

Progesterone to prevent miscarriage in women with early pregnancy bleeding: the PRISM RCT

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Scientific summary

The PRISM RCT

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Scientific summary

Background

Progesterone, produced by the corpus luteum in the ovaries, helps to prepare the endometrium for implantation of the embryo and thus is an essential hormone for a successful pregnancy. Evidence from several controlled clinical trials suggested that there was a benefit from progesterone therapy, but with insufficient certainty owing to the size of the trials and their methodological weaknesses. This prompted the National Institute for Health and Care Excellence (NICE) (Clinical Guideline 154 on 'Ectopic Pregnancy and Miscarriage'; National Collaborating Centre for Women's and Children's Health. *NICE Clinical Guidelines [CG154]. Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management*. London: NICE; 2012) to call for a definitive trial to answer this question.

Objectives

The Progesterone in Spontaneous Miscarriage study was designed to test the hypothesis that, in women with vaginal bleeding in the first 12 weeks of pregnancy, receiving vaginal progesterone (400-mg pessaries, twice daily) as soon as possible after the identification of an intrauterine gestation sac until 16 weeks of gestation increases the rate of live births at ≥ 34 completed weeks of pregnancy by at least 5% compared with placebo. In addition, an economic evaluation was conducted alongside the trial to assess the relative cost-effectiveness of progesterone compared with placebo.

Design

The Progesterone in Spontaneous Miscarriage trial was a multicentre, double-blind, placebo-controlled randomised trial, with economic evaluation.

Setting

The study was conducted in hospital settings across the UK (48 sites) between 2015 and 2018.

Participants

Participants were women who presented with early pregnancy bleeding that had started in the preceding 4 days, who were in the first 12 weeks of pregnancy and who had an intrauterine gestation sac visible on ultrasonography. Participants were aged 16–39 years at randomisation and gave informed consent.

Interventions

Each participant in the Progesterone in Spontaneous Miscarriage trial received either progesterone or placebo pessaries at a dose of 400 mg twice daily, which were administered vaginally from the day of randomisation to 16 completed weeks of gestation.

Main outcome measures

The primary outcome measure was live birth at ≥ 34 completed weeks of gestation. The secondary outcome measures included ongoing pregnancy at 12 weeks, miscarriage, gestation at delivery, neonatal survival at 28 days of life, congenital anomalies and resource use.

Methods

Participants were randomised online in a 1 : 1 ratio using a secure internet facility through an integrated trial management system. Minimisation was implemented for age (< 35 or ≥ 35 years), body mass index (< 30 or ≥ 30 kg/m²), fetal heart activity (present or absent), gestation at presentation by date of last menstrual bleed (≤ 42 or > 42 days) and amount of bleeding (pictorial bleeding assessment chart score of ≤ 2 or ≥ 3). Data were collected at three points of outcome assessment after randomisation, up to 28 days after birth. The primary analysis was by intention to treat. A within-trial cost-effectiveness analysis was conducted from the NHS and NHS/Personal Social Services perspective based on the main clinical outcome of this trial.

Results

A total of 4153 women from 48 hospitals in the UK received either progesterone (2079 participants) or placebo (2074 participants). The follow-up rate for the primary outcome was 97.2% (4038 out of 4153 participants). The live birth rate was 75% (1513 out of 2025 participants) in the progesterone group compared with 72% (1459 out of 2013 participants) in the placebo group (relative rate 1.03, 95% confidence interval 1.00 to 1.07; $p = 0.08$). A significant subgroup effect (interaction test $p = 0.007$) was identified for prespecified subgroups by the number of previous miscarriages: none (74% progesterone vs. 75% placebo; relative rate 0.99, 95% confidence interval 0.95 to 1.04; $p = 0.72$); one or two (76% progesterone vs. 72% placebo; relative rate 1.05, 95% confidence interval 1.00 to 1.12; $p = 0.07$); and three or more (72% progesterone vs. 57% placebo; relative rate 1.28, 95% confidence interval 1.08 to 1.51; $p = 0.004$), thus demonstrating a biological gradient by the increasing number of previous miscarriages. A significant post hoc subgroup effect (interaction test $p = 0.01$) was found when we grouped all participants with any number of previous miscarriage(s) (75% in the progesterone group vs. 70% in the placebo group; relative rate 1.09, 95% confidence interval 1.03 to 1.15; $p = 0.003$). There were no significant differences in the occurrence of adverse events.

For secondary outcomes, there was evidence that progesterone may increase the rate of ongoing pregnancy at 12 weeks (83% in the progesterone group vs. 80% in the placebo group; relative rate 1.04, 95% confidence interval 1.01 to 1.07; $p = 0.01$). There was no evidence of a difference in the safety outcomes.

The results of the health economics analysis show that the average cost per participant was £7655 in the progesterone arm and £7572 in the placebo arm, a mean cost difference of £83 (adjusted mean difference £76, 95% confidence interval -£559 to £711) between the two arms. The incremental cost-effectiveness ratio of progesterone compared with placebo was estimated at £3305 per additional live birth at ≥ 34 weeks of gestation. These results suggest that progesterone is likely to be perceived by decision-makers as cost-effective.

Conclusions

Progesterone therapy in the first trimester of pregnancy did not result in a significantly higher rate of live births among women with threatened miscarriage overall. However, an increase in live births was observed in the subgroup of women with early pregnancy bleeding and a history of previous miscarriages. A conclusion on the cost-effectiveness of the PRISM trial would depend on the amount that society is willing to pay to increase the chances of an additional live birth at ≥ 34 weeks.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN14163439, EudraCT 2014-002348-42 and Integrated Research Application System (IRAS) 158326.

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This report

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