatment.

Type of pregnancy loss was also analysed separately. The ICER of surgery was \$4415 for embryonic or fetal death, and \$1445 for anembryonic gestation. For incomplete or inevitable miscarriage, medical treatment was cost saving versus surgery.

The patient preference utility analysis showed that medication was more effective and less costly if surgery was preferred 14% less than medication. Namely, a patient would need to prefer surgery 14% less than medication for its treatment efficacy to be outweighed by wanting to avoid surgery.

Limitations of the evidence included that:

- The study was based on trial data and costs in the USA which may limit generalisability of the results to the UK.
- The original RCT included few women with incomplete or inevitable miscarriage (a stringent definition for incomplete miscarriage of a 30 mm endometrial thickness was used), and excluded women with active, heavy bleeding at presentation. Therefore, women with anembryonic gestation or embryonic or fetal death were over-represented.
- Rare but serious adverse events such as intrauterine adhesions were not factored into the cost-effectiveness analysis because no cases occurred in the original RCT.

The evidence suggests that the cost effectiveness of medical and surgical management of miscarriage appears to depend on the circumstances. For example, manual vacuum aspiration in an outpatient setting appears to be cost saving versus medical management. However, for incomplete or inevitable miscarriage, medical management appears to be cost saving versus surgery. These results are broadly consistent with recommendations in [NICE CG154](#) that both medical and surgical management should be available to women with miscarriage, and that all treatment options should be discussed with the woman.

The Evidence Update Advisory Group additionally noted that manual vacuum aspiration in an outpatient setting is becoming more common in the UK, and that this therapy may also have particular utility in an emergency setting. These cost-effectiveness data may therefore be of use to units that are considering or currently offering manual vacuum aspiration. However,

replication of the study in a UK setting, particularly including a focus on acceptability of and preferences for treatments among women, would be useful.

Key reference

Rausch M, Lorch S, Chung K et al. (2012) [A cost-effectiveness analysis of surgical versus medical management of early pregnancy loss](#). *Fertility and Sterility* 97: 355–60 [NIH Public Access author manuscript – full text]

Supporting reference

Zhang J, Gilles JM, Barnhart K et al. (2005) [A comparison of medical management with misoprostol and surgical management for early pregnancy failure](#). *The New England Journal of Medicine* 353: 761–9

1.6 [Management of ectopic pregnancy](#)

Expectant management of ectopic pregnancy

[NICE CG154](#) recommends that women with ectopic pregnancy should be offered systemic methotrexate⁷, surgery, or a choice of either treatment, depending on the woman's circumstances. Expectant management is not a currently recommended treatment strategy (although a period of expectant management may occur before commencing medical or surgical treatment to ensure that an intrauterine pregnancy is not treated inappropriately).

Two studies examined expectant management for ectopic pregnancy.

A multicentre RCT (n=73) across 11 hospitals in The Netherlands by [van Mello et al. \(2013\)](#) compared systemic methotrexate with expectant management in women with ectopic pregnancy or pregnancy of unknown location. All haemodynamically stable women aged 18 years or over with an ectopic pregnancy or a pregnancy of unknown location were eligible. Ectopic pregnancies needed to be visible on transvaginal ultrasound and accompanied by a stabilising serum hCG concentration of less than 1500 IU/litre. For pregnancy of unknown location, serum hCG concentration had to be stabilising at less than 2000 IU/litre. Serum hCG levels were defined as stable if they increased or decreased by less than 50% between day 0 (first clinical suspicion of ectopic pregnancy) and day 4. Exclusion criteria were: viable ectopic pregnancy; signs of tubal rupture, active intra-abdominal bleeding, or both; or contraindication for methotrexate.

