

# Appendix A: Summary of evidence from surveillance

## 4-year surveillance (2017) – [Ectopic pregnancy and miscarriage: diagnosis and initial management](#) (2012) NICE guideline CG154

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### Summary of evidence from surveillance

#### [Support and information giving](#)

#### **154 – 01 What interventions are the most effective for improving women’s psychological and/or emotional health following pain, bleeding or pregnancy loss, in the first trimester of pregnancy?**

#### Recommendations derived from this question

- 1.1.1 Treat all women with [early pregnancy](#) complications with dignity and respect. Be aware that women will react to complications or the loss of a pregnancy in different ways. Provide all women with information and support in a sensitive manner, taking into account their individual circumstances and emotional response\*.
- 1.1.2 Healthcare professionals providing care for women with early pregnancy complications in any setting should be aware that early pregnancy complications can cause significant distress for some women and their partners. Healthcare professionals providing care for these women should be given training in how to communicate sensitively and breaking bad news. Non-clinical staff such as receptionists working in settings where early pregnancy care is provided should also be given training on how to communicate sensitively with women who experience early pregnancy complications.
- 1.1.3 Throughout a woman's care, give her and (with agreement) her partner specific evidence-based information in a variety of formats. This should include (as appropriate):
  - When and how to seek help if existing symptoms worsen or new symptoms develop, including a 24-hour contact telephone number.
  - What to expect during the time she is waiting for an ultrasound scan.
  - What to expect during the course of her care (including [expectant management](#)), such as the potential length and extent of pain and/or bleeding, and possible side effects. This information should be tailored to the care she receives.
  - Information about post-operative care (for women undergoing surgery).
  - What to expect during the recovery period – for example, when it is possible to resume sexual activity and/or try to conceive again, and what to do if she becomes pregnant again. This information should be tailored to the care she receives.
  - Information about the likely impact of her treatment on future fertility.
  - Where to access support and counselling services, including leaflets, web addresses and helpline numbers for support organisations.

Ensure that sufficient time is available to discuss these issues with women during the course of their care and arrange an additional appointment if more time is needed.

- 1.1.4 After an early pregnancy loss, offer the woman the option of a follow-up appointment with a healthcare professional of her choice.

\* For further guidance about providing information, see [Patient experience in adult NHS services](#) (NICE clinical guidance 138).

### Surveillance decision

This review question should not be updated.

#### *Supportive counselling*

##### **2-year Evidence Update and 3-year surveillance review summary**

No relevant evidence was identified.

##### **4-year surveillance summary**

A randomised controlled trial (RCT)<sup>1</sup> compared supportive counselling from a nurse against routine care after miscarriage (n=280 participants). There was no significant difference in the proportion of women suffering psychological distress at 3 months. However, women with high levels of psychological distress at baseline (n=152 participants) had significantly lower psychological distress at follow-up in the supportive counselling group compared to the routine care group.

##### **Topic expert feedback**

No topic expert feedback was relevant to this evidence.

##### **Impact statement**

During the 4-year surveillance review, new evidence was found about the benefit of supportive counselling after miscarriage in women with high levels of psychological distress. It was considered this evidence was in line with current [recommendation 1.1.1](#) which suggests providing all women with early pregnancy complications information and support in a sensitive manner, taking into account their individual circumstances and emotional response.

New evidence is unlikely to change guideline recommendations.

#### *Early pregnancy assessment services*

**154 – 02 What is the clinical and cost effectiveness of early pregnancy assessment unites (EPAUs) compared with other models of service provision in improving women’s clinical and psychological outcomes?**

#### **Recommendations derived from this question**

- 1.2.1 Regional services should be organised so that an early pregnancy assessment service is available 7 days a week for women with early pregnancy complications, where scanning can be carried out and decisions about management made.
- 1.2.2 An early pregnancy assessment service should:
- be a dedicated service provided by healthcare professionals competent to diagnose and care for women with pain and/or bleeding in early pregnancy **and**
  - offer ultrasound and assessment of serum human chorionic gonadotrophin (hCG) levels **and**
  - be staffed by healthcare professionals with training in sensitive communication and breaking bad news.
- 1.2.3 Early pregnancy assessment services should accept self-referrals from women who have had recurrent miscarriage\* or a previous ectopic or molar pregnancy. All other women with pain

and/or bleeding should be assessed by a healthcare professional (such as a GP, accident and emergency [A&E] doctor, midwife or nurse) before referral to an early pregnancy assessment service.

- 1.2.4 Ensure that a system is in place to enable women referred to their local early pregnancy assessment service to attend within 24 hours if the clinical situation warrants this. If the service is not available, and the clinical symptoms warrant further assessment, refer women to the nearest accessible facility that offers specialist clinical assessment and ultrasound scanning (such as a gynaecology ward or A&E service with access to specialist gynaecology support).

\*Although additional care for women with recurrent miscarriage is not included in the scope of the guideline, the Guideline Development Group recognised that it is common clinical practice to allow these women to self-refer to an early pregnancy assessment service and wished this to remain the case.

### Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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## 154 – 03 What is the appropriate model for service organisation and delivery of EPAUs?

### Recommendations derived from this question

The full version of the guideline addressed evidence for this question in conjunction with the evidence for question [154-02](#) above to make recommendations 1.2.1 to 1.2.4.

### Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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## *Symptoms and signs of ectopic pregnancy and initial assessment*

## 154 – 04 What are the signs and symptoms associated with ectopic pregnancy?

### Recommendations derived from this question

- 1.3.1 Refer women who are haemodynamically unstable, or in whom there is significant concern about the degree of pain or bleeding, directly to A&E.
- 1.3.2 Be aware that atypical presentation for ectopic pregnancy is common.
- 1.3.3 Be aware that ectopic pregnancy can present with a variety of symptoms. Even if a symptom is less common, it may still be significant. Symptoms of ectopic pregnancy include:
- common symptoms:
    - abdominal or pelvic pain
    - amenorrhoea or missed period
    - vaginal bleeding with or without clots

- other reported symptoms:
    - breast tenderness
    - gastrointestinal symptoms
    - dizziness, fainting or syncope
    - shoulder tip pain
    - urinary symptoms
    - passage of tissue
    - rectal pressure or pain on defecation.
- 1.3.4 Be aware that ectopic pregnancy can present with a variety of signs on examination by a healthcare professional. Signs of ectopic pregnancy include:
- more common signs:
    - pelvic tenderness
    - adnexal tenderness
    - abdominal tenderness
  - other reported signs:
    - cervical motion tenderness
    - rebound tenderness or peritoneal signs
    - pallor
    - abdominal distension
    - enlarged uterus
    - tachycardia (more than 100 beats per minute) or hypotension (less than 100/60 mmHg)
    - shock or collapse
    - orthostatic hypotension.
- 1.3.5 During clinical assessment of women of reproductive age, be aware that:
- they may be pregnant, and think about offering a pregnancy test even when symptoms are non-specific **and**
  - the symptoms and signs of ectopic pregnancy can resemble the common symptoms and signs of other conditions – for example, gastrointestinal conditions or urinary tract infection.
- 1.3.6 All healthcare professionals involved in the care of women of reproductive age should have access to pregnancy tests.
- 1.3.7 Refer immediately to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) for further assessment women with a positive pregnancy test and the following on examination:
- pain and abdominal tenderness **or**
  - pelvic tenderness **or**
  - cervical motion tenderness.
- 1.3.8 Exclude the possibility of ectopic pregnancy, even in the absence of risk factors (such as previous ectopic pregnancy), because about a third of women with an ectopic pregnancy will have no known risk factors.
- 1.3.9 Refer to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) women with bleeding or other symptoms and signs of early pregnancy complications who have:
- pain **or**

- a pregnancy of 6 weeks gestation or more **or**
- a pregnancy of uncertain gestation.

The urgency of this referral depends on the clinical situation.

