

# Is there a new role for metformin in the management of gestational diabetes?

Metformin has long been used for the management of diabetes mellitus in nonpregnant persons, whereas insulin has been viewed as the standard treatment for the management of diabetes in pregnancy. In this RCT setting, **treatment with metformin upon diagnosis of gestational diabetes did not reduce the need to initiate insulin or reduce fasting blood glucose levels** at 32 or 38 weeks' gestation.

Dunne F, Newman C, Alvarez-Iglesia A, et al. Early metformin in gestational diabetes: a randomized clinical trial. *JAMA*. 2023;330:1547-1556. doi:10.1001/jama.2023.19869

## EXPERT COMMENTARY BY

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**G**estational diabetes mellitus occurs in 4% to 7% of pregnancies, and the prevalence is likely to continue to increase given the rising rates of hypertension, obesity, advanced maternal age, and other medical comorbidities in pregnant persons in the United States.<sup>1,2</sup> Uncontrolled hyperglycemia in pregnancy is associated with many adverse perinatal outcomes,

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including stillbirth, macrosomia, admission to the neonatal intensive care unit (NICU), development of hypertensive disorders, and cesarean deliveries. Hence, it is important to investigate and identify the optimal management of gestational diabetes.

Metformin, an oral biguanide, although studied for gestational diabetes treatment in phase 3 randomized clinical open-label trials, often is avoided in patients who are pregnant (with the exception of patients who have needle aversions, are financially unable to use insulin, or are unable to administer insulin safely).<sup>1,2</sup> Metformin is a highly effective first-line agent in the management of both prediabetes and type 2 diabetes, which begs us to question if there is a role for it in the management of gestational diabetes.

## Details about the study

The study by Dunne and colleagues was a randomized controlled trial (RCT) conducted in a 1:1 parallel fashion at two institutions in Ireland from 2017–2022. The primary outcome assessed if treatment with metformin would reduce fasting blood glucose levels and the initiation of insulin among women

## FAST TRACK

*An insignificant difference in required insulin and fasting blood glucose levels were found among the metformin and placebo groups at 32 or 38 weeks' gestation ( $P = .13$ )*

## WHAT THIS EVIDENCE MEANS FOR PRACTICE

The study findings by Dunne and colleagues reinforce the current standard practice for the management of gestational diabetes: prescribe medical nutrition therapy and exercise followed by insulin initiation in the setting of persistently elevated blood glucose levels. Knowing that metformin crosses the placenta, future studies should also address the long-term metabolic and health outcomes of fetuses exposed to metformin.

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diagnosed with gestational diabetes. A total of 510 participants enrolled in the study, with 268 receiving metformin (up to a maximum dose of 2,500 mg) at diagnosis and 267 receiving an identical placebo. Blood sugar levels were monitored 7 times a day, and medication adherence was assessed every 4 weeks.

**Results.** At 32 or 38 weeks' gestation, 56.8% of patients in the metformin arm, and 63.7% of patients in the placebo arm required insulin or had fasting blood glucose levels above 5.1 mmol/L (91.8mg/dL), which was a statistically insignificant difference ( $P = .13$ ). Although there was similarly no difference in the total amount of insulin used in each study group, the percentage of patients who required insulin initiation was decreased in the metformin arm (38.4% vs 51.1%;  $P = .004$ ).

### Study strengths and weaknesses

The authors conducted a well-designed double-blinded RCT—in both rural and tertiary care settings. Additionally, the study had an impressive 90% patient adherence rate for home blood glucose monitoring 7 times per day. The study arms were balanced for body mass index, as obesity is a known contributor to the development of gestational diabetes and response to insulin.

This study findings' generalizability is limited across subpopulations given the lack of ethnic and racial diversity—the study population was 80% White. Additionally, utilization of the World Health Organization guidelines for diagnosing gestational diabetes, although adopted by most associations across the world, limits its application to areas of the world that use the National Diabetes Data Group or the Carpenter-Coustan diagnosis guidelines.<sup>3,4</sup> Furthermore, the diagnosis of gestational diabetes, which was based on 1 elevated value of a 2-hour glucose tolerance test, has limited scientific support, has not been proven to improve obstetric outcomes, and may increase health care costs when compared with the 2-step method.<sup>5</sup> The criteria for insulin initiation in the trial was based on having 2 elevated measures of blood glucose during home glucose monitoring, a criteria that is much stricter than what is used in other countries or clinical practice. The trial authors concluded that use of metformin had a statistically significant reduction in neonates weighing > 4,000 g and > 90th% of weight, but they did not assess study group differences in neonatal skin fold thickness or anthropometric measurements, as reported in the Metformin in Gestational Diabetes trials.<sup>6</sup> ●

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