NICE National Institute for Health and Care Excellence

2021 exceptional surveillance of ectopic pregnancy and miscarriage: diagnosis and initial management (NICE guideline NG126)

Surveillance report

Published: 21 October 2021

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Contents

Surveillance decision

The current exceptional review considered 2 areas of the guideline:

Medical management of miscarriage

We will update the guideline recommendations on medical management of missed miscarriage (recommendations 1.5.9 to 1.5.11). There is new evidence from a large UK study that treatment with mifepristone plus misoprostol was more clinically effective than misoprostol alone, which is currently recommended in the guideline.

Early pregnancy assessment services

We will not update the guideline recommendations on early pregnancy assessment units (EPAUs; recommendations 1.2.1 to 1.2.4). New evidence on EPAUs from a UK based study were inconclusive.

Exceptional surveillance review methods

Methods

To review these sections of the guideline, we took the following approach:

- Considered the evidence used to develop the guideline.
- Considered how the guideline was updated in 2019.
- Obtained feedback from topic experts.
- Assessed the new evidence and intelligence against the current recommendations.

Full updated literature searches were not needed because the information we obtained was enough to establish whether an update to the guideline was needed.

For further information, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Feedback from topic experts

In this exceptional review we engaged with topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. We sent online questionnaires about the new evidence that is relevant to the guideline and received feedback from 4 topic experts comprising of 2 gynaecology consultant nurses, 1 obstetrics/gynaecology consultant and 1 emergency medicine consultant.

Medical management of miscarriage

Reason for considering this area

The purpose of this section of the exceptional review was to examine any impact on NICE's guideline following completion of the MifeMiso trial, a National Institute for Health Research (NIHR) funded study, which published findings in the The Lancet.

The full Health Technology Assessment (HTA) report and economic analysis is awaiting publication and is expected in the second-half of 2021 (see the NIHR webpage for updates).

Information considered when developing the guideline

Evidence on misoprostol and mifepristone for the management of missed miscarriage was considered as part of guideline development in 2012.

The guideline was updated in April 2019 and focused on progesterone in treating threatened miscarriage and did not cover the medical management of missed miscarriage.

The committee responsible for developing the guideline in 2012 considered the evidence from 1 study (Stockheim et al. 2006), which suggested that there was no difference in the success rate of medical treatment (no need for surgical intervention) for women who received combined regimen of mifepristone and misoprostol compared with women who received misoprostol alone (relative risk [RR] 0.89, confidence interval [CI] 0.7 to 1.13, n=115 participants). Because of the low quality and limited evidence base and high cost of mifepristone compared with misoprostol identified at the time, the committee agreed that mifepristone should not be used in the management of miscarriage. These considerations form the background to recommendation 1.5.9, which states: Do not offer

mifepristone as a treatment for missed or incomplete miscarriage.

The lack of evidence to determine whether mifepristone plus misoprostol improves the success rate of medical management made this an area for a NICE research recommendation to answer the following question: Is the combination of mifepristone and misoprostol more effective than misoprostol alone in the medical management of miscarriage? (see the full guideline).

For the management of miscarriage, the NICE guideline recommends 3 alternative strategies: surgical management, expectant management and medical management. The guideline currently recommends misoprostol for the medical treatment of missed or incomplete miscarriage (see recommendations 1.5.10 to 1.5.13).

New published evidence

The NIHR funded MifeMiso trial triggered this exceptional review with findings published in The Lancet and BJOG (British Journal of Obstetrics and Gynaecology):

- Mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage (MifeMiso): a randomised, double-blind, placebo-controlled trial (Lancet).
- Cost-effectiveness of mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage: an economic evaluation based on the MifeMiso trial (BJOG).

MifeMiso study methods

The MifeMiso trial was a multicentre, pragmatic design, double-blind placebo-controlled trial of mifepristone and misoprostol versus placebo and misoprostol in the management of missed miscarriage in the first 14 weeks of pregnancy, diagnosed by pelvic ultrasound up to 14 weeks gestation. Participants were randomly allocated to a single dose of oral mifepristone 200 mg or an oral matched placebo tablet, followed by a single dose of vaginal, oral, or sublingual misoprostol (800 micrograms) 48 hours later. Participants in both arms (mifepristone or placebo) did not receive the subsequent misoprostol if they had successfully passed the gestational sac within the 48 hours. Outcome was assessed by pelvic ultrasound performed 7 days after random assignment. The participants were discharged from the trial if they passed the gestational sac within 7 days and had a negative urinary pregnancy test 3 weeks after randomisation. If participants failed to pass

the gestational sac within 7 days after randomisation, they were managed according to local hospital practice, which generally involved offering participants further doses of misoprostol 800 micrograms or surgical management if clinically indicated.