- 1.3.10 Use expectant management for women with a pregnancy of less than 6 weeks gestation who are bleeding but not in pain. Advise these women:
- to repeat a urine pregnancy test after 7–10 days and to return if it is positive
  - a negative pregnancy test means that the pregnancy has miscarried
  - to return if their symptoms continue or worsen.
- 1.3.11 Refer women who return with worsening symptoms and signs that could suggest an ectopic pregnancy to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) for further assessment. The decision about whether she should be seen immediately or within 24 hours will depend on the clinical situation.
- 1.3.12 If a woman is referred to an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available), explain the reasons for the referral and what she can expect when she arrives there.

### Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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

### **154 – 05 What is the diagnostic value of ultrasound for determining a viable intrauterine pregnancy?**

#### Recommendations derived from this question

##### *Using ultrasound for diagnosis*

- 1.4.1 Offer women who attend an early pregnancy assessment service (or out-of-hours gynaecology service if the early pregnancy assessment service is not available) a transvaginal ultrasound scan to identify the location of the pregnancy and whether there is a fetal pole and heartbeat.
- 1.4.2 Consider a transabdominal ultrasound scan for women with an enlarged uterus or other pelvic pathology, such as fibroids or an ovarian cyst.
- 1.4.3 If a transvaginal ultrasound scan is unacceptable to the woman, offer a transabdominal ultrasound scan and explain the limitations of this method of scanning.
- 1.4.4 Inform women that the diagnosis of miscarriage using 1 ultrasound scan cannot be guaranteed to be 100% accurate and there is a small chance that the diagnosis may be incorrect, particularly at very early gestational ages.
- 1.4.5 When performing an ultrasound scan to determine the viability of an intrauterine pregnancy, first look to identify a fetal heartbeat. If there is no visible heartbeat but there is a visible fetal pole, measure the crown–rump length. Only measure the mean gestational sac diameter if the fetal pole is not visible.
- 1.4.6 If the crown–rump length is less than 7.0 mm with a transvaginal ultrasound scan and there is no visible heartbeat, perform a second scan a minimum of 7 days after the first before making a diagnosis. Further scans may be needed before a diagnosis can be made.

- 1.4.7 If the crown–rump length is 7.0 mm or more with a transvaginal ultrasound scan and there is no visible heartbeat:
- seek a second opinion on the viability of the pregnancy and/or
  - perform a second scan a minimum of 7 days after the first before making a diagnosis.
- 1.4.8 If there is no visible heartbeat when the crown–rump length is measured using a transabdominal ultrasound scan:
- record the size of the crown–rump length **and**
  - perform a second scan a minimum of 14 days after the first before making a diagnosis.
- 1.4.9 If the mean gestational sac diameter is less than 25.0 mm with a transvaginal ultrasound scan and there is no visible fetal pole, perform a second scan a minimum of 7 days after the first before making a diagnosis. Further scans may be needed before a diagnosis can be made.
- 1.4.10 If the mean gestational sac diameter is 25.0 mm or more using a transvaginal ultrasound scan and there is no visible fetal pole:
- seek a second opinion on the viability of the pregnancy **and/or**
  - perform a second scan a minimum of 7 days after the first before making a diagnosis.
- 1.4.11 If there is no visible fetal pole and the mean gestational sac diameter is measured using a transabdominal ultrasound scan:
- record the size of the mean gestational sac diameter **and**
  - perform a second scan a minimum of 14 days after the first before making a diagnosis.
- 1.4.12 Do not use gestational age from the last menstrual period alone to determine whether a fetal heartbeat should be visible.
- 1.4.13 Inform women that the date of their last menstrual period may not give an accurate representation of gestational age because of variability in the menstrual cycle.
- 1.4.14 Inform women what to expect while waiting for a repeat scan and that waiting for a repeat scan has no detrimental effects on the outcome of the pregnancy.
- 1.4.15 Give women a 24-hour contact telephone number so that they can speak to someone with experience of caring for women with early pregnancy complications who understands their needs and can advise on appropriate care\*.
- 1.4.16 When diagnosing complete miscarriage on an ultrasound scan, in the absence of a previous scan confirming an intrauterine pregnancy, always be aware of the possibility of ectopic pregnancy. Advise these women to return for further review if their symptoms persist.
- 1.4.17 All ultrasound scans should be performed and reviewed by someone with training in, and experience of, diagnosing ectopic pregnancies.

\*See also [recommendation 1.1.3](#) for details of further information that should be provided.

### Surveillance decision

This review question should not be updated.

#### *Tools for predicting viability of intrauterine pregnancy and miscarriage*

##### **2-year Evidence Update and 3-year surveillance review summary**

A prospective observational cohort study<sup>2</sup> developed and evaluated a simple scoring system to predict viable intrauterine pregnancy beyond the first trimester (n=1,435 women with 84 days gestation or less). The 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) appeared able to predict pregnancy viability beyond the first trimester.

During the Evidence Update, it was concluded that NICE guideline CG154 did not 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.

#### 4-year surveillance summary

No relevant evidence was identified.

#### Topic expert feedback

Topic experts referred to a prospective multicentre observational study<sup>3</sup> which evaluated cut-off values for embryo crown-rump length and mean gestational sac diameter to diagnose miscarriage with high levels of certainty (n=2,845 women with intrauterine pregnancy of unknown viability). Transvaginal ultrasonography was carried out initially and around 7 to 14 days later. During the initial scan, the following cut-off points indicated a miscarriage with high specificity values: mean gestational sac diameter >25 mm with an empty sac (n=364 participants), embryo with crown-rump length >7 mm without visible embryo heart activity (n=110 participants), mean gestational sac diameter >18 mm for gestational sacs without an embryo presenting after 70 days' gestation (n=907 participants), embryo with crown-rump length >3 mm without visible heart activity presenting after 70 days' gestation (n=87 participants). During the repeat scan, specificity was also high for the following cut-off points which were indicative of miscarriage: initial scan and repeat scan after seven days or more showing an embryo without visible heart activity (n=103 participants), pregnancies without an embryo and mean gestational sac diameter <12 mm where the mean diameter has not doubled after 14 days or more (n=478 participants), pregnancies without an embryo and mean gestational sac diameter >12 mm showing no embryo heartbeat after seven days or more (n=150 participants). All the cut-off values were likely to predict a miscarriage.

A topic expert also expressed concerns that there is a danger for misdiagnosing

miscarriages as some services are unable to implement a second opinion or offer the woman a rescan.

#### Impact statement

During the Evidence Update, evidence was found about a simple scoring system predicting viable intrauterine pregnancy beyond the first trimester. During the 3-year surveillance review, the panel of experts agreed that the value of the study was limited as psychological morbidity was not considered as an outcome. The panel also recognised that, as the study was conducted in a single centre and involved 1,500 patients, further research would be beneficial in validating the findings before considering for inclusion in the guideline. New evidence was also found about different cut-off values for embryo crown-rump length and mean gestational sac diameter to diagnose miscarriage with initial and repeat transvaginal ultrasonography. The validated cut-off values for crown-rump length during the initial scan are similar to current recommendations which state that if there is no visible heart beat and the crown-rump length is <7.0 mm ([recommendation 1.4.6](#)) or 7.0 mm or more ([recommendation 1.4.7](#)), then a second scan is required after 7 days to confirm diagnosis. The validated cut-off values for mean gestational sac diameter during the initial scan from the observational study are also similar to current recommendations which state that if there is no visible fetal pole and the mean gestational sac diameter is <25.0 mm ([recommendation 1.4.9](#)) or 25.0 mm or more ([recommendation 1.4.9](#)), then a second scan is required after 7 days to confirm diagnosis. Both validated cut-off values at initial and repeat scans were likely to predict a miscarriage and therefore, a second scan might not be necessary. It was considered that further research would be beneficial before updating current recommendations regarding the number of scans to diagnose miscarriage.

New evidence is unlikely to change guideline recommendations.

## 154 – 06 What is the accuracy of transvaginal ultrasound compared with transabdominal ultrasound for diagnosing ectopic pregnancy?

### Recommendations derived from this question

The full version of the guideline addressed evidence for this question in conjunction with the evidence for question [154-05](#) above to make recommendations 1.4.1 to 1.4.17.

### Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

## 154 – 07 What is the diagnostic accuracy of two or more hCG measurements for determining an ectopic pregnancy in women with pain and bleeding and pregnancy of unknown location?

