

# **PROMISE: first-trimester progesterone therapy in women with a history of unexplained recurrent miscarriages – a randomised, double-blind, placebo-controlled, international multicentre trial and economic evaluation**

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## Scientific summary

### **The PROMISE trial and economic evaluation**

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# Scientific summary

## Background

Progesterone is essential to maintain a healthy pregnancy. As progesterone plays an important role in maintaining the lining of the uterus and fetal development, some researchers have hypothesised that maternal levels of progesterone could play a role in the pathogenesis of miscarriage. Hence it has been hypothesised that progesterone supplementation in the first trimester of pregnancy may reduce the miscarriage rate and increase the live birth rate among women at high risk of miscarriage, for example women with a history of recurrent miscarriage (RM). The evidence achieved in four controlled clinical trials conducted before the PROMISE trial suggested a benefit from progesterone therapy, but without sufficient certainty to usefully guide clinical practice. Therefore, a Royal College of Obstetricians and Gynaecologists guideline and a Cochrane review called for a definitive trial to evaluate this research question.

## Objectives

The PROMISE study was designed to test the hypothesis that in women with unexplained RM, progesterone (400-mg vaginal capsules, twice daily), started as soon as practicable after a positive urinary pregnancy test (and no later than 6 weeks of gestation) and continued to 12 weeks of gestation, compared with placebo, would increase live births beyond 24 completed weeks of pregnancy by at least 10%. A concurrent economic evaluation for cost-effectiveness was conducted.

## Design

The trial was a randomised, double-blind, placebo-controlled, international multicentre study, with health economic evaluation.

## Setting

The study was conducted in hospital settings across the UK (36 sites) and in the Netherlands (nine sites).

## Participants

Participants were women with unexplained RM (three or more consecutive or non-consecutive first-trimester losses), aged between 18 and 39 years at randomisation, conceiving naturally, and willing and able to give informed consent.

## Interventions

Each participant in the PROMISE trial received either micronised progesterone at a dose of 400 mg (two vaginal capsules of 200 mg) or placebo vaginal capsules twice daily, administered vaginally from the date of randomisation soon after a positive urinary pregnancy test (and no later than 6 weeks of gestation) until 12 completed weeks of gestation (or earlier if the pregnancy ended before 12 weeks).

## Main outcome measures

Outcome measures included live birth beyond 24 completed weeks of gestation (primary outcome), clinical pregnancy at 6–8 weeks, ongoing pregnancy at 12 weeks, miscarriage, gestation at delivery, neonatal survival at 28 days of life, congenital abnormalities, various exploratory outcomes and resource use.

## Methods

Participants were randomised after receiving confirmation of pregnancy. Third-party randomisation was performed online via a secure internet facility, and treatment commenced as soon as practicable after randomisation. Data were collected on four occasions of outcome assessment after randomisation, up to 28 days after birth. The primary analysis was by intention to treat. The primary health economic analysis was to estimate the incremental cost-effectiveness ratio (ICER) for additional live births beyond 24 weeks.

## Results

A total of 1568 participants were screened for eligibility. Of the 836 women randomised, 404 participants received progesterone therapy and 432 received placebo. The baseline data (age, body mass index, maternal ethnicity, smoking status and parity) of the participants were comparable between the two arms of the trial.

The follow-up rate for the primary outcome was 826 out of 836 (98.8%). The live birth rate in the progesterone group was 65.8% (262/398), and in the placebo group it was 63.3% (271/428), giving a relative risk (RR) of 1.04 [95% confidence interval (CI) 0.94 to 1.15;  $p = 0.45$ ].

There was no evidence of a significant difference between the groups for any of the secondary outcomes:

- clinical pregnancy at between 6 and 8 weeks of gestation [progesterone group 81.9% (326/398) vs. placebo group 78.0% (334/428); RR 1.05, 95% CI 0.98 to 1.12;  $p = 0.16$ ]
- ongoing pregnancy at 12 weeks of gestation [progesterone group 67.1% (267/398) vs. placebo group 64.7% (277/428); RR 1.04, 95% CI 0.94 to 1.14;  $p = 0.47$ ]
- miscarriage [progesterone group 32.2% (128/398) vs. placebo group 33.4% (143/428); RR 0.96, 95% CI 0.79 to 1.17;  $p = 0.70$ ]
- ectopic pregnancy [progesterone group 1.5% (6/398) vs. placebo group 1.6% (7/428); RR 0.92, 95% CI 0.31 to 2.72;  $p = 0.88$ ]
- stillbirth [progesterone group 0.3% (1/398) vs. placebo group 0.5% (2/428); RR 0.54, 95% CI 0.05 to 5.92;  $p = 0.61$ ]
- neonatal survival at 28 days of life [progesterone group 99.6% (260/261) vs. placebo group 100% (269/269); RR 1.00, 95% CI 0.99 to 1.00;  $p = 0.32$ ]
- neonatal congenital anomalies [progesterone group 3.0% (8/266) vs. placebo group 4.0% (11/276); RR 0.75, 95% CI 0.31 to 1.85;  $p = 0.54$ ].

In the health economic evaluation, the ICER associated with progesterone therapy was £18,053 per live birth beyond 24 weeks of gestation. However, this analysis should be interpreted with caution given the high level of uncertainty in the health benefits. Additional sensitivity analysis [extrapolating health gains in terms of quality-adjusted life-years (QALYs)] suggested the probability that progesterone would fall within the National Institute for Health and Care Excellence's threshold (£20,000–30,000 per QALY) as between 0.7145 and 0.7341.

## Conclusions

The PROMISE trial is the largest clinical trial ever conducted on the subject of recurrent pregnancy loss. The trial was adequately sized and methodologically robust to conclude that vaginal progesterone therapy in the first trimester of pregnancy in women with RM is of no benefit and, therefore, should not be used in clinical settings. Future work could investigate the effectiveness of progesterone therapy during the luteal phase of the menstrual cycle, or for patients who have threatened miscarriage.

## Trial registration

This trial is registered as ISRCTN92644181; EudraCT 2009-011208-42; and Research Ethics Committee 09/H1208/44.

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