The primary outcome was failure to spontaneously pass the gestational sac within 7 days after randomisation, which was confirmed by pelvic ultrasound scan. Participants who did not undergo ultrasound scan on day 6 or 7 had their clinical data (including vaginal bleeding, abdominal pain, and passage of pregnancy tissues) assessed by a masked endpoint review committee who decided whether the primary outcome was met. Secondary outcomes included: surgical intervention to complete the miscarriage up to and including day 7 after randomisation and up to discharge from hospital; need for further doses of misoprostol within 7 days after randomisation and up to discharge; infection associated with miscarriage; duration of bleeding; negative pregnancy test result 21 days after randomisation and time from random assignment to discharge.

Sample size was calculated, and 710 women included to provide 90% power to detect a minimally important absolute difference of 10% points between the mifepristone plus misoprostol group and the placebo plus misoprostol group for the primary outcome (failure to pass the gestational sac within 7 days). Log binomial regression and liner regression models were used to calculate adjusted risk ratios for binary outcomes and to estimate adjusted mean differences for continuous outcomes.

All estimates of treatment effects between groups were adjusted for maternal age, body mass index, gestational age, parity, bleeding score and randomising centre.

MifeMiso results

The study recruited 711 women (aged 16 to 39 years) diagnosed by pelvic ultrasound with a missed miscarriage across 28 hospitals in the UK (696 women had available data for the primary outcome).

Key findings included:

- For the primary outcome, 59 (17%) of 348 women in the mifepristone plus misoprostol group did not pass the gestational sac spontaneously within 7 days versus 82 (24%) of 348 women in the placebo plus misoprostol group (RR 0.73, 95% CI 0.54 to 0.99). A further sensitivity analysis (excluding women for whom the primary outcome was determined using information from the masked endpoint review committee) showed statistically non-significant finding (RR 0.75, 95% CI 0.55 to 1.02). However, there is uncertainty whether these findings suggested any clinical important differences.
- For the key secondary outcome, 62 (17%) of 355 women in the mifepristone plus misoprostol group required surgical intervention to complete the miscarriage up to discharge versus 87 (25%) of 353 women in the placebo plus misoprostol group (RR 0.71, 95% CI 0.53 to 0.95).

There was no statistically significant difference between intervention and placebo group in any of the following outcomes: duration of bleeding reported by women, negative pregnancy test result 21 days after randomisation, incidence of serious adverse events, infection rate requiring inpatient antibiotic treatment, and need for further doses of misoprostol within 7 days after randomisation.

Economic analysis based on the MifeMiso trial

The cost effectiveness analysis published in the BJOG was carried out to assess mifepristone and misoprostol (MifeMiso) compared with placebo and misoprostol for the medical management of a missed miscarriage. The analysis was based on the primary outcome of the MifeMiso trial (failure to spontaneously pass the gestational sac within 7 days after randomisation) and was reported in terms of cost per successfully managed miscarriage and quality-adjusted life years (QALYs). The findings from the cost effectiveness analysis suggest that the MifeMiso intervention was more effective than misoprostol alone, with a benefit of 7 successfully managed miscarriages per 100 women. The MifeMiso intervention resulted in a cost saving of £182 (95% CI £26 to £338) per successfully managed miscarriage and a QALYs difference of 0.04% (95% CI -0.01 to 0.1%).

The model-based analysis showed that the MifeMiso intervention was more effective and less costly when compared with expectant management and with the current NICE recommended medical management strategy of misoprostol alone.

The analysis also looked at the surgical management of miscarriage, which is covered in the NICE guideline. Surgical management was found to be more costly and more effective than the MifeMiso intervention.