### Recommendations derived from this question

#### *Human chorionic gonadotrophin measurements in women with pregnancy of unknown location*

- 1.4.18 Be aware that women with a [pregnancy of unknown location](#) could have an ectopic pregnancy until the location is determined.
- 1.4.19 Do not use serum hCG measurements to determine the location of the pregnancy.
- 1.4.20 In a woman with a pregnancy of unknown location, place more importance on clinical symptoms than on serum hCG results, and review the woman's condition if any of her symptoms change, regardless of previous results and assessments.
- 1.4.21 Use serum hCG measurements only for assessing trophoblastic proliferation to help to determine subsequent management.
- 1.4.22 Take 2 serum hCG measurements as near as possible to 48 hours apart (but no earlier) to determine subsequent management of a pregnancy of unknown location. Take further measurements only after review by a senior healthcare professional.
- 1.4.23 Regardless of serum hCG levels, give women with a pregnancy of unknown location written information about what to do if they experience any new or worsening symptoms, including details about how to access emergency care 24 hours a day. Advise women to return if there are new symptoms or if existing symptoms worsen.
- 1.4.24 For a woman with an increase in serum hCG concentration greater than 63% after 48 hours:
- Inform her that she is likely to have a developing intrauterine pregnancy (although the possibility of an ectopic pregnancy cannot be excluded).
  - Offer her a transvaginal ultrasound scan to determine the location of the pregnancy between 7 and 14 days later. Consider an earlier scan for women with a serum hCG level greater than or equal to 1500 IU/litre.
    - If a viable intrauterine pregnancy is confirmed, offer her routine antenatal care\*
    - If a viable intrauterine pregnancy is not confirmed, refer her for immediate clinical review by a senior gynaecologist.
- 1.4.25 For a woman with a decrease in serum hCG concentration greater than 50% after 48 hours:
- inform her that the pregnancy is unlikely to continue but that this is not confirmed **and**



- provide her with oral and written information about where she can access support and counselling services\*\* and
  - ask her to take a urine pregnancy test 14 days after the second serum hCG test, and explain that:
    - if the test is negative, no further action is necessary
    - if the test is positive, she should return to the early pregnancy assessment service for clinical review within 24 hours.
- 1.4.26 For a woman with a change in serum hCG concentration between a 50% decline and 63% rise inclusive, refer her for clinical review in the early pregnancy assessment service within 24 hours.
- 1.4.27 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.

\* See [Antenatal care](#) (NICE clinical guideline 62).

\*\* See also [recommendation 1.1.3](#) for details of further information that should be provided.

## Surveillance decision

This review question should not be updated.

### Diagnosis

#### 2-year Evidence Update and 3-year surveillance review summary

A systematic review and meta-analysis<sup>4</sup> of 23 cohort studies (n=9,078 participants) analysed the diagnostic accuracy of various serum hCG strategies in women with pregnancy of unknown location. The strategies included single serum hCG cut-off level (10 studies), serum hCG ratio (hCG 48 h/hCG 0 h [4 studies]), logistic regression modelling (6 studies), serum hCG (1 study), serum progesterone and/or uterine curettage findings (1 study each). Meta-analysis was only possible for the outcome of ectopic pregnancy. Serum hCG ratios (alone, or in and logistic regression models) appeared to be effective in diagnosing ectopic pregnancy. It was highlighted the substantial heterogeneity in the definition of the outcome.

#### 4-year surveillance summary

No relevant evidence was identified.

#### Topic expert feedback

No topic expert feedback was relevant to this evidence.

#### Impact statement

During the Evidence Update, evidence was found showing that in women with a pregnancy of unknown location, the ratio of serum hCG levels appeared to be effective in diagnosing ectopic pregnancy. During the 3-year surveillance review, it was concluded that this was consistent with [recommendation 1.4.22](#) to base management decisions on the percentage change in 2 serum hCG measurements taken as near as possible to 48 hours apart.

New evidence is unlikely to change guideline recommendations.

**154 – 08 What is the diagnostic accuracy of two or more hCG measurements plus progesterone for determining an ectopic pregnancy in women with pain and bleeding and pregnancy of unknown location?**

**Recommendations derived from this question**

The full version of the guideline addressed evidence for this question in conjunction with the evidence for question [154-07](#) above to make recommendations 1.4.18 to 1.4.27.

**Surveillance decision**

No new information was identified at any surveillance review.

This review question should not be updated.

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**154 – 09 What is the diagnostic accuracy of two or more hCG measurements for determining a viable intrauterine pregnancy in women with pain and bleeding and pregnancy of unknown location?**

The full version of the guideline addressed evidence for this question in conjunction with the evidence for question [154-07](#) above to make recommendations 1.4.18 to 1.4.27.

**Surveillance decision**

No new information was identified at any surveillance review.

This review question should not be updated.

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**154 – 10 What is the diagnostic accuracy of two or more hCG measurements plus progesterone for determining a viable intrauterine pregnancy in women with pain and bleeding and pregnancy of unknown location?**

**Recommendations derived from this question**

The full version of the guideline addressed evidence for this question in conjunction with the evidence for question [154-07](#) above to make recommendations 1.4.18 to 1.4.27.

**Surveillance decision**

No new information was identified at any surveillance review.

This review question should not be updated.

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## Management of miscarriage

### **154 – 11 What is the effectiveness of progesterone in improving outcomes in women with threatened miscarriage?**

#### **Recommendations derived from this question**

- 1.5.1 Advise a woman with vaginal bleeding and a confirmed intrauterine pregnancy with a fetal heartbeat that:
- if her bleeding gets worse, or persists beyond 14 days, she should return for further assessment
  - if the bleeding stops, she should start or continue routine antenatal care.

#### **Surveillance decision**

No new information was identified at any surveillance review.

This review question should not be updated.

### **154 – 12 How effective is expectant management of miscarriage compared with active treatment for improving women's clinical and psychological outcomes?**

#### **Recommendations derived from this question**

- 1.5.2 Use expectant management for 7–14 days as the first-line management strategy for women with a confirmed diagnosis of miscarriage. Explore management options other than expectant management if:
- the woman is at increased risk of haemorrhage (for example, she is in the late first trimester) **or**
  - she has previous adverse and/or traumatic experience associated with pregnancy (for example, stillbirth, miscarriage or antepartum haemorrhage) **or**
  - she is at increased risk from the effects of haemorrhage (for example, if she has coagulopathies or is unable to have a blood transfusion) **or**
  - there is evidence of infection.
- 1.5.3 Offer medical management to women with a confirmed diagnosis of miscarriage if expectant management is not acceptable to the woman.
- 1.5.4 Explain what expectant management involves and that most women will need no further treatment. Also provide women with oral and written information about further treatment options.
- 1.5.5 Give all women undergoing expectant management of miscarriage oral and written information about what to expect throughout the process, advice on pain relief and where and when to get help in an emergency\*.
- 1.5.6 If the resolution of bleeding and pain indicate that the miscarriage has completed during 7–14 days of expectant management, advise the woman to take a urine pregnancy test after 3 weeks, and to return for individualised care if it is positive.
- 1.5.7 Offer a repeat scan if after the period of expectant management the bleeding and pain:

- have not started (suggesting that the process of miscarriage has not begun) **or**
- are persisting and/or increasing (suggesting incomplete miscarriage).

Discuss all treatment options (continued expectant management, medical management, and surgical management) with the woman to allow her to make an informed choice.

1.5.8 Review the condition of a woman who opts for continued expectant management of miscarriage at a minimum of 14 days after the first follow-up appointment.

\* See also [recommendation 1.1.3](#) for details of further information that should be provided.

## Surveillance decision

This review question should not be updated.

### *Preterm labour*

#### **2-year Evidence Update and 3-year surveillance review summary**

No relevant evidence was identified.

#### **4-year surveillance summary**

A systematic review and meta-analysis<sup>5</sup> of 21 cohort and case-control studies (n=1,853,017 participants) showed that dilation and curettage (D&C) for first trimester miscarriage or termination of pregnancy significantly increased the risk of preterm labour compared to women who had no history of D&C. The authors highlighted that not all included studies controlled for confounding factors. Therefore, confounding might be present.