Women were randomised to outpatient treatment with either methotrexate or expectant management, stratified by hospital and serum hCG concentration (<1000 versus 1000–2000 IU/litre). Women in the methotrexate arm received a single injection (1 mg/kg, maximum 100 mg), plus a maximum of 3 additional injections if serum hCG did not fall by at least 15% in the weekly follow-up, followed by surgery if needed. Expectant management did not comprise any specific treatment, but women were given an injection of methotrexate (1 mg/kg) if serum hCG concentration at a weekly follow-up visit had risen compared with the previous value. In case of a persistent stabilising of hCG, serum levels were reassessed after 48 hours. For any increases of more than 15%, a maximum of 4 injections of methotrexate were given, followed by surgery if needed. Rhesus-negative women in both arms received anti-D rhesus prophylaxis. Serum hCG was measured weekly in both groups until it was no longer detected. The primary outcome was an uneventful decline of serum hCG to an undetectable level (<2 IU/litre). Safety issues were assessed as secondary outcomes.

The treatment success rate did not differ significantly between the methotrexate group (31/41, 76%) and the expectant management group (19/32, 59%; RR=1.3, 95% CI 0.9 to 1.8). Similar numbers of women needed additional injections in the methotrexate group (9/41, 22%) or to

⁷ Although this use is common in UK clinical practice, at the time of publication of this Evidence Update, methotrexate did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

start methotrexate in the expectant management group (9/32, 28%; RR=0.8, 95% CI 0.4 to 1.7). No significant differences between the groups were seen for either the number of women needing surgery (1 with methotrexate, 4 with expectant management; RR=0.2, 95% CI 0.02 to 1.7) or reporting nausea (9 with methotrexate, 3 with expectant management; RR=1.5, 95% CI 0.5 to 4.6). No serious adverse events were reported.

Limitations of the evidence included that:

- An unequal number of women were randomised to each arm (as a result of block randomisation, stratification, a large number of centres, and a small total number of women). The uneven distribution also reduced the trial power from 80% to 78%.
- Recruitment was not evenly spread across the 11 hospitals (63 of the 73 women came from 5 centres) and took 5 years in total. The authors stated that stabilising serum hCG in women with an ectopic pregnancy or a pregnancy of unknown location is not very common. Therefore clinicians did not encounter relevant cases on a daily basis, and eligible women were sometimes missed.
- The study was an open rather than a placebo-controlled RCT.
- Safety issues were secondary outcomes therefore the study may have been underpowered to fully investigate safety.
- The study was not powered to analyse possible predictors of treatment failure.

A prospective observational study (n=333) in the UK by [Mavrellos et al. \(2013\)](#) evaluated the efficacy and safety of expectant management in women with tubal ectopic pregnancy. All women presenting to a single early pregnancy unit between January 2008 and May 2011 with suspected early pregnancy complications were assessed clinically and by transvaginal ultrasound. Those with a conclusive ultrasound diagnosis of tubal ectopic pregnancy were selected for surgical or expectant management. Criteria for immediate surgery were: moderate or severe pelvic pain; cardiovascular instability; or evidence of significant haemoperitoneum on ultrasound. Criteria for expectant management were: clinical stability with minimal abdominal pain; no evidence of significant haemoperitoneum on ultrasound; ectopic pregnancy less than 30 mm in mean diameter; no fetal cardiac activity; and serum hCG less than 1500 IU/litre.

All women receiving expectant management were followed up as outpatients until spontaneous regression of the ectopic pregnancy (resolution of clinical symptoms, serum hCG <20 IU/litre, or negative urine pregnancy test), or until surgery was needed (for example, in women with an increase in serum hCG to ≥ 2000 IU/litre). The primary outcome was successful expectant management (resolution of clinical symptoms and decline of serum hCG to <20 IU/litre or negative urine pregnancy test without the need for medical intervention). Safety issues were assessed as secondary outcomes.