Other considerations

At the time of the NICE guideline publication in 2012 misoprostol did not have a UK marketing authorisation for treatment of missed or incomplete miscarriage. As of September 2021, it still doesn't have a UK marketing authorisation for the treatment of missed miscarriage. Use of mifepristone in combination with misoprostol for the treatment of missed miscarriage would be off-label.

The current price (NHS indicative price) of mifepristone 200 mg is £10.14 per tablet (see BNF monograph) and misoprostol price is £10.03 for a pack of 60 × 200 microgram (August Drug Tariff).

The cost effectiveness analysis of the MifeMiso trial showed that women in the placebo arm used more resources (hospital visits/admissions, need for surgery, additional dose of misoprostol) than women in the MifeMiso intervention arm and these differences were reflected in the costs.

Topic expert feedback

Feedback from all topic experts (n=4) indicated that the recommendations on medical management of missed miscarriage (recommendations 1.5.9 to 1.5.17) should be updated based on the MifeMiso evidence. One expert commented that mifepristone is included in medical management regimens in their service following the MifeMiso trial publication.

Impact

The NICE guideline does not make recommendations on the combined use of mifepristone and misoprostol (MifeMiso) for the management of missed miscarriage as, at the time of guideline development in 2012, there was insufficient evidence and there was relatively high cost of mifepristone (although no cost effectiveness analysis was performed). The data from the MifeMiso trial indicates that treatment with mifepristone plus misoprostol was more clinically and cost effective than misoprostol alone, which is currently recommended in the guideline for management of missed miscarriage (recommendations 1.5.9 to 1.5.11).

Therefore, we will update the recommendations on medical management of missed miscarriage.

Early pregnancy assessment services

Reason for considering this area

The purpose of this section of the exceptional review was to examine the impact on NICE's guideline following completion of Variations in the organisation of and outcomes from Early Pregnancy Assessment Units: the VESPA mixed-methods study, (an NIHR funded study).

Information considered when developing the guideline

When developing the NICE guideline in 2012, the committee wanted to establish whether the different models of service provision within EPAUs affected women's clinical outcomes and experiences of care. In particular, they wanted to establish whether the staffing structure, the ability of women to self-refer and the accessibility of the service might affect outcomes such as the length of hospital stay and need for admission. The guideline therefore sought to address the review question: What is the appropriate model for service organisation and delivery of EPAUs?

The available evidence at the time showed that EPAUs operate a number of different staffing models, ranging from those led by a medical consultant to a team-based approach with varying levels of input by clinicians. However, there was insufficient evidence to associate staffing structures with outcomes, and it was recognised that any recommendations on personnel would have significant cost implications. Therefore, the committee did not feel able to recommend that units adopt a specific staffing model without further conclusive evidence. The committee made recommendations 1.2.1 to 1.2.4, based on their own experiences about how early pregnancy assessment services should be provided.

The committee identified that research was needed to elucidate the most appropriate model of service organisation and delivery, in order to maximise the benefit to women and cost effectiveness of the service. Given there was heterogenous and inconclusive data linking aspects of the service organisation within the EPAU to the outcomes, the guideline committee made a recommendation for research on EPAUs. This stated that a national evaluation of EPAU 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 EPAUs compared with other models of care.

New evidence: the VESPA mixed-methods study

The NIHR funded Variations in the organisation of and outcomes from Early Pregnancy Assessment Units: the VESPA mixed-methods study was published in December 2020.

The primary aim of the study was to assess the impact of consultant presence on the rate of emergency admissions to hospital of women presenting with early pregnancy complications.

One of the secondary aims was to test the hypothesis that increased consultant presence in EPAUs improves other clinical outcomes, including the proportion of women having follow-up visits, ultrasound scans that fail to diagnose the location of the pregnancy (pregnancy of unknown location), negative laparoscopies for suspected ectopic pregnancies and ruptured ectopic pregnancies requiring blood transfusion.

VESPA study methods

The VESPA study employed a multimethod approach and included a:

- prospective cohort study of women attending EPAUs (to measure clinical outcomes)
- health economic evaluation (including skill mix and cost–utility model development)
- patient satisfaction survey
- qualitative interviews with service users
- EPAU staff survey
- hospital emergency care audit for women presenting with early pregnancy complications.