#### **Topic expert feedback**

No topic expert feedback was relevant to this evidence.

#### **Impact statement**

During the 4-year surveillance review, there was new evidence showing that D&C for first trimester miscarriage or termination of pregnancy might increase the risk of subsequent preterm labour. Surgical management is included in [recommendation 1.5.18](#) but D&C is not specifically recommended. It was considered to wait for high quality evidence before adding recommendations on if professionals should or should not use D&C for the management of miscarriage.

New evidence is unlikely to change guideline recommendations.

### *Success rates and safety*

#### **2-year Evidence Update and 3-year surveillance review summary**

A systematic review<sup>6</sup> of 7 RCTs (n=1521 participants) compared the safety and effectiveness of expectant management against surgical management (vacuum aspiration or dilation and curettage) for miscarriage. The Evidence Update concluded that for women with miscarriage at less than 14 weeks' gestation, rates of incomplete miscarriage, the need for blood transfusion, and unplanned surgery appeared to be higher with expectant management of miscarriage than with surgery. Costs of expectant management appeared to be lower than for surgery, and infection rates between the strategies are similar. Existing evidence did not

firmly indicate the superiority of either strategy, and women's preferences should be a key consideration.

#### **4-year surveillance summary**

An RCT<sup>7</sup> compared expectant management against surgical management (n=217 women with first trimester incomplete or missed miscarriage). The total success rate at 4 weeks was significantly lower for expectant management compared to surgical management. The duration of bleeding and pain was significantly longer in the expectant group compared to the surgical group. Pelvic infection was significantly lower in the expectant group compared to the surgical group. In general, the findings showed that surgical management might be more effective and safer than expectant management for

miscarriage apart from pelvic infection which was lower in the expectant management group.

An RCT<sup>8</sup> compared expectant management against surgical evacuation (n=360 women with missed or incomplete miscarriage). Success rates were defined as curettage without complications (surgical group) or complete spontaneous expulsion of products without complications (expectant group). There was no significant difference in the success rates between the groups. The rates of unplanned admissions and unplanned surgical evacuations in the expectant group were significantly higher than the rates in the surgical group.

#### **Topic expert feedback**

No topic expert feedback was relevant to this evidence.

#### **Impact statement**

During the Evidence Update, evidence was found about the safety of expectant management compared to surgical management without a firm indication of the

superiority of either strategy. During the 3-year surveillance review, it was considered the evidence was consistent with [recommendations 1.5.4, 1.5.18 – 1.5.19](#) that both expectant and surgical management should be available to women with miscarriage, and that all treatment options should be discussed with the woman. During the 4-year surveillance review, new evidence was found showing inconsistent results regarding the success rates between expectant management and surgical management of miscarriage. One RCT reported lower success rates with expectant management compared to surgical management while another RCT reported no differences in success rates between the interventions. Therefore, it was considered that more evidence is needed before considering any changes in current recommendations regarding the management of miscarriage.

New evidence is unlikely to change guideline recommendations.

## **154 – 13 How effective is surgical management of miscarriage compared with medical management for improving women's clinical and psychological outcomes?**

### **Recommendations derived from this question**

The full version of the guideline addressed evidence for this question in conjunction with the evidence for question [154-12](#) above to make recommendations 1.5.2 to 1.5.8.

### **Surveillance decision**

This review question should not be updated.

### *Cost effectiveness*

#### **2-year Evidence Update and 3-year surveillance review summary**

A cost-effectiveness analysis<sup>9</sup> of a multicentre RCT (n=652 women with first-trimester pregnancy loss) compared medical management against surgical management of miscarriage. The Evidence Update concluded that cost-effectiveness appeared to depend on circumstances. For example, manual vacuum aspiration in an outpatient setting appeared to be cost saving versus medical treatment

However, for incomplete or inevitable miscarriage, medical management appeared to be cost saving versus surgery.

#### **4-year surveillance summary**

No relevant evidence was identified.

#### **Topic expert feedback**

No topic expert feedback was relevant to this evidence.

#### **Impact statement**

During the 3-year surveillance review, it was concluded that evidence was broadly

consistent with [recommendations 1.5.9 – 1.5.19](#) that both medical and surgical management should be available to women with miscarriage and that all treatment options should be discussed with the woman.

New evidence is unlikely to change guideline recommendations.

## 154 – 14 What is the most appropriate dose of misoprostol and mifepristone to provide for managing miscarriage?

### Recommendations derived from this question

- 1.5.9 Do not offer mifepristone as a treatment for missed or incomplete miscarriage.
- 1.5.10 Offer vaginal misoprostol for the medical treatment of missed or incomplete miscarriage. Oral administration is an acceptable alternative if this is the woman's preference\*.
- 1.5.11 For women with a missed miscarriage, use a single dose of 800 micrograms of misoprostol\*.
- 1.5.12 Advise the woman that if bleeding has not started 24 hours after treatment, she should contact her healthcare professional to determine ongoing individualised care.
- 1.5.13 For women with an incomplete miscarriage, use a single dose of 600 micrograms of misoprostol. (800 micrograms can be used as an alternative to allow alignment of treatment protocols for both missed and incomplete miscarriage\*.)
- 1.5.14 Offer all women receiving medical management of miscarriage pain relief and anti-emetics as needed.
- 1.5.15 Inform women undergoing medical management of miscarriage 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.
- 1.5.16 Advise women to take a urine pregnancy test 3 weeks after medical management of miscarriage unless they experience worsening symptoms, in which case advise them to return to the healthcare professional responsible for providing their medical management.
- 1.5.17 Advise women with a positive urine pregnancy test after 3 weeks to return for a review by a healthcare professional to ensure that there is no molar or ectopic pregnancy.

\*Although this use is common in UK clinical practice, at the time of publication (December 2012), misoprostol did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing medicines – guidance for doctors](#) for further information.

### Surveillance decision

This review question should not be updated.

#### *Mifepristone*

##### **2-year Evidence Update and 3-year surveillance review summary**

No relevant evidence was identified.

##### **4-year surveillance summary**

A systematic review<sup>10</sup> of 16 trials (5 RCTs and 11 non-randomised trials) looked at the added value of mifepristone to misoprostol alone for the treatment of early pregnancy failure (EPF). The success rates of sequential treatment with

mifepristone and misoprostol in case of EPF varied with the authors concluding that the evidence was insufficient to draw any conclusions of mifepristone's added value because heterogeneity was high regarding treatment regimens and comparators between included studies.

##### **Topic expert feedback**

No topic expert feedback was relevant to this evidence.

### Impact statement

During the 4-year surveillance review, new evidence was found regarding the addition of mifepristone to misoprostol for the management of pregnancy failure. However, it was concluded that evidence was highly heterogeneous and conclusions could not be drawn. Therefore, it was considered that

evidence was insufficient to change [recommendation 1.5.9](#) which states do not offer mifepristone as a treatment for missed or incomplete miscarriage.

New evidence is unlikely to change guideline recommendations.

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### *Dose of misoprostol*

#### **2-year Evidence Update and 3-year surveillance review summary**

A randomised controlled equivalence study<sup>11</sup> of 310 women compared the safety and effectiveness of 400 micrograms against 800 micrograms of intravaginal misoprostol for outpatient management of miscarriage. The Evidence Update concluded that in outpatient management miscarriage, a 400 microgram dose of vaginal misoprostol appeared to be as effective at inducing complete miscarriage as an 800 microgram dose, and was associated with a reduced rate of fever and rigors, and improved patient satisfaction.

#### **4-year surveillance summary**

No relevant evidence was identified.

#### **Topic expert feedback**

No relevant evidence was identified.

### Impact statement

During the Evidence Update, evidence showed that a 400 microgram dose of vaginal misoprostol appeared to be as effective at inducing complete miscarriage as an 800 microgram dose. However, during the 3-year surveillance review, the panel of experts felt that there was insufficient evidence at that stage to justify updating this question from recommendations of 600–800 microgram misoprostol ([recommendations 1.5.11 and 1.5.13](#)) to a lower dose of 400 microgram. In addition, it was considered that the dose change would not have an economic impact due to the low drug costs. However, there could be additional costs if more people end up needing a second dose if the initial dose is unsuccessful.