Of all 333 women with tubal ectopic pregnancy entering the study, 165/333 (49.5%) met the criteria for expectant management. Of these 165 women, 146 opted for expectant management, among which 104 ectopic pregnancies resolved without any intervention (success rate of expectant management=71.2%). All women with unsuccessful expectant management were treated by salpingectomy or salpingotomy and no blood transfusions were needed. Compared with women who had successful expectant management, those with unsuccessful expectant management had a significantly lower gestational age at diagnosis (5.0 vs 6.0 weeks, $p=0.019$), and significantly higher initial levels of both serum hCG (451.0 vs 242.5 IU/litre, $p=0.028$) and progesterone (23.0 vs 11.7 nmol/litre, $p=0.016$).

Limitations of the evidence included that:

- The study was based at a single centre which may affect generalisability to other settings.
- The study was observational and relationships may be associative rather than causal.

- Elements of the protocol were individualised (for example, the interval of repeat serum hCG measurement varied between 2 and 7 days across all patients).

The evidence from these 2 studies suggests that among selected women with an ectopic pregnancy or a pregnancy of unknown location, who also have low and stabilising serum hCG levels, expectant management for many women appears to be successful (that is, leads to an uneventful decline of serum hCG without the need for further intervention). From the van Mello et al. (2013) RCT, it appears that expectant management has an efficacy similar to methotrexate. [NICE CG154](#) does not currently recommend expectant management for ectopic pregnancy, therefore these results may have a potential impact on the guideline. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will be made when the need to update guidance is reviewed by NICE.

It was additionally noted by the Evidence Update Advisory Group that further research in the form of a national RCT to investigate expectant management of ectopic pregnancy would also be useful.

Key references

Mavrelou D, Nicks H, Jamil A et al. (2013) [Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy](#). *Ultrasound in Obstetrics & Gynecology* 42: 102–7

van Mello NM, Mol F, Verhoeve HR et al. (2013) [Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? A randomized comparison](#). *Human Reproduction* 28: 60–7

Fertility after medical or surgical management of ectopic pregnancy

[NICE CG154](#) recommends that women with ectopic pregnancy should be offered systemic methotrexate⁸, surgery, or a choice of either treatment, depending on the woman's circumstances (including ability to return for follow-up, pain, size of adnexal mass, visible fetal heartbeat, serum hCG level, and acceptability of the treatment).

For women undergoing surgery for an ectopic pregnancy, [NICE CG154](#) recommends offering a salpingectomy unless there are other risk factors for infertility. Salpingotomy should be considered as an alternative to salpingectomy for women with risk factors for infertility such as contralateral tube damage.

Two studies examined fertility after medical or surgical interventions for ectopic pregnancy.

A multicentre RCT (n=406) at 17 centres in France by [Fernandez et al. \(2013\)](#) examined whether management of ectopic pregnancy with methotrexate, salpingotomy or salpingectomy affected ongoing fertility. Women were eligible if they had an ultrasound-confirmed ectopic pregnancy (mass, sac, or fetal pole seen outside the uterus) between 2005 and 2009. Women undergoing infertility treatment were included, but any women who conceived while using this treatment were considered as lost to follow-up. Women were excluded if their ectopic pregnancy at study inclusion occurred while on contraception, or if they had a single fallopian tube.

Women were first divided into 2 arms according to the activity of their ectopic pregnancy defined by Fernandez score (based on 6 items: gestational age; abdominal pain; serum hCG; progesterone; tubal mass size; and haemoperitoneum). In arm 1 (less active ectopic pregnancies: Fernandez score <13 and no haemodynamic failure), women were then randomised to either salpingotomy plus post-operative methotrexate (n=97), or to

⁸ Although this use is common in UK clinical practice, at the time of publication of this Evidence Update, methotrexate did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented.

methotrexate alone (n=110). In arm 2 (active ectopic pregnancies: Fernandez score ≥ 13 or clinical suspicion of rupture), women were randomised to either salpingectomy (n=98), or to salpingotomy plus post-operative methotrexate (n=101). Methotrexate was an intramuscular injection (1 mg/kg) in all cases. Hazard ratios (HRs) were calculated using intention-to-treat analyses. The primary endpoint was spontaneous intrauterine pregnancy 2 years after treatment for the ectopic pregnancy (measured only during periods in which couples were attempting to conceive).