Corresponding to the study methods, data collection was organised into 7 data strands: 1. clinical outcomes in EPAUs; 2. emergency hospital care audit; 3. patient satisfaction; 4. staff satisfaction; 5. qualitative interviews; 6. health economic evaluation and 7. workforce analysis.

Main outcome measure:

- The primary outcome of the study was the proportion of women attending EPAUs who were admitted to hospital for further investigations and treatment (data strand 1).

Secondary outcome measures:

- Total number of emergency admissions of women presenting with early pregnancy complications (data strands 1 and 2).
- Ratio of new to follow-up visits (data strand 1).
- Rate of non-diagnostic ultrasound scans (pregnancy of unknown location; data strand 1).
- Proportion of laparoscopies performed for a suspected ectopic pregnancy with a negative finding (data strand 2).
- Patient satisfaction with the quality of care received (data strand 3).
- Staff experience of providing care in EPAUs (data strand 4).
- Quality-of-life measures, and anxiety levels of women before and after assessment at the EPAU (data strand 6).
- Cost effectiveness of different staffing models (data strand 7).

VESPA study results

Clinical data were collected from 6,606 women who attended the 44 participating EPAUs in the UK. The majority of the EPAUs (37/44) had a unit volume of <4,000 visits per year and 22 EPAUs had a volume of <2,500 visits per year. A cut-off point of 2,500 visits was used to describe the units as high or low volume in the study's data analysis. A large number of the EPAUs (25/44) had no planned consultant presence. Out of the 19 remaining EPAUs 15 had planned consultant presence of <35% of opening time.

Findings from the 7 data strands:

1. Clinical outcomes in EPAUs

Data collection was carried out over a period of 8 months from 6,606 participants. The hospital admission rate among units varied between 0.7% and 13.7%. The highest admission rate (64%) was recorded in women diagnosed with ectopic pregnancies.

There was no evidence of an association between the admission rate and consultant presence (p=0.497). There was evidence that the number of visits per year increases as unit volume increases (p=0.002). There was no evidence of an association between the proportion of women attending for multiple follow-up visits and planned consultant time (p=0.281) or weekend opening (p=0.443). There was no association between pregnancy of unknown location rate and consultant presence (p=0.955). The findings showed that 18% of all laparoscopies carried out in 21 EPAUs for suspected ectopic pregnancies were negative, with a wide variation between different EPAUs. There was also no evidence of an association between consultant presence and the rate of negative laparoscopies (p=0.51).

2. Emergency hospital care audit

Audit of emergency care was carried out in 42 EPAUs that operated with a co-terminus A&E department. Data from 29/42 EPAUs were available. The primary outcome was the proportion of women attending EPAUs who were admitted to hospital for further investigations and treatment (emergency hospital admissions). Additionally, emergency hospital admissions via A&E and the contribution of admissions through EPAUs to the total emergency admissions were also analysed.

The primary outcome analysis showed that consultant presence had no significant effect on emergency admission rates from EPAUs. The number of emergency hospital admissions from A&E was higher than the number of emergency admissions from EPAUs. There was some evidence of an association between emergency admission from A&E and EPAUs with weekend opening (p=0.037; a 1-hour increase in weekend opening of EPAUs was associated with 2.4% lower odds of an emergency admission from A&E). There was no evidence of an association between emergency admission rate from A&E and EPAUs' planned consultant time (p=0.280) or EPAUs' unit volume (p=0.647).

3. Patient satisfaction

A total of 3,803 out of 4,217 women who agreed to take part in the study completed the patient satisfaction questionnaires. Patient satisfaction rate varied from 99% to 66% across units. There was no significant association between patient satisfaction with consultant presence (p=0.075).

4. Staff satisfaction

A total of 158 out of 338 staff members who were approached to take part in the study

fully completed the staff satisfaction questionnaires. There was a difference of 17% in the percentage of staff who 'witnessed potentially harmful errors, near-misses or incidents in the last month' between the units with (58%) and units without consultant presence (41%).

5. Qualitative interviews

A total of 153 women were contacted to take a part in the qualitative interviews. Of the 60 women who responded, 39 were interviewed. Women worried about 'sensitive patient management' and privacy issues when personal information was discussed in a confined space. They preferred a separate EPAU waiting area or a separate building to maintain privacy. They also indicated that the services need to be accessible out of regular working hours, during weekends and bank holidays.