New evidence is unlikely to change guideline recommendations.

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### *Cervical dilation*

#### **2-year Evidence Update and 3-year surveillance review summary**

No relevant evidence was identified.

#### **4-year surveillance summary**

A systematic review and meta-analysis<sup>12</sup> included 9 RCTs (n=469 participants) reporting on benefits and harms of using cervical ripening (also called cervical dilation) agents prior to surgical evacuation of non-viable pregnancy prior 14 weeks gestation. Meta-analysis was limited to 6 RCTs (n=383 participants). The primary outcome (cervical or uterine injury) was not reported by any of the included RCTs. Four comparisons were carried out. There were no significant differences between isosorbide compounds and misoprostol for the need of manual cervical dilation and for adverse effects (headache,

nausea or hypotension) but misoprostol was significantly associated with more vomiting. Misoprostol was significantly more effective than placebo for cervical dilation and reduced surgical time. There were no significant differences between misoprostol and placebo for adverse effects (nausea, vomiting, headache or fever) but misoprostol was significantly associated with more abdominal pain. There were no significant differences between chemical (use of medications) and mechanical dilators (Dilapan-S hygroscopic) for difficulty in cervical dilation, excessive bleeding and adverse effects. Any cervical preparation significantly reduced the need for manual cervical dilatation compared with placebo. The authors highlighted that the included studies were small with mixed methodological quality and not well-described and that the dosing regimens differed between RCTs.

### Topic expert feedback

No topic expert feedback was relevant to this evidence.

### Impact statement

During the 4-year surveillance review, new evidence was found showing no significant differences for most of the outcomes between different cervical dilation agents such as isosorbide compounds, misoprostol, chemical and mechanical dilators. However, misoprostol was associated with more vomiting and abdominal pain. This evidence was considered

to be of low methodological quality and therefore unlikely to impact on current recommendations which suggest offering surgical management for miscarriage including the provision of oral and written information about treatment options and what to expect during and after the procedure ([recommendations 1.5.18 – 1.5.19](#)).

New evidence is unlikely to impact on the guideline.

## 154 – 15 What is the effectiveness of surgical management of miscarriage in an outpatient (office) setting compared with any other setting for improving women’s clinical and psychological outcomes?

### Recommendations derived from this question

- 1.5.18 Where clinically appropriate, offer women undergoing a miscarriage a choice of:
- manual vacuum aspiration under local anaesthetic in an outpatient or clinic setting **or**
  - surgical management in a theatre under general anaesthetic.
- 1.5.19 Provide oral and written information to all women undergoing surgical management of miscarriage about the treatment options available and what to expect during and after the procedure\*.

\*See also [recommendation 1.1.3](#) for details of further information that should be provided.

### Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

## [Management of ectopic pregnancy](#)

## 154 – 16 How effective is surgical management of tubal ectopic pregnancy compared with medical management for improving women’s clinical and psychological outcomes?

### Recommendations derived from this question

- 1.6.1 Inform women who have had an ectopic pregnancy that they can self-refer to an early pregnancy assessment service in future pregnancies if they have any early concerns.
- 1.6.2 Give all women with an ectopic pregnancy oral and written information about:
- how they can contact a healthcare professional for post-operative advice if needed, and who this will be **and**
  - where and when to get help in an emergency\*.



- 1.6.3 Offer systemic methotrexate\*\* as a first-line treatment to women who are able to return for follow-up and who have all of the following:
- no significant pain
  - an unruptured ectopic pregnancy with an adnexal mass smaller than 35 mm with no visible heartbeat
  - a serum hCG level less than 1500 IU/litre
  - no intrauterine pregnancy (as confirmed on an ultrasound scan).
- 1.6.4 Offer surgery as a first-line treatment to women who are unable to return for follow-up after methotrexate treatment or who have any of the following:
- an ectopic pregnancy and significant pain
  - an ectopic pregnancy with an adnexal mass of 35 mm or larger
  - an ectopic pregnancy with a fetal heartbeat visible on an ultrasound scan
  - an ectopic pregnancy and a serum hCG level of 5000 IU/litre or more.
- 1.6.5 Offer the choice of either methotrexate\*\* or surgical management to women with an ectopic pregnancy who have a serum hCG level of at least 1500 IU/litre and less than 5000 IU/litre, who are able to return for follow-up and who meet all of the following criteria:
- no significant pain
  - an unruptured ectopic pregnancy with an adnexal mass smaller than 35 mm with no visible heartbeat
  - no intrauterine pregnancy (as confirmed on an ultrasound scan).

Advise women who choose methotrexate that their chance of needing further intervention is increased and they may need to be urgently admitted if their condition deteriorates.

- 1.6.6 or women with ectopic pregnancy who have had methotrexate, take 2 serum hCG measurements in the first week (days 4 and 7) after treatment and then 1 serum hCG measurement per week until a negative result is obtained. If hCG levels plateau or rise, reassess the woman's condition for further treatment.

\*See also [recommendation 1.1.3](#) for details of further information that should be provided.

\*\*Although this use is common in UK clinical practice, at the time of publication (December 2012), methotrexate did not have UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Good practice in prescribing medicines – guidance for doctors](#) for further information.

## Surveillance decision

This review question should not be updated.

### *Fertility outcomes*

#### **2-year Evidence Update and 3-year surveillance review summary**

A multicentre RCT<sup>13</sup> (n=406 participants) at 17 centres examined whether management of ectopic pregnancy with methotrexate, salpingotomy or salpingectomy affected ongoing fertility. The Evidence Update concluded that, in arm 1 (less active ectopic pregnancies), the 2-year rate of intrauterine pregnancy did not differ significantly after methotrexate alone or salpingotomy plus methotrexate. Similarly in arm 2 (active ectopic

pregnancies), the 2-year rate of intrauterine pregnancy did not differ significantly after salpingotomy plus methotrexate or salpingectomy alone.

#### **4-year surveillance summary**

No relevant evidence was identified.

#### **Topic expert feedback**

Topic experts referred to a retrospective study<sup>14</sup> of women diagnosed with tubal ectopic pregnancy and who desired to conceive following tubal ectopic pregnancy (n=112 participants). Three types of treatment were compared: expectant management (n=27

participants), systemic methotrexate (n=53 participants), and surgery (n=32 participants). Treatment was successful for all women in both expectant and surgery groups. Methotrexate failed in 2 women. Spontaneous intrauterine pregnancy rates were significantly different between expectant management, methotrexate and surgery. Surgery appeared to be the most successful treatment for spontaneous intrauterine pregnancy rates following tubal ectopic pregnancy.

#### Impact statement

Through surveillance, evidence was found comparing medical and surgical treatment for ectopic pregnancy. During the 3-year surveillance review, it was concluded that among women receiving medical or surgical treatment for ectopic pregnancy appropriate to their circumstances, ongoing fertility in the 2 years after treatment appeared to be similar between methotrexate, salpingotomy and salpingectomy. This was consistent with

[recommendations 1.6.1 – 1.6.6](#) 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. However, that evidence was inconsistent with the observational study found during the 4-year surveillance review. The RCT showed similar fertility outcomes between medical and surgical treatment and the retrospective study showed successful fertility outcomes with surgery compared to expectant management or medical treatment. It was considered to wait for more evidence before changing current recommendations on surgical and medical treatment for ectopic pregnancy ([recommendations 1.6.1 – 1.6.6](#)). See [NQ – 04](#) for an impact statement on expectant management of ectopic pregnancy.

New evidence is unlikely to change guideline recommendations.

## 154 – 17 What is the effectiveness of laparotomy compared with laparoscopic techniques for managing tubal ectopic pregnancy?

### Recommendations derived from this question

- 1.6.7 When surgical treatment is indicated for women with an ectopic pregnancy, it should be performed laparoscopically whenever possible, taking into account the condition of the woman and the complexity of the surgical procedure.
- 1.6.8 Surgeons providing care to women with ectopic pregnancy should be competent to perform laparoscopic surgery.
- 1.6.9 Commissioners and managers should ensure that equipment for laparoscopic surgery is available.

