



# 2019 exceptional surveillance of ectopic pregnancy and miscarriage: diagnosis and initial management (NICE guideline NG126)

Surveillance report

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## Surveillance decision

We will update the guideline on [ectopic pregnancy and miscarriage: diagnosis and initial management](#). This update will focus on progesterone in treating threatened miscarriage.

## Background

### Guideline development

Evidence on progesterone treatment for threatened miscarriage was considered as part of the guideline development in April 2012. Overall, the committee that developed the guideline felt that the evidence was insufficient to recommend the use of progesterone for treating threatened miscarriage in pregnant women. At the time the guideline was developed, it was not usual UK practice to offer progesterone for threatened miscarriage, and the committee had concerns about recommending a significant change in practice based on poor quality evidence. This was partly because the evidence was of low or very low quality with low numbers of participants, but also because the committee was concerned that available studies did not adopt an end point beyond the birth and none included neonatal congenital abnormalities as an outcome. The lack of strong evidence made this a priority area for research: a recommendation for research was made to answer the following question [are progesterone or progestogens effective in treating threatened miscarriage?](#)

## Reasons for the decision

### New published evidence

The purpose of this exceptional review was to examine any impact on NICE's guideline on ectopic pregnancy and miscarriage: diagnosis and initial management following completion of the [PRISM Trial](#) (PRogesterone In Spontaneous Miscarriage Trial), a National Institute for Health Research (NIHR) funded study (NIHR HTA 12/167/26) which published findings in the *New England Journal of Medicine*: [A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy](#) (2019).

The full Health Technology Assessment (HTA) report and economic analysis is awaiting publication (see the [NIHR webpage](#) for updates). There is, however, a recent NIHR Signal which discusses the findings: [Routine use of progesterone does not prevent miscarriage](#) (2019).

We also considered 1 Cochrane systematic review as part of this exceptional review, as it was referenced in the NIHR Signal; the Cochrane review, which was updated in 2018, is summarised below. The earlier version of the Cochrane review (published 2011) was not included in the evidence considered during development of the NICE guideline as the 4 included studies were already covered in the full guideline.

## PRISM study methods

This PRISM trial was a multicentre, double blind, placebo-controlled trial of progesterone in women with early pregnancy vaginal bleeding. Women recruited from across the UK were randomly assigned to vaginal progesterone (400 mg twice daily) or placebo until 16 weeks of pregnancy. The primary outcome was live birth after 34 weeks. Primary analysis was by intention to treat. Pre-planned analyses were undertaken for 10 subgroups (limited to the primary outcome measure and miscarriage rate): maternal age, BMI, foetal heart activity, estimated gestation at presentation, amount of vaginal bleeding, number of previous miscarriages, number of gestational sacs, race, history of polycystic ovaries and previous cervical excision. For further information on the study methods see the [NIHR Signal](#) and [New England Journal of Medicine](#). Whilst survival at 28 days of neonatal life was recorded, longer term follow-up was outside the scope of the trial.

## PRISM results

The PRISM study recruited 4,153 women (aged 16 to 39 years) across 48 hospitals in the UK. Key findings include:

- For the primary outcome, incidence of live births after 34 weeks was 75% and 72% in the progesterone and placebo groups respectively (relative rate [RR], 1.03; 95% confidence interval [CI], 1.00 to 1.07).
- However, a significant effect was identified in analysis for 1 of 10 prespecified subgroups: among women who had 3 or more previous miscarriages (n=285), incidence of live births after 34 weeks was 72% and 57% in the progesterone and placebo groups respectively (RR, 1.28; 95% CI, 1.08 to 1.51).

For secondary outcomes:

- The incidence of miscarriage was 20% and 22% in the progesterone and placebo groups respectively (RR, 0.91; 95% CI, 0.81 to 1.01).
- There was no difference between groups in the rate of maternal or neonatal adverse effects, which affected 5% of both groups.

## Cochrane review

The following Cochrane systematic review was updated in 2018, before the PRISM trial results were available: [Progestogen for treating threatened miscarriage](#). It included 7 trials of women with threatened miscarriage at or less than 23 weeks (696 women). The meta-analysis for both oral and vaginal progestogen supplementation showed a statistically significant effect for reducing the risk of miscarriage compared to placebo or no treatment controls (RR 0.64, 95% CI 0.47 to 0.87; 7 trials; 696 women; moderate-quality evidence). Conversely, for a secondary outcome, use of progestogens compared to placebo or no treatment showed no statistically significant difference in the rate of preterm birth (RR 0.86, 95% CI 0.52 to 1.44; 5 trials; 588 women; low-quality evidence). Analysis of live births was not reported in this review. The authors also report uncertainty around treatment effect on congenital abnormalities, when comparing progestogens to placebo or no treatment, because the quality of evidence is very low (RR 0.70, 95% CI 0.10 to 4.82; 2 trials; 337 infants; very low quality evidence).

## Views of 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 received feedback from 4 topic experts (2 consultant obstetrician and gynaecologists and 2 consultant nurse gynaecologists) with 3 indicating that the guideline should be updated to take account of the PRISM trial. Based on the findings of the PRISM trial the 3 experts noted use of progesterone in women with a history of recurrent miscarriage specifically warranted consideration in the guideline. One expert did not believe the new PRISM trial would support a change to the guideline – mainly because subgroup was not identified in the randomisation and stratification variables of the PRISM study and therefore concluded it offers an unsound basis for any conclusion to be drawn.

## Impact

The NICE guideline does not make recommendations on the use progestogen for treating threatened miscarriage as there was insufficient good quality evidence at the time of guideline development.

- The PRISM trial is a large, well-conducted study which provides evidence that progesterone did not affect the chance of live birth among women presenting with vaginal bleeding in the first 12 weeks of pregnancy.

Although the Cochrane review, [Progestogen for treating threatened miscarriage](#), tentatively concluded that progestogens are probably effective in the treatment of threatened miscarriage,

the PRISM trial included a greater number of participants than the combined number of participants across the 7 trials included in the Cochrane review (4,153 versus 696 women).

- Considering the findings of both the PRISM trial and the Cochrane review, the evidence may not support the routine use of progesterone in women with early pregnancy vaginal bleeding.

A prespecified analysis in the PRISM trial found that progesterone improved the chance of live birth among 285 women with 3 or more previous miscarriages.

- The findings of the PRISM trial, may support the use of progesterone in women with early pregnancy vaginal bleeding and a history of 3 or more miscarriages.

Regarding existing evidence on the effect of progesterone treatment on maternal or neonatal congenital abnormalities, the Cochrane review which updated in 2018, [Progestogen for treating threatened miscarriage](#), identified that there is very limited evidence available - and resulting uncertainty - on the treatment effect of progesterone on congenital abnormalities. The subsequent publication of the PRISM trial helps address uncertainty in the safety of progestogen for treating threatened miscarriage as there was no significant difference in the rate of maternal or neonatal adverse events for treatment compared with placebo control participants (5% in both groups). However, it should be noted that the outcomes of the PRISM trial were limited to 28 days of neonatal life with longer term outcomes beyond the scope of the trial.

Following consideration of the results from the PRISM study and relevant Cochrane reviews, as well as topic expert feedback, the new evidence is directly relevant to the recommendation for research ([are progesterone or progestogens effective in treating threatened miscarriage?](#)) and may have an impact on the guideline, particularly in relation to women with early pregnancy vaginal bleeding and a history of 3 or more miscarriages.

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