NICE National Institute for Health and Care Excellence

2022 exceptional surveillance of twin and triplet pregnancy (NICE guideline NG137)

Surveillance report

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Surveillance decision

We will update section 1.5 on the use of progesterone for preventing preterm birth in the NICE guideline on twin and triplet pregnancy.

Reasons for the exceptional review

The NICE surveillance team have been actively tracking the EPPPIC: meta-analysis of individual participant data from randomised controlled trials (RCTs), which has now published.

Methods

The exceptional surveillance process consisted of:

- Considering new evidence being tracked by NICE as it publishes and assessing it for an impact on the guideline.
- Considering relevant information from previous surveillance reviews of the guidelines.
- Considering the evidence used to develop the guidelines.
- Examining related NICE guidance and quality standards.
- Examining the NICE event tracker for relevant ongoing and published events.
- A search for ongoing research.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

We decided that full updated literature searches were not needed because the information we had from the new published evidence was enough to establish whether an update to the guideline was needed.

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

Information considered in this exceptional surveillance review

The EPPPIC meta-analysis of individual participant data from RCTs compared vaginal progesterone, intramuscular 17-hydroxyprogesterone caproate (17-OHPC), or oral progesterone with control, or with each other, in asymptomatic women at risk of preterm birth (31 trials, 11,644 women). Fourteen trials compared vaginal progesterone with control; 6 in singleton pregnancies, 5 in multiple pregnancies, and 3 with mixed populations (mainly singletons). Thirteen trials compared 17-OHPC with control, 5 in singleton and 8 in multiple pregnancies. Two compared oral progesterone with placebo, and 2 trials compared vaginal progesterone and 17-OHPC in singleton pregnancies. Trials were generally at low risk of bias.

For twins, vaginal progesterone did not reduce preterm birth before 34 weeks (8 trials, 2,046 women: relative risk [RR] 1.01, 95% confidence interval [CI] 0.84 to 1.20) nor did 17-OHPC for twins or triplets (8 trials, 2,253 women: 1.04, 0.92 to 1.18). Preterm premature rupture of membranes was significantly increased with 17-OHPC exposure in multifetal gestations (rupture less than 34 weeks RR 1.59, 95% CI 1.15 to 2.22), but the authors found no consistent benefit or harm for other outcomes with either vaginal progesterone or 17-OHPC. Trials in multiple pregnancies mostly included women without additional risk factors.

The authors noted several limitations in the study. Individual patient data was unavailable for 17 potentially eligible trials, but the authors deemed that most of these studies were small single centre studies, apart from 1. The authors noted that sensitivity analysis incorporating aggregated data from these trials did not alter conclusions. Further network meta-analysis (NMA) was conducted to compare all treatments and found no evidence of any difference in effect between vaginal progesterone and 17-OHPC. There is uncertainty of the findings from the NMA due to limited data and it being based mostly on indirect comparisons. The authors also noted there were few data for certain subpopulations.

The authors concluded that for unselected multiple pregnancies, treatment with a progesterone was not supported by the evidence. The effectiveness of progesterone for women with multiple pregnancies and additional risk factors such as short cervix or prior preterm birth was uncertain.

The authors noted a recently published trial of vaginal progesterone in twins (Rehal et al. 2021), which was not included within EPPPIC. The trial included 1,194 women with twin

pregnancies randomised to progesterone or placebo and the results were generally consistent with EPPPIC in finding no overall reduction in the incidence of preterm birth with progesterone in twins. However, this trial conducted a post hoc time-to-event analysis which suggested that progesterone may reduce the risk of spontaneous birth before 32 weeks of pregnancy in women carrying twins with a cervical length of less than 30 mm, but it may increase the risk for those with a cervical length of 30 mm or greater.

There is also an ongoing trial of pessary and progesterone for preterm prevention in 630 women with twin gestations with a short cervix (PROSPECT trial) but this is not due to complete until 2025. This study will be tracked by NICE so its results can be assessed for impact on the guideline when it publishes.

Information considered in previous surveillance of this guideline

There has been no surveillance of the NICE guideline on twin and triplet pregnancy since it was published in 2019. However, the NICE team have been tracking the EPPPIC study as part of its proactive surveillance process.

Information considered when developing the guideline

During the 2019 update, the committee did not make any recommendations on vaginal progesterone for preventing preterm birth in twin pregnancies because they were awaiting evidence in this area, particularly about the use of progesterone in subgroups of women with a short cervix. As such the section on preventing preterm birth states that NICE will carry out an exceptional update based on the new evidence when it becomes available.

Impact on the guideline

During the 2019 update, the committee did not make any recommendations on vaginal progesterone for preventing preterm birth in twins. The new evidence from EPPPIC found that treatment with a progesterone is not supported by the evidence in women with multiple pregnancies. A further study provided some indication that this treatment effect is modified by cervical length. As such, an update to the guideline is warranted.

Other relevant NICE guidance

NICE's quality standard on multiple pregnancy: twin and triplet pregnancies does not currently cover treatment with a progesterone.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

We will update section 1.5 on the use of progesterone for preventing preterm birth in the NICE guideline on twin and triplet pregnancy.

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