

		Word count
Authors:	Pedro Melo, Rima Smith, Lee Priest, Georgia Mitchell, Peace Nnamani, Versha Cheed, Lee Middleton, Kuga Vigneswaran, Adam J Devall and Arri Coomarasamy.	
Title:	Letrozole versus clomifene, with or without metformin, for ovulation induction in polycystic ovary syndrome (LOCI): a multicentre, 2x2, randomised controlled trial	21/25
Study question:	In women with anovulatory polycystic ovary syndrome (PCOS), which oral ovulation-induction strategy achieves the highest live birth rate?	18/25
Summary answer:	The comparative effectiveness and safety of letrozole, clomifene, metformin and their combinations for live birth will be presented.	18/25
What is known already:	Polycystic ovary syndrome (PCOS) is the leading cause of anovulatory infertility worldwide. Letrozole, clomifene citrate and metformin are widely used first-line oral treatments, targeting altered folliculogenesis and insulin resistance. International guidelines recommend letrozole as first-line therapy; however, this is based on trials with small sample sizes, heterogeneous designs and moderate risk of bias. Evidence for adding metformin to ovulation-induction agents remains limited and conflicting, and robust comparative data on clinically meaningful outcomes such as live birth are lacking. There remains a need for well-powered randomised controlled trials directly comparing these strategies.	91/100
Study design, size, duration:	LOCI was a multicentre, randomised, double-blind, placebo-controlled trial using a 2x2 factorial design, conducted in 48 hospitals in the United Kingdom. A total of 1,739 women were enrolled and randomised between November 2020 and February 2024.	36/75
Participants/materials, settings, methods:	Women aged 18–42 years with anovulatory PCOS defined by the Rotterdam criteria and desiring pregnancy were randomised (1:1:1:1) to letrozole plus metformin, letrozole plus placebo, clomifene plus metformin or clomifene plus placebo for up to six ovulatory cycles. Metformin or placebo was initiated pre-conception and continued until 14 weeks'	73/75

	gestation if pregnancy occurred. The primary outcome was live birth at ≥ 34 weeks' gestation. Analyses followed the intention-to-treat principle using adjusted regression models.	
Main results and the role of chance:	The complete results of the LOCI trial will be presented at the conference. Primary analyses will report live birth rates and relative treatment effects for the three prespecified comparisons: letrozole versus clomifene, metformin versus placebo, and letrozole plus metformin versus clomifene plus metformin, with corresponding risk estimates, 95% confidence intervals and P values derived from regression models adjusted for minimisation variables. Secondary outcomes will include ovulation rate, time to pregnancy, ongoing pregnancy at 12 weeks, live birth ≥ 24 weeks, pregnancy loss before 24 weeks, multiple pregnancy, mode of birth, maternal pregnancy complications and neonatal outcomes. Prespecified subgroup analyses will evaluate effect modification by body mass index, maternal age and previous pregnancy history. Safety analyses will summarise maternal and neonatal serious adverse events and congenital abnormalities across treatment groups, providing a comprehensive assessment of both effectiveness and safety of competing first-line ovulation-induction strategies.	142/200
Limitations, reasons for caution:	The trial was not powered to detect small differences in rare adverse maternal or neonatal outcomes. Findings apply to oral ovulation induction treatments and may not generalise to gonadotropin-based protocols or assisted reproductive technologies.	34/50
Wider implications of the findings:	LOCI is the largest trial ever conducted comparing oral regimens for ovulation induction in anovulatory PCOS. Our findings will provide the most definitive comparative evidence to date and are likely to directly influence future international clinical guidelines and routine fertility practice.	41/50
Study funding/competing interest(s):	Funded by the UK National Institute for Health and Care Research Health Technology Assessment programme. The authors declare no competing interests.	

Trial registration number:	ISRCTN11828358	25
Keywords	polycystic ovary syndrome; ovulation induction; letrozole; clomifene; metformin	