Survveillance report 2017 – Ectopic pregnancy and miscarriage: diagnosis and initial management (2012) NICE guideline CG154

Survveillance report
Published: 23 February 2017
nice.org.uk
## Contents

Surveillance decision .................................................................................................................................................... 3  
Reason for the decision .................................................................................................................................................. 3

Commentary on selected evidence .......................................................................................................................... 6
  Management of miscarriage – Medical management ............................................................................................... 6

How we made the decision ........................................................................................................................................ 10
  Evidence........................................................................................................................................................................ 10
  Views of topic experts ................................................................................................................................................. 10
  Views of stakeholders .................................................................................................................................................. 10
  NICE Surveillance programme project team ........................................................................................................... 11
Survveillance decision

We will plan an update of the guideline on ectopic pregnancy and miscarriage. The update will focus on the accuracy of ultrasound for diagnosing ectopic pregnancy.

An extension to the scope will be needed to incorporate a new review question about the effectiveness of expectant management compared to medical management for ectopic pregnancy.

A change in the title of the NICE guideline will be needed to make clear that the guideline only refers to tubal ectopic pregnancy rather than any type of ectopic pregnancy.

Reason for the decision

Assessing the evidence

We found 30 studies through surveillance of this guideline.

Evidence that could affect recommendations was identified. Topic experts, including those who helped to develop the guideline, advised us about whether the following sections of the guideline should be updated and any new sections added:

Diagnosis of viable intrauterine pregnancy and of ectopic pregnancy

- New review question – What ultrasound features are most diagnostic of an ectopic pregnancy?

Stakeholders highlighted that ultrasound criteria to make a diagnosis of ectopic pregnancy might improve care for women experiencing early pregnancy loss and that NICE guideline CG154 does not discuss such criteria. There was also evidence from a systematic review and meta-analysis that an empty uterus, a pseudosac, adnexal mass or free fluid in an ultrasound might be useful for 'ruling in' a tubal pregnancy. Therefore, it was considered to update recommendations 1.4.1 to 1.4.17 which currently do not include diagnostic criteria for ectopic pregnancy.

Decision: This review question should be added.

Expectant management of ectopic pregnancy

- New review question – How effective is expectant management compared to medical management for ectopic pregnancy?
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 the 4-year surveillance review, recommendations 1.6.1 to 1.6.14 might need to be revised because expectant management is not currently considered as an option for the management of ectopic pregnancy.

**Decision:** This review question should be added.

We also found evidence that supports current recommendations on:

- support and information giving
- management of miscarriage
- management of ectopic pregnancy.

We did not find any evidence related to:

- early pregnancy assessment services
- symptoms and signs of ectopic pregnancy and initial assessment
- anti-D rhesus prophylaxis.

We found evidence which was not covered in the guideline. However, the evidence was insufficient to add new recommendations in these areas at this time:

- Medical management of miscarriage in outpatient settings
- Diagnostic accuracy of serum biomarkers
- Active treatments for managing non-tubal ectopic pregnancy
- Single and double dose of methotrexate for ectopic pregnancy.

**Equalities**

No equalities issues were identified during the surveillance process.
Overall decision

After considering all the evidence and views of topic experts, we decided that a partial update and a modification in scope are necessary for this guideline.

See how we made the decision for further information.
Commentary on selected evidence

With advice from topic experts we selected 1 study for further commentary.

Management of miscarriage – Medical management

We selected a systematic review by van den Berg et al. (2015) for a full commentary because it reinforces guideline recommendations on the appropriate dose of misoprostol for the management of miscarriage. The systematic review discusses whether there is any added value of using mifepristone to the management of miscarriage.

What the guideline recommends

NICE guideline CG154 recommends the following medical management for missed or incomplete miscarriage (recommendations 1.5.9 to 1.5.17):

Do not offer mifepristone as a treatment for missed or incomplete miscarriage.

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.

For women with a missed miscarriage, use a single dose of 800 micrograms of misoprostol.

Advise the woman that if bleeding has not started 24 hours after treatment, she should contact her healthcare professional to determine ongoing individualised care.

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).

Offer all women receiving medical management of miscarriage pain relief and anti-emetics as needed.

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.
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.

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.

Methods

A systematic search was conducted from 1983 to May 2015 for randomised controlled trials (RCTs) and non-randomised studies considering the added value of mifepristone to current non-surgical treatment regimens in women with early pregnancy failure (EPF) which was defined as 'either an anembryonic gestation with a blighted ovum or as an early embryonic/foetal demise showing an embryo without cardiac activity'. The reviewers searched PubMed, Cochrane Library, as well as 2 databases for clinical trials (Current Controlled Trials and ClinicalTrials.gov). Two reviewers independently assessed the results of the search to identify relevant trials. Reviews, case reports, and unavailable full texts were excluded as well as studies on vital pregnancies, pregnant women in second or third trimester, or only incomplete miscarriages. Studies were extracted into a template data extraction sheet and risk of bias was assessed using the Cochrane Collaboration Risk of Bias tool. Meta-analysis was not performed because there was heterogeneity in treatment protocols.

Results

The search identified 155 studies, of which 16 were included in the final systematic review. Five of the included studies were RCTs and 11 were non-randomised studies.

