

**Abstract title: Pre-conception and first trimester metformin on miscarriage risk in women with polycystic ovary syndrome: a randomised, placebo-controlled trial**

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**Study question:** What is the effect of pre-conception metformin continued through the first trimester on miscarriage risk in women with polycystic ovary syndrome?

**Summary answer:** The findings from this multicentre, double-blind, randomised, placebo-controlled trial investigating metformin for miscarriage prevention in women with polycystic ovary syndrome will be presented.

**What is known already:** Women with polycystic ovary syndrome (PCOS) have an increased risk of miscarriage, with reported rates ranging from 20% to 34%. Insulin resistance is a key metabolic abnormality in PCOS, potentially contributing to pregnancy loss through mitochondrial dysfunction or impaired endometrial decidualisation. While metformin improves insulin sensitivity and has been proposed to reduce miscarriage risk, evidence from randomised controlled trials remains inconclusive due to small sample sizes and variation in treatment timing. International guidelines highlight the lack of high-quality evidence, emphasising the urgent need for well-designed, adequately powered trials.

**Study design, size, duration:** This study is a pre-specified miscarriage prevention study nested within the LOCI 2x2 factorial design randomised trial that evaluated letrozole versus clomifene, with or without metformin, for ovulation induction in women with polycystic ovary syndrome. This study investigated whether exposure to metformin through to the end of the first trimester influenced miscarriage rate compared with placebo in those women who conceived.

**Participants/materials, setting, methods:** Women aged 18–42 years with PCOS (Rotterdam criteria) and anovulation were randomised (1:1) to oral metformin (500–1500 mg daily) or matched placebo at 48 hospitals across the United Kingdom. Treatment was initiated preconception and, in those who conceived, continued until 14 weeks' gestation. The primary outcome was miscarriage before 24 weeks. Analysis followed the intention-to-treat principle using a Poisson regression model with robust standard errors, adjusted for minimisation variables including maternal age and body mass index.

**Main results and the role of chance:** A total of 1,739 women with anovulatory PCOS seeking pregnancy were randomised between November 2020 and February 2024. The full findings of the trial will be presented at the conference. The primary analyses will report incidence of miscarriage before 24 weeks of gestation in women assigned to metformin compared with placebo. Risk estimates, 95% confidence intervals and P values derived from regression models adjusted for minimisation variables will be presented. Results for secondary outcomes, including ongoing pregnancy at 12 weeks and live birth beyond 24 weeks, multiple pregnancy, ectopic pregnancy, stillbirth and termination of pregnancy will also be described. Prespecified subgroup analyses will evaluate treatment effects according to maternal age, BMI, and previous pregnancy history, will be presented. Finally, safety data concerning maternal and neonatal serious adverse events, alongside congenital abnormality rates, will be discussed to provide a complete profile of the intervention's efficacy and safety in this population.

**Limitations, reasons for caution:** The analysis may not be powered to detect differences in rare outcomes such as stillbirth. Additionally, the intervention was discontinued at 14 weeks' gestation; therefore, the effects of continuing metformin beyond the first trimester remain unknown.

**Wider implications of the findings:** If metformin is shown to reduce miscarriage risk, these findings will directly challenge current international guidelines that often recommend stopping metformin upon pregnancy confirmation. This evidence would support a safe and effective strategy to improve pregnancy outcomes in the high-risk PCOS population globally.

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**Trial registration number:** ISRCTN1828358

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