6. Health economic evaluation

The analysis measured the costs associated with ultrasounds, blood tests, admissions and staff time. Data for 6,531 women were available for analysis. The mean total cost per patient was £225 (standard deviation £537). The main contributor to total costs was surgical admissions, followed by ultrasounds. Lower volume units, no consultant presence and weekend closure were associated with lower costs.

Women were also requested to complete health economic questionnaires (standardised measure of health-related quality of life EQ-5D-5L) at 2 weeks (n=3,803) and 3 months (n=1,415) after the participant's final visit to the EPAU. The questionnaire asked patients to score their own health based on 5 elements: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each element had 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Many patients returned either the 2-week or 3-month questionnaires late (assessment made for 4 and 18 weeks) and the response rate was also low (26%). A total of 889 questionnaires for 2 phases were collected and analysed. The result was converted into a number between 0 (equivalent to death) and 1 (full health) and then converted to an index score that was used to calculate QALYs. The findings showed very small differences in expected QALYs at 4 and 18 weeks post EPAU visits in different EPAUs. Care provided in the EPAU had a positive effect on women's health and emotional wellbeing, with three-quarters of women reporting a decrease in anxiety scores and a positive change in their overall health at 4 weeks.

7. Workforce analysis

Workforce analysis was carried out to determine the ideal workforce configuration for EPAUs. Data was collected for overall salary cost per 1,000 patients, average time spent with a patient across all staff types, number of admissions, proportion of multiple visits (3 or more), and number of pregnancy of unknown location per 1,000 patients. A total of 6,531 completed records were used for the workforce analysis. The largest salary cost across all the units was for sonographers. Diagnoses of ectopic pregnancies costs up to 4.5 times more than a normal/live intrauterine pregnancy.

Overall, the salary costs variations were not statistically significant across different units. There was a significant increase in the salary cost between the strata when grouped as consultant present compared with consultant not present (p=0.037). Workforce analysis indicated that consultant-delivered care might be more cost-effective in high-volume units, as the consultants' time may not be well utilised in low volume units.

Overall

The finding showed that the highest admission rate was recorded in women diagnosed with ectopic pregnancies. The study showed that consultant presence in EPAUs has limited impact on the clinical outcomes measured (that is the proportion of women who are admitted to hospital for further investigations/treatment, proportion of women who are admitted as emergencies, pregnancy of unknown location rates, negative laparoscopy rate and patient satisfaction). The study indicated that this finding could be explained by the generally low level of consultant presence in EPAUs.

Study limitations

The authors stated that they were unable to establish the amount of time that a consultant should spend to deliver optimal patient care because the time that consultants spent in the units were generally very low. Another limitation of the study was inconsistent use of clinical care pathway protocols across EPAUs, a lack of information regarding the competencies of ultrasound operators, variations in patient diagnosis, and the low response rates to health economic and patient satisfaction questionnaires.

Topic expert feedback

Topic experts were asked whether the VESPA study has any impact on the NICE guideline recommendations on appropriate models for EPAU. Three out of 4 topic experts who responded believed that the recommendations should not be updated in response to

evidence from the VESPA study. One expert expressed a lack of confidence in the findings because of the heterogeneity present in the included EPAUs (remote versus on-site, different access hours and varied staff skill, consultant presence) and felt the findings may not be applicable to all institutions in the UK. One expert responded that they could not anticipate how the VESPA results could be interpreted into recommendations and that the existing recommendations were satisfactory. One topic expert who responded 'yes' to update, indicated that units are safer when they are staffed by people experienced in the area of expertise. This is in line with current recommendations that 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 (recommendation 1.2.2).

Impact

Current recommendations suggest that 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 (recommendation 1.2.2). Recommendations do not suggest a specific staffing model for EPAUs.

Although the VESPA trial provides valuable insight into EPAUs model organisation, it was unable to estimate the potential impact of factors such as level of supervision, quality of ultrasound equipment, variation in clinical care pathway protocols, and staff experience or competence on the primary and secondary outcomes.

Following consideration of the results from the VESPA study, previous evidence, as well as topic expert feedback, we will not update the guideline recommendations on EPAUs.

Equalities

No equalities issues were identified during the surveillance process.

ISBN: 978-1-4731-4319-7