Randomised controlled trials:

- One study (n=122 women with EPF or incomplete miscarriage <13 weeks) reported that complete evacuation rates were higher with sequential mifepristone and oral misoprostol (intervention) compared to expectant management (control) but the difference was not significant (rates were 82% and 76%, odds ratio [OR] 0.70 95% confidence interval [CI] 0.29 to 1.68, calculated by the systematic review).

- One study (n=115 women with EPF) reported that complete evacuation rates were lower with mifepristone followed by misoprostol (intervention) compared to 2 doses of misoprostol without mifepristone (control) but the difference was not significant (rates were 65.5% and 73.6%, OR 1.47, 95% CI 0.66 to 3.28, calculated by the systematic review).
One study (n=100 women with EPF >6 weeks and <13 weeks) randomised women after receiving mifepristone to receive misoprostol either sublingually or orally. Complete evacuation rates were higher with sublingual misoprostol compared to oral misoprostol but the difference was not significant (rates were 92% and 84%, OR 0.45, 95% CI 0.12 to 1.62, calculated by the systematic review).

One study (n=17 women with EPF) reported evacuation rates of 62.5% for sequential mifepristone with buccal misoprostol and 55.6% for placebo with buccal misoprostol (OR 0.50, 95% CI 0.03 to 6.86, calculated by the systematic review).

One study (n=174 women with EPF or incomplete miscarriage <14 weeks) compared complete evacuation rates between sequential mifepristone and vaginal misoprostol at immediate treatment (after diagnosis) or delayed treatment (1 week after expectant management). Complete evacuation rates for immediate treatment were significantly higher compared to delayed treatment (rates were 81% and 53%, OR 0.30 95% CI 0.15 to 0.60, calculated by the systematic review).

Treatment success rates (complete uterine evacuation) were higher in the intervention groups compared to the control groups in 4 of the 5 RCTs (n=413 women, 4 studies) but the difference was only significant for one of them (n=174 women). Four of the 5 RCTs were considered to be at high risk of blinding. In general, most of the RCTs had low risk of selection, attrition, reporting and other bias.

_Non-randomised studies:_

- 11 non-randomised studies were included by the systematic review (n=1475 women).
- 3 studies had a control group (2 studies were prospective and 1 retrospective). Eight studies did not have a control group (6 studies were prospective and 2 retrospective).
- There were differences between the included studies in terms of dose of mifepristone (from 200 mg to 600 mg) as well as dose and route of administration of misoprostol (oral, sublingual, or vaginal).
- Evacuation success rates for the intervention of mifepristone and misoprostol varied between 52% and 95%. Treatment estimates (for example odds ratios) were not calculated for any of the non-randomised studies.

All non-randomised studies were considered to be at low risk of attrition bias. All of these studies were considered to be at high risk of blinding. Most of the studies were considered to be at low risk of reporting and other bias.
Strengths and limitations

Strengths

The population included in the systematic review matches the population described in the guideline. The authors have used sound robust methods and the systematic review had low risk of bias. The analyses and interpretation of the findings were appropriate. The authors did not perform a meta-analysis because the studies were heterogeneous in terms of treatment protocols.

Limitations

The authors acknowledged that it was not possible to draw conclusions because the studies had limitations such as small sample sizes and non-blinded designs. They also mentioned that there was no international consensus for the definition of EPF (miscarriage). Therefore, inclusion of women in the reported studies was based on different definitions of EPF. Treatment protocols and definition of successful treatment also varied between studies.

Impact on guideline

This systematic review does not provide evidence of the added value of mifepristine to misoprostol. Therefore, this new evidence is unlikely to have an impact on NICE guideline CG154 which currently recommends do not offer mifepristone as a treatment for missed or incomplete miscarriage (recommendation 1.5.9).
How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of NICE's guideline on ectopic pregnancy and miscarriage (CG154) in 2012.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Previous surveillance update decisions for the guideline are on our website.

Evidence

We found 17 studies in a search for randomised controlled trials and systematic reviews published between 8 July 2014 and 2 May 2016. We also considered 2 additional studies identified by members of the guideline committee who originally worked on this guideline. A further study was identified through post-publication communications.

We also considered evidence identified in previous surveillance 2 years after publication of the guideline. This included 10 studies identified by search.

From all sources, we considered 30 studies to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: summary of evidence from surveillance and references for all evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline.

Views of stakeholders

Stakeholders commented on the decision not to update the guideline. Overall, 8 stakeholders commented. See appendix B for stakeholders' comments and our responses.
Eight stakeholders commented on the proposal to not update the guideline: 6 disagreed with the decision and 2 noted that they had no comments on the proposal. Most of the comments were related to expectant management for ectopic pregnancy. This area is currently out of scope in NICE guideline CG154. Therefore, it was decided to propose the inclusion of a new review question about expectant management for ectopic pregnancy. Stakeholders also commented that ultrasound criteria to make a diagnosis of ectopic pregnancy are not discussed in NICE guideline CG154. Therefore, it was considered to propose an update of recommendations 1.4.1 to 1.4.17 which currently do not include diagnostic criteria for ectopic pregnancy.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

**NICE Surveillance programme project team**

Sarah Willett  
Associate Director

Philip Alderson  
Consultant Clinical Adviser

Katrina Sparrow  
Technical Adviser

Yolanda Martinez  
Technical Analyst

The NICE project team would like to thank the topic experts who participated in the surveillance process.

ISBN: 978-1-4731-2286-4