### Surveillance decision

This review question should not be updated.

#### *Second-look laparoscopy*

##### **2-year Evidence Update and 3-year surveillance review summary**

No relevant evidence was identified.

##### **4-year surveillance summary**

An RCT<sup>15</sup> reported the potential value of second-look laparoscopy in improving fertility outcomes after laparoscopic salpingostomy for

ectopic pregnancy (n=216 participants). Participants were randomised into 2 groups: one group received second-look laparoscopy (3 months after primary surgery) whilst second group did not. At 3-year follow-up, the intrauterine pregnancy rate was significantly higher in the second-look laparoscopy group compared with the control group, and the incidence of recurrent ectopic pregnancy was

significantly lower in the second-look laparoscopy group than in the control group. Second-look laparoscopy appeared to be valuable for improving fertility outcomes after laparoscopic salpingostomy for ectopic pregnancy.

#### Topic expert feedback

No topic expert feedback was relevant to this evidence.

#### Impact statement

During the 4-year surveillance review, new evidence was found showing that second-look

laparoscopy appeared to be valuable for improving fertility outcomes after laparoscopic salpingostomy for ectopic pregnancy. There are not current recommendations to offer a second-look laparoscopy after laparoscopic salpingostomy for ectopic pregnancy. However, it was considered that evidence was insufficient to recommend second-look laparoscopy because the study was small.

New evidence is unlikely to change guideline recommendations.

## 154 – 18 What is the effectiveness of salpingectomy compared with salpingotomy in improving outcomes in women with tubal ectopic pregnancy?

### Recommendations derived from this question

- 1.6.10 Offer a salpingectomy to women undergoing surgery for an ectopic pregnancy unless they have other risk factors for infertility.
- 1.6.11 Consider salpingotomy as an alternative to salpingectomy for women with risk factors for infertility such as contralateral tube damage.
- 1.6.12 Inform women having a salpingotomy that up to 1 in 5 women may need further treatment. This treatment may include methotrexate and/or a salpingectomy.
- 1.6.13 For women who have had a salpingotomy, take 1 serum hCG measurement at 7 days after surgery, then 1 serum hCG measurement per week until a negative result is obtained.
- 1.6.14 Advise women who have had a salpingectomy that they should take a urine pregnancy test after 3 weeks. Advise women to return for further assessment if the test is positive.

### Surveillance decision

This review question should not be updated.

### Fertility outcomes

#### 2-year Evidence Update and 3-year surveillance review summary

An open-label, multicentre RCT<sup>16</sup> (n=446 participants) examined ongoing fertility after salpingotomy and salpingectomy in women with a laparoscopically confirmed tubal pregnancy and a healthy contralateral tube. The study excluded women who were unlikely to become pregnant in the future if assigned to salpingectomy owing to the condition of the contralateral fallopian tube (e.g. absence or malformation). The Evidence Update concluded that ongoing pregnancy by natural conception within 36 months after surgery did

not differ significantly after salpingotomy or salpingectomy.

During the 3-year surveillance review, it was concluded that among women receiving surgical treatment for ectopic pregnancy appropriate to their circumstances, ongoing fertility in the 3 years after treatment appeared to be similar between salpingotomy and salpingectomy. This was consistent with NICE guideline CG154 which recommends that surgical treatment should be available, and treatment should take into account the circumstances of the ectopic pregnancy and any risk factors for infertility.

#### 4-year surveillance summary

A systematic review and meta-analysis<sup>17</sup> of 2 RCTs and 8 cohort studies compared intrauterine pregnancy (IUP) and repeat ectopic pregnancy (REP) between salpingotomy and salpingectomy in women treated for ectopic pregnancy (n=1,229 participants). There were no significant differences in IUP and REP rates between salpingotomy and salpingectomy from the RCTs. Cohort studies showed that IUP rates and risk of REP rate were significantly higher with salpingotomy compared to salpingectomy. Findings from RCTs and cohort studies appeared to be inconsistent regarding the differences between salpingotomy and salpingectomy in women treated for ectopic pregnancy.

#### Topic expert feedback

Topic experts referred to the open-label, multicentre RCT<sup>16</sup> noted in the 3-year surveillance review.

#### Impact statement

Through surveillance, evidence was found about fertility outcomes between salpingotomy and salpingectomy after ectopic pregnancy. RCTs did not show a difference in fertility outcomes between types of surgery but cohort studies showed higher IUP and REP rates in salpingotomy compared to salpingectomy. RCTs are considered the best evidence for the effectiveness of an intervention. Therefore, it was concluded that evidence from cohort studies was insufficient to change [recommendations 1.6.10 – 1.6.14](#) which offer either salpingectomy or salpingotomy depending on the circumstances of the ectopic pregnancy and any risk factors for infertility.

New evidence is unlikely to change guideline recommendations.

#### *Cost effectiveness*

#### 2-year Evidence Update and 3-year surveillance review summary

No relevant evidence was identified.

#### 4-year surveillance summary

A multicentre RCT<sup>18</sup> compared cost-effectiveness between salpingotomy (n=215 participants) and salpingectomy (n=231 participants) in women with tubal pregnancy and a healthy contralateral tube. Salpingotomy was not considered to be cost-effective over salpingectomy for ectopic pregnancy because its costs were higher without a better ongoing pregnancy rate and higher risks of persistent trophoblast.

#### Topic expert feedback

No topic expert feedback was relevant to this evidence.

#### Impact statement

During the 4-year surveillance review, new evidence was found showing that salpingotomy was not more cost-effective than salpingectomy for ectopic pregnancy. Therefore, it was considered that evidence was in line with [recommendations 1.6.10 – 1.6.14](#) which offer either salpingectomy or salpingotomy depending on the circumstances of the ectopic pregnancy and any risk factors for infertility.

New evidence is unlikely to change guideline recommendations.

#### *Anti-D rhesus prophylaxis*

### 154 – 19 Should anti-D rhesus prophylaxis be given to women with a threatened miscarriage, miscarriage or ectopic pregnancy in the first trimester?

#### Recommendations derived from this question

- 1.7.1 Offer anti-D rhesus prophylaxis at a dose of 250 IU (50 micrograms) to all rhesus negative women who have a surgical procedure to manage an ectopic pregnancy or a miscarriage.

- 1.7.2 Do not offer anti-D rhesus prophylaxis to women who:
- receive solely medical management for an ectopic pregnancy or miscarriage **or**
  - have a threatened miscarriage **or**
  - have a complete miscarriage **or**
  - have a pregnancy of unknown location.
- 1.7.3 Do not use a Kleihauer test for quantifying feto–maternal haemorrhage.

### Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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**154 – 20 What is the appropriate dose of anti-D that should be administered to women with a threatened miscarriage, miscarriage or ectopic pregnancy in the first trimester?**

### Recommendations derived from this question

The full version of the guideline addressed evidence for this question in conjunction with the evidence for question [154-19](#) above to make recommendations 1.7.1 to 1.7.3.

### Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

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**NQ – 01 What is the effectiveness of medical management of miscarriage in an outpatient setting compared with any other setting for improving women’s clinical and psychological outcomes?**

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

### Surveillance decision

This question should not be added.

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#### *Intravaginal misoprostol*

#### **2-year Evidence Update and 3-year surveillance review summary**

No relevant evidence was identified.

#### **4-year surveillance summary**

An RCT<sup>19</sup> compared outpatient against inpatient administration of intra-vaginal misoprostol (800 micrograms eight hourly to a maximum of three doses) for first-trimester

incomplete miscarriage (n=154 participants). Success rate (complete evacuation), side effects, and duration of bleeding were not significantly different between the groups.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

During the 4-year surveillance review, new evidence was found showing no differences between outpatient and inpatient administration of intra-vaginal misoprostol. The evidence is in line with [recommendation 1.5.10](#) to offer vaginal misoprostol for incomplete miscarriage.

