NIHR Signal Updated evidence on progesterone to prevent preterm birth in at-risk pregnancies

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Progesterone administered via the vagina may reduce the risk of preterm birth in women who are at risk of giving birth early when compared to a placebo, treatment as usual or no intervention. Other treatments, such as oral or injected progesterone, cervical stitch, and pessary, appear not to show the same level of effectiveness.

A recent trial suggested that vaginal progesterone provided little or no benefit in preventing preterm birth. Those results have been pooled with 39 other trials in this updated systematic review and network analysis. Looked at all together, this review suggests that vaginal progesterone is the only consistently effective option. But a more cautious interpretation is required because the trials are not all reliable.

The NICE guidance for preterm labour and birth is currently being updated. This review and the UK-based trial should help to inform the expert discussion regarding any update.

Fertility and childbirth, Medicines, Metabolic disorders, Nursing, Primary care, Acute and general medicine

Why was this study needed?

In the UK, about eight babies in every hundred are born prematurely (before the 37th week of pregnancy). Preterm birth is the biggest cause of death and serious complications in newborn babies (up to 28 days old). Risk of death increases the earlier a baby is born. Babies who survive have increased rates of disability, particularly neurodevelopment problems.

Risk factors for mothers giving birth prematurely include having already had a preterm birth and having a short cervix (less than 25mm).

There are several interventions for reducing the chances of giving birth prematurely for women at increased risk. Treating with progesterone provides one set of options. Another possibility is a cervical stitch (also known as cerclage), which helps to keep the cervix closed.

Previous research has resulted in conflicting conclusions about the best treatment. This study aimed to review all the evidence, including a number of new trials.

What did this study do?

This systematic review included 40 randomised controlled trials comparing progesterone, cervical stitch or pessary with a control group. Progesterone was given either vaginally, orally or a synthesised version called 17α-hydroxyprogesterone caproate (17-OHPC) was injected into a muscle. The control groups received placebo, no intervention, or usual treatment.

The 11,311 women in the trials were expecting a single baby and were at risk of preterm birth.

A network meta-analysis was carried out, which enabled indirect comparisons of the different interventions against each other.

A quarter of the trials took place in the US, eight were labelled as 'multinational' (some of which included UK participants) and included participants from Europe, Asia, Africa and Australia. The trials were of moderate to low quality, casting some uncertainty in the findings.

What did it find?

In women with any risk factor:

- Progesterone (in any form, administered by any route) reduced preterm births before 34 weeks by 55% compared to control (odds ratio [OR] 0.45, 95% credible interval (CrI) 0.23 to 0.81; 9 studies, moderate-quality evidence). It also reduced preterm births before 37 weeks by 48% (OR 0.52, 95% CrI 0.36 to 0.73; 15 studies, low-quality evidence).
- Vaginal progesterone reduced preterm birth before 34 weeks (OR 0.43, 95% CrI 0.21 to 0.78; 7 studies; low-quality evidence), and before 37 weeks (OR 0.51, 05% CrI 0.34 to 0.74; 8 studies; low-quality evidence). It also reduced neonatal death (OR 0.41, 95% CrI 0.20 to 0.83; 5 studies; moderate-quality evidence).
- Intramuscular 17-OHPC only reduced preterm birth at less than 37 weeks (OR 0.61, 95% CrI 0.39 to 0.92; 5 studies, moderate-quality evidence). Oral progesterone or cervical stitch did not reduce preterm birth or neonatal death.

In women with a previous preterm birth:

- Vaginal progesterone reduced preterm birth at less than 34 weeks (OR 0.29, 95% confidence interval [CI] 0.12 to 0.68; 3 studies, moderate-quality evidence), and at less than 37 weeks (OR 0.43, 95% CrI 0.23 to 0.74; 5 studies, moderate-quality evidence). Oral progesterone reduced preterm birth at less than 34 weeks (OR 0.42, 95% CI 0.22 to 0.83; 1 study, low-quality evidence), but not at 37 weeks and didn't reduce neonatal death. Intramuscular 17-OHPC reduced preterm birth at less than 37 weeks (OR 0.53, CrI 0.27 to 0.95; 4 studies, moderate-quality evidence) and reduced neonatal deaths (OR 0.39, 95% CI 0.16 to 0.95; 2 studies, low-quality evidence). Cervical stitch did not show any reduction in risks.

In women with a short cervix:

- Vaginal progesterone reduced preterm birth at less than 34 weeks (OR 0.45, 95% CI 0.24 to 0.84; 1 study, low-quality evidence). No other intervention showed a significant result.

What does current guidance say on this issue?

NICE published a guideline in 2015 on preterm labour and birth. It recommends that a choice of vaginal progesterone or a cervical stitch should be offered to women with both a previous preterm birth and a cervix measuring less than 25mm on an ultrasound scan carried out between 16 and 24 weeks. It also says that vaginal progesterone should be offered to women with a short cervix but no history of preterm birth.

This guideline is currently being updated, due for publication in March 2020.

What are the implications?

Progesterone was the only intervention that appeared to reduce the risk of preterm birth and neonatal death in at-risk pregnancies, though the benefit was less in the better quality trials. This suggests that it could be the preferred option offered to women at risk.

However, as this finding runs contrary to the lack of benefit in the recent large UK-based OPPTIMUM trial, reported in a previous Signal, further assessment of the strength of both studies and expert clinical assessment is required. The OPPTIMUM trial was placebo-controlled and undertaken in the NHS with women receiving the usual care for this country.

That trial reported longer-term outcomes than those in this systematic review. The review has included smaller, less reliable studies and studies using a variety of different doses and routes of administration; this reduces its applicability to the UK.

In this situation, expert views on the evidence will be required to decide on the role of progesterone in the revised NICE guidelines.

Citation and Funding

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Expert commentary

In response to a lack of consensus over the best preventative strategies for preterm birth, Jarde et al. argue the case for progesterone being the only intervention with consistent, proven effectiveness.

However, the underlying progesterone studies exhibit challenges with data quality and heterogeneity, and the lack of good quality data from cerclage and pessary trials makes direct comparison problematic.

We need further trials, not only to understand the heterogeneity of progesterone but also to provide better quality studies and more up-to-date evidence for the use of pessary and cerclage.

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The commentators declare no conflicting interests