In arm 1, fertility did not differ significantly after the 2 interventions: the 2-year rate of intrauterine pregnancy was 67% after methotrexate alone and 71% after salpingotomy plus methotrexate (HR=0.85, 95% CI 0.59 to 1.22, p=0.37). Similarly in arm 2, fertility did not differ significantly after the 2 interventions: the 2-year rate of intrauterine pregnancy was 70% after salpingotomy plus methotrexate and 64% after salpingectomy (hazard ratio=1.06, 95% CI 0.69 to 1.63, p=0.78). Similar results for fertility were also seen in per-protocol analyses, and in analyses adjusted for age and centre. Ongoing ectopic pregnancy rates between treatment groups were not compared statistically, but ranged from 8–9% in the 2 salpingotomy plus methotrexate groups, up to 12.5% in the salpingectomy group.

Limitations of the evidence included that:

- In arm 2, some women were reluctant to undergo salpingectomy and so did not consent to enter the study (although fewer women were lost to follow-up than expected, therefore the statistical power was not substantially affected).
- Sample sizes differed between centres and at some centres were small.
- Women were allocated to the trial arms based on their Fernandez score, which is not widely used in the UK.
- The study did not consider past experience of the operating surgeons.
- The trial was in France and results may not be fully generalisable to the UK (for example, the salpingotomy groups also received methotrexate, which is not standard treatment in the UK).

A multicentre, multinational RCT (n=446) by [Mol et al. \(2014\)](#) also examined ongoing fertility after salpingotomy and salpingectomy. Women aged 18 years and over who were scheduled for surgery for a presumptive tubal pregnancy (later confirmed laparoscopically) and had a healthy contralateral tube were recruited from hospitals in the Netherlands, Sweden, the UK, and the USA. The study excluded women who: were haemodynamically unstable; did not want a future pregnancy; were pregnant after in vitro fertilisation; or were unlikely to become pregnant in the future if assigned to salpingectomy owing to the condition of the contralateral fallopian tube (for example, absence, occlusion, malformations or hydrosalpinx of the tube). Women with tubal rupture were eligible as long as it did not affect the possibility of performing a salpingotomy.

Consenting women were then randomised to salpingotomy (n=215) or salpingectomy (n=231), stratified by hospital, age (under or over 35 years), and history of tubal disease. The primary outcome was ongoing pregnancy by natural conception within 36 months after surgery. Differences in cumulative ongoing pregnancy rates were expressed as a fecundity rate ratio. All endpoints were analysed by intention to treat.

Fertility did not differ significantly after the 2 interventions: the cumulative ongoing pregnancy rate after salpingotomy was 60.7% and after salpingectomy was 56.2% (fecundity rate ratio=1.06, 95% CI 0.81 to 1.38, log-rank p=0.678). Persistent trophoblast occurred more frequently after salpingotomy than salpingectomy (14 [7%] versus 1 [$<1\%$]; RR=15.0, 95% CI 2.0 to 113.4, p=0.01) but repeat ectopic pregnancy did not differ significantly between the groups. A non-prespecified meta-analysis by the authors, combining the present results of Mol et al. (2014) with those of Fernandez et al. (2013; see previous commentary for details),

confirmed that fertility prospects and repeat ectopic pregnancy risk were not significantly different after salpingotomy or salpingectomy.

Limitations of the evidence included that:

- Researchers collecting data for fertility outcomes were blinded to interventions, but patients and the investigators analysing the data were not.
- Of the 215 women in the salpingotomy group, 51 (24%) were converted to salpingectomy (although a per-protocol analysis of only women who had their assigned intervention [164 salpingotomy, 231 salpingectomy], did not substantially alter results).
- The study did not consider past experience of the operating surgeons.