However, [recommendation 1.5.13](#) suggests using a single dose up to 800 micrograms of misoprostol which is lower than the highest dose used by the RCT (2,400 micrograms). The setting for administration of misoprostol was not discussed during guideline development. It was considered to wait for more evidence before suggesting any changes to recommendations of medical management for miscarriage as evidence comes from a small RCT.

New evidence is unlikely to impact on the guideline.

**NQ – 02 What is the diagnostic accuracy of serum biomarkers for determining a viable intrauterine pregnancy in women with threatened miscarriage or a pregnancy of unknown location?**

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

**Surveillance decision**

This question should not be added.

*Serum biomarkers*

**2-year Evidence Update and 3-year surveillance review summary**

A systematic review and meta-analysis<sup>20</sup> of 26 cohort studies (n=9,436 participants) examined the accuracy of a single progesterone measurement in early pregnancy to discriminate between viable and non-viable pregnancy. During the evidence update, it was concluded that a single progesterone measurement for women in early pregnancy with bleeding or pain appeared able to distinguish between viable and non-viable pregnancy.

**4-year surveillance summary**

A systematic review and meta-analysis<sup>21</sup> of 19 studies investigated the diagnostic accuracy of biochemical markers to predict outcomes in women with threatened miscarriage at 5-32 weeks (n=1,263 participants). Cancer antigen

125 (CA 125) had the best performance in terms of sensitivity and specificity (n=648 participants, 7 studies) at predicting viable pregnancies compare to other biochemical markers including serum progesterone, hCG, pregnancy associated plasma protein A, and estradiol.

**Topic expert feedback**

No topic expert feedback was relevant to this evidence.

**Impact statement**

Through surveillance, evidence was found showing that a single progesterone measurement and CA 125 appeared to predict viable pregnancies. During the 3-year surveillance review, the panel of experts felt that a single progesterone measurement could not be considered in isolation without regard to full clinical assessment of the patient, in particular, symptoms. Ultrasound scan was

considered the main test used for determining viability. It was concluded that the guideline currently recommends serial hCG testing which requires 2 patient visits 48 hours apart, so a progesterone measurement (or another serum biomarker) might be useful in reducing appointments (reducing two visits to one). But there was no difference in the cost of tests per se, and the panel agreed that a follow-up scan

would still be necessary to check the location of the pregnancy. In addition, the data relating to emergency cases that occur before this scheduled follow up scan appointment would also need to be captured.

New evidence is unlikely to impact on the guideline.

### **NQ – 03 What ultrasound features are most diagnostic of an ectopic pregnancy?**

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

#### **Surveillance decision**

This question should be added.

#### *Accuracy of ultrasound*

##### **2-year Evidence Update and 3-year surveillance review summary**

No relevant evidence was identified.

##### **4-year surveillance summary**

A systematic review and meta-analysis<sup>22</sup> of 31 studies (n=5,858 participants) aimed to determine the accuracy of ultrasound in the diagnosis of tubal ectopic pregnancy in the absence of an obvious extrauterine embryo. The meta-analysis showed that an empty uterus from ultrasound predicted ectopic pregnancy with moderate values of sensitivity and specificity (81.1% and 79.5%, respectively). Pseudosac (sensitivity 5.5% and specificity 94.2%), adnexal mass (sensitivity 63.5% and specificity 91.4%) and free fluid (sensitivity 47.2% and specificity 92.3%) had lower sensitivity and higher specificity. It was concluded that ultrasound might be more useful for 'ruling in' a tubal pregnancy than 'ruling out' one. Limitations were highlighted such as poor quality of included studies and heterogeneity in the index test and reference standard.

##### **Topic expert feedback**

Stakeholders highlighted that ultrasound criteria to make a diagnosis of ectopic

pregnancy are not discussed in NICE guideline CG154. Stakeholders felt that this area requires attention in order to improve care for women experiencing early pregnancy loss and that management of ectopic pregnancy relies on diagnosis.

##### **Impact statement**

During the 4-year surveillance review, new evidence was found about the accuracy of ultrasound in the diagnosis of tubal ectopic pregnancy from a systematic review suggesting that an empty uterus, a pseudosac, adnexal mass or free fluid in an ultrasound might be useful for 'ruling in' a tubal pregnancy. Stakeholders highlighted that ultrasound criteria to make a diagnosis of ectopic pregnancy might improve care for women experiencing early pregnancy loss. Therefore, new evidence and stakeholder feedback were considered to have an impact on current [recommendations 1.4.1 – 1.4.17](#) which currently do not include diagnostic criteria for ectopic pregnancy.

New evidence identified that may impact on the guideline.

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**NQ – 04 How effective is expectant management compared to medical management for ectopic pregnancy?**

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

### Surveillance decision

This question should be added.

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#### 2-year Evidence Update and 3-year surveillance review summary

A multicentre RCT<sup>23</sup> (n=73 participants) across 11 hospitals compared systemic methotrexate with expectant management in women with ectopic pregnancy or pregnancy of unknown location.

A prospective observational study<sup>24</sup> (n=333 participants) in the UK evaluated the efficacy and safety of expectant management in women with tubal ectopic pregnancy.

The Evidence Update concluded from these 2 studies that among selected women with an ectopic pregnancy or a pregnancy of unknown location, who also had low and stabilising serum hCG levels, expectant management for many women appeared to be successful (that is, leads to an uneventful decline of serum hCG without the need for further intervention). From the RCT, it appeared that expectant management had an efficacy similar to methotrexate.

#### 4-year surveillance summary

##### *Health-related quality of life*

An RCT<sup>25</sup> randomised participants to receive expectant management or systemic methotrexate (n=64 women with ectopic pregnancy or pregnancy of an unknown location) and compared their health-related quality of life (HRQoL). Using standardised questionnaires, there was no difference in HRQoL of women receiving expectant management or methotrexate.

##### *Treatment success*

Another RCT<sup>26</sup> (n=23 women with ectopic pregnancy) compared the effectiveness of expectant management (saline solution) against management with methotrexate (50 mg/m<sup>2</sup>). Both methotrexate and placebo were administered in a single intramuscular dose. There were no significant differences between the groups for treatment success (negative titers of beta-hCG) and for the time of beta-hCG becoming undetectable.

##### **Topic expert feedback**

Topic experts referred to a retrospective study<sup>14</sup> of women diagnosed with tubal ectopic pregnancy and who desired to conceive following tubal ectopic pregnancy (n=112 participants). Three types of treatment were compared: expectant management (n=27 participants), systemic methotrexate (n=53 participants), and surgery (n=32 participants). Treatment was successful for all women in both expectant and surgery groups. Methotrexate failed in 2 women. Spontaneous intrauterine pregnancy rates were significantly different between expectant management, methotrexate and surgery. Surgery appeared to be the most successful treatment for spontaneous intrauterine pregnancy rates following tubal ectopic pregnancy.

During the 3-year surveillance review, an ongoing RCT was highlighted which was published during the time of the 4-year surveillance review. This RCT<sup>27</sup> compared the success rates of methotrexate against placebo (expectant management) for the conservative treatment of tubal ectopic pregnancies (n=42



women with methotrexate, n=38 women with placebo). Clinically stable women were included who had a conclusive ultrasound diagnosis of a tubal ectopic pregnancy and low serum hCG less than 1500 IU/l. The main outcome was success of conservative management which was defined as 'resolution of clinical symptoms and decline of serum hCG to <20 IU/l or negative urine pregnancy test without the need for any additional medical intervention'. The success rates were not statistically different between methotrexate and placebo. The authors concluded that the results did not support routine use of methotrexate for tubal ectopic pregnancy. Although the success rates were similar for methotrexate and expectant management, this conclusion might be based on the side effects caused by the use of methotrexate.

#### Impact statement

Through surveillance, evidence was found showing comparable HRQoL and treatment success between expectant management and methotrexate treatment for ectopic pregnancy

(data from RCTs). However, an observational study showed that surgery appeared to be the most successful treatment for ectopic pregnancy compared to expectant management and methotrexate. During the 3-year surveillance review, the panel of experts suggested that expectant management for ectopic pregnancy may have a place for very early pregnancies that naturally resolve on their own without needing to give a drug with unpleasant side effects to the patient or intervene surgically. However, the panel agreed that further research in this area was needed before considering for inclusion in the guideline. As new evidence has been found during this 4-year surveillance review, [recommendations 1.6.1 – 1.6.14](#) might need to be revised because expectant management is not currently considered as an option for the management of ectopic pregnancy.