The evidence from the 2 studies suggests that among women receiving medical or surgical treatment for ectopic pregnancy appropriate to their circumstances (for example, their accompanying symptoms, and the status of the contralateral fallopian tube), ongoing fertility in the 2–3 years after treatment appears to be similar between methotrexate, salpingotomy and salpingectomy. This is consistent with recommendations in [NICE CG154](#) that both medical and surgical treatment should be available, and treatment should take into account the circumstances of the ectopic pregnancy and any risk factors for infertility.

Key references

Fernandez H, Capmas P, Lucot JP et al. (2013) [Fertility after ectopic pregnancy: the DEMETER randomized trial](#). *Human Reproduction* 28: 1247–53

Mol F, van Mello NM, Strandell A et al. (2014) [Salpingotomy versus salpingectomy in women with tubal pregnancy \(ESEP study\): an open-label, multicentre, randomised controlled trial](#). *The Lancet* 383: 1483–9

1.7 [Anti-D rhesus prophylaxis](#)

No new key evidence for this section was selected for inclusion in this Evidence Update.

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Diagnosis of viable intrauterine pregnancy and of ectopic pregnancy

- [Serum hCG for diagnostic resolution of pregnancies of unknown location](#)
- [A single serum progesterone measurement as an adjunct test for predicting early pregnancy outcome in women with pain or bleeding](#)

Management of miscarriage

- [Expectant care versus surgical treatment for miscarriage](#)

Management of ectopic pregnancy

- [Expectant management of ectopic pregnancy](#)

Further evidence uncertainties for ectopic pregnancy and miscarriage can be found in the [UK DUETs database](#) and in the [NICE research recommendations database](#).

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- [Ectopic pregnancy and miscarriage](#). NICE clinical guideline 154 (2012)

The area of 'Expectant management for ectopic pregnancy' was included in the Evidence Update scope (whereas the reference guidance did not explicitly include or exclude this).

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 8 February 2012 (the end of the search period of NICE clinical guideline 154) to 8 July 2014:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- MEDLINE In-Process
- NHS EED (Economic Evaluation Database)
- PsycINFO

The Evidence Update search strategy replicates the strategy used by NICE CG154 (for key words, index terms and combining concepts) as far as possible. Where necessary, the strategy is adapted to take account of changes in search platforms and updated indexing language.

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network [search filters for RCTs, systematic reviews, observational studies and diagnostic studies](#). The 'information and support' filter from the reference guidance was also used.

The Evidence Update search strategy was developed by tabulating the search terms for all review questions in the guideline (each of which used a different population search). All unique condition terms were copied into a single core condition search, to be combined with the study design filters to ensure no key terms were missed. Key terms for early pregnancy assessment services were taken from the guideline and combined with the study design filters. The 'support and information giving' theme was searched by rerunning the guideline terms for support and information giving and combining this strategy with the core condition/early pregnancy assessment service search.

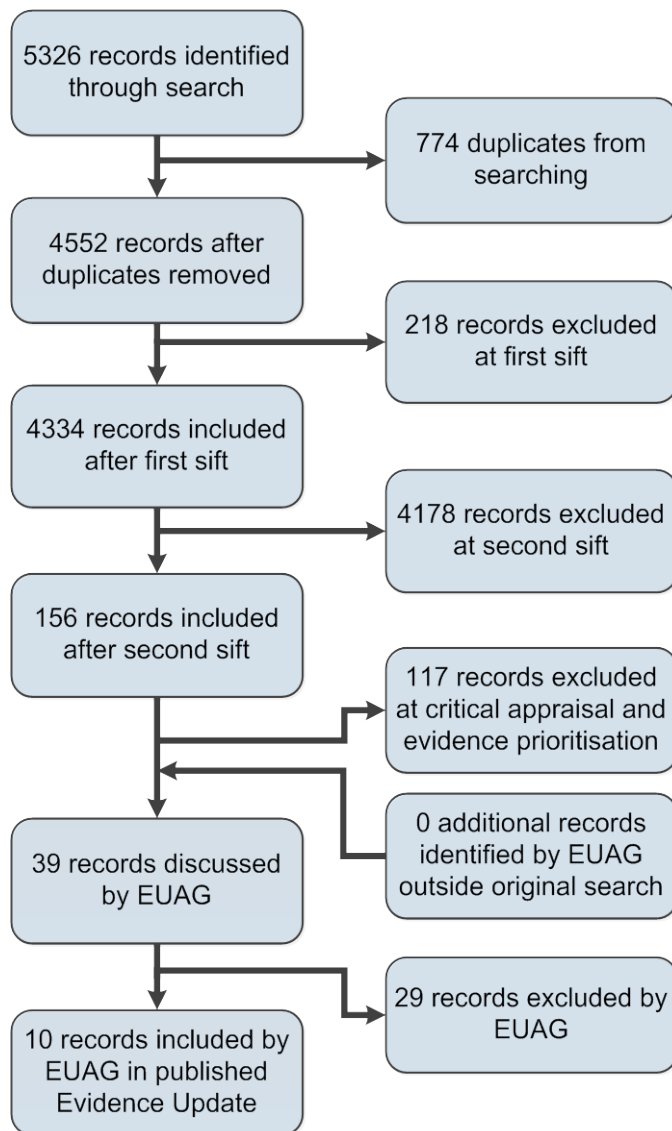
Figure 1 provides details of the evidence selection process. The list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

See the [NICE Evidence Services](#) website for more information about [how NICE Evidence Updates are developed](#).

Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp Abortion, Spontaneous/	13	exp GESTATIONAL TROPHOBLASTIC DISEASE/
2	exp Pregnancy, Ectopic/	14	(trophoblast\$ adj3 (gestat\$ or pregnan\$ or disease\$ or tumo?r\$ or neoplas\$)).ti,ab.
3	miscarr\$.ti,ab.	15	((hydavid\$ or invasi\$) adj3 mol\$).ti,ab.
4	((miscarr\$ or abort\$ or pregnan\$ loss\$) adj3 (threat\$ or imminen\$)).ti,ab.	16	molar pregnan\$.ti,ab.
5	((spontaneous or threatened or imminent or imminens or missed or delay\$ or inevitable or incomplete\$ or early or silent or quiescent) adj2 abort\$).ti,ab.	17	(placenta\$ adj3 (tumo?r\$ or neoplas\$)).ti,ab.
6	((pregnan\$ or embryo\$ or f?etal or f?etus\$) adj3 (loss\$ or demise or death\$ or resorp\$ or disintegrat\$ or wast\$ or reject\$ or fail\$ or viab?l\$ or non?viab?l\$)).ti,ab.	18	(chorio carcinoma\$ or chorio?carcinoma\$).ti,ab.
7	(anembryo\$ or empty sac\$).ti,ab.	19	FETAL VIABILITY/
8	(blight\$ adj2 (ova or ovum)).ti,ab.	20	Fetal Death/
9	((ectopic or extra uterine or extra?uterine or tub\$ or ampullary or isthm\$ or fimbrial or cornual or interstitial or abdom\$ or ovar\$ or cervi\$ or oviduct\$ or fallopian) adj3 (pregnan\$ or gestat\$)).ti,ab.	21	(early pregnancy adj3 (unit? or clinic? or cent\$ or service?)).ti,ab
10	(pregnan\$ adj3 ((unknown or uncertain) adj (location\$ or site\$))).ti,ab.	22	(EPAU? or EPU? or EPAC? or EPC? or EPS? or EPAS?).ti,ab
11	PUL.ti,ab.	23	((acute or emergency or casualty) adj3 (gyn?ecolog\$ or early pregnancy)).ti,ab.
12	eccyesi\$.ti,ab	24	Or/1-23
		25	limit 24 to (english language and yr="2012 -Current")

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who reviewed the prioritised evidence from the literature search and advised on the development of the Evidence Update.

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