**New evidence identified that may impact on the guideline.**

### **NQ – 05 What is the effectiveness of different active treatments for managing non-tubal ectopic pregnancy?**

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

#### Surveillance decision

This question should not be added.

#### *Efficacy and safety*

##### **2-year Evidence Update and 3-year surveillance review summary**

No relevant evidence was identified.

##### **4-year surveillance summary**

A systematic review<sup>28</sup> compared different treatments for the management of caesarean section ectopic pregnancy (CSEP). The lowest success rate was for systemic methotrexate followed by uterine artery embolisation (UAE), hysteroscopy, D&C, and hysterotomy with the highest success rate. Hysterectomy rates were

higher for D&C compared to the rest of the treatments: systemic methotrexate, hysterotomy, UAE, and hysteroscopy. Subsequent term pregnancy was significantly related to successful systemic methotrexate treatment or hysterotomy. Systemic methotrexate and D&C were also associated with high complication rates. Number and type of included studies as well total number of participants were not reported in abstract.

##### **Topic expert feedback**

A topic expert noted that molar (hydatidiform mole) pregnancy was excluded from the scope

of NICE guideline CG154 but may need a small mention in the guideline recommendations regarding information and referral.

#### **Impact statement**

During the 4-year surveillance review, new evidence was found showing that hysterectomy appeared to be the most effective and safe treatment for the management of caesarean section ectopic pregnancy. The management of non-tubal ectopic pregnancies was not considered in the original guideline. The new

evidence identified might suggest that non-tubal ectopic pregnancies could be considered by the guideline, however the evidence was limited. Therefore, it was considered to wait for more evidence before including the management of non-tubal ectopic pregnancies to NICE guideline CG154.

New evidence is unlikely to impact on the guideline.

### **NQ – 06 What is the effectiveness of single dose of methotrexate compared to double dose of methotrexate for managing ectopic pregnancy?**

This question was not addressed by the guideline.

New evidence has subsequently been identified and considered for possible addition to the guideline as a new question.

#### **Surveillance decision**

This question should not be added.

#### *Success rates*

##### **2-year Evidence Update and 3-year surveillance review summary**

No relevant evidence was identified.

##### **4-year surveillance summary**

An RCT<sup>29</sup> of 76 women with ectopic pregnancy were randomised to receive either a single dose of 50 mg/m<sup>2</sup> of methotrexate given at day 0 or a double dose at day 0 and 4. Successful treatment was defined as 15% reduction in beta-hCG level between day 4 and 7. Success rate was not significantly different between the groups, nor were the operation rates and additional methotrexate doses. Duration of hospitalisation was significantly lower in double dose compared to single dose.

Another RCT<sup>30</sup> randomised participants to receive a single-dose or two-dose protocol of systemic methotrexate (n=92 women with a tubal ectopic pregnancy). The success rates between the single-dose and two-dose groups were not significantly different. The authors suggested being cautious at interpreting the results because the sample size was calculated

based on the biggest difference between the groups as reported in the literature.

##### **Topic expert feedback**

No topic expert feedback was relevant to this evidence.

##### **Impact statement**

During the 4-year surveillance review, new evidence was found showing no significant differences between single and double dose of systemic methotrexate for the treatment of ectopic pregnancy. Current recommendations do not include the dose for methotrexate but refer to a footnote because methotrexate is not licensed for the management of ectopic pregnancy in the UK. The use of methotrexate is common in UK clinical practice and the footnote suggests that prescribers should follow relevant professional guidance such as the General Medical Council's [Good practice in prescribing medicines – guidance for doctors](#).

New evidence is unlikely to impact on the guideline.



## Research recommendations

### *Prioritised research recommendations*

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the [NICE database for research recommendations](#). The research recommendations will remain in the full versions of the guideline. See NICE's [research recommendations process and methods guide 2015](#) for more information.

These research recommendations were deemed priority areas for research by the Guideline Committee; therefore, at this 4-year surveillance review time point a decision **will** be taken on whether to retain the research recommendations or stand them down.

We applied the following approach:

- New evidence relevant to the research recommendation was found and an update of the related review question is planned.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database. If needed, a new research recommendation may be made as part of the update process.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because the new evidence is insufficient to trigger an update.
  - The research recommendation will be retained because there is evidence of research activity in this area.
- New evidence relevant to the research recommendation was found but an update of the related review question is not planned because evidence supports current recommendations.
  - The research recommendation will be removed from the NICE version of the guideline and the NICE research recommendations database because further research is unlikely to impact on the guideline.
- Ongoing research relevant to the research recommendation was found.
  - The research recommendation will be retained and evidence from the ongoing research will be considered when results are published.
- No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
  - The research recommendation will be removed from the NICE version of guideline and the NICE research recommendations database because there is no evidence of research activity in this area.
- The research recommendation would be answered by a study design that was not included in the search (usually systematic reviews or randomised controlled trials).
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.
- The new research recommendation was made during a recent update of the guideline.
  - The research recommendation will be retained in the NICE version of the guideline and the NICE research recommendations database.

**RR – 01 A national evaluation of early pregnancy assessment unit service provision should be carried out to identify factors affecting outcomes. Factors should include whether care is provided in a dedicated unit, staffing configuration and opening hours of dedicated services. Outcomes should include both process (service) outcomes and pregnancy-related outcomes. Data collected should be used to analyse the cost effectiveness of early pregnancy assessment units compared with other models of care.**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

#### Surveillance decision

No new evidence was found but it is not expected that this research recommendation would be answered by systematic reviews or RCTs. Therefore it is proposed to keep this research recommendation.

**RR – 02 How does the timing and frequency of ultrasound examination affect diagnosis and outcomes of early pregnancy complications, including women's experience and cost effectiveness?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

#### Surveillance decision

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because there is no evidence of research activity in this area. We considered the views of stakeholders through consultation. It was decided to retain this research recommendation based on the feedback from stakeholder consultation.

**RR – 03 Are progesterone or progestogens effective in treating threatened miscarriage?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

#### Surveillance decision

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because there is no evidence of research activity in this area. We considered the views of stakeholders through consultation. It was decided to retain this research recommendation based on the feedback from stakeholder consultation.

**RR – 04 In women with confirmed miscarriage, does the type of management strategy (expectant, medical and surgical) impact on women's experience, including psychological and emotional outcomes?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

#### Surveillance decision

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because there is no evidence of research activity in this area. We considered the views of stakeholders through consultation. It

was decided to retain this research recommendation based on the feedback from stakeholder consultation.

**RR – 05 In women with ectopic pregnancy, does the type of intervention (laparoscopy or medical management) impact on women's experience, including psychological and emotional outcomes?**

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

**Surveillance decision**

It was proposed to remove the research recommendation from the NICE version of the guideline and the NICE research recommendations database because there is no evidence of research activity in this area. We considered the views of stakeholders through consultation. It was decided to retain this research recommendation based on the feedback from stakeholder consultation.

*Other research recommendations*

The following research recommendations were not deemed as priority areas for research by the guideline committee. No decisions will be taken the status of these research recommendations.

**RR – 01 What interventions improve emotional and psychological outcomes for women following ectopic pregnancy?**

No new information was identified at any surveillance review.

**RR – 02 Research should be undertaken to design and validate a decision tool for evaluating signs, symptoms and risk factors for correctly identifying ectopic pregnancy.**

No new information was identified at any surveillance review.

**RR – 03 Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of miscarriage?**

New evidence was found (see review question [154 - 14](#)) but an update is not planned because the evidence is consistent with current guideline recommendations.

**RR – 04 Does the administration of anti-D rhesus prophylaxis following pain and bleeding in early pregnancy improve outcomes? Outcomes should include rhesus sensitisation in the woman attributable to the early pregnancy event and morbidity related to rhesus disease in subsequent unborn and newborn babies.**

No new information was identified at any surveillance review.

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