

Metformin plus Insulin for diabetes during pregnancy: a systematic review and meta-analysis



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Objective

This systematic review aims to assess the effectiveness and safety of metformin combined with insulin (M+I) compared to insulin alone in pregnant women with type 2 diabetes mellitus (T2DM) or gestational diabetes mellitus (GDM), with a primary focus on reducing the risk of stillbirth.

Design

A systematic review of randomised controlled trials (RCTs) following PRISMA guidelines.

Method

A comprehensive search was conducted in PubMed, Embase, and Cochrane databases, with the last search performed in January 2025. Eligible RCTs comparing M+I with insulin alone were included. Data on maternal and neonatal outcomes were extracted, with stillbirth defined as the primary outcome. Secondary outcomes included neonatal intensive care unit admission, respiratory distress syndrome, transient tachypnoea of the newborn, neonatal hypoglycaemia, birth weight, small for gestational age, macrosomia, large for gestational age, neonatal death, gestational age at delivery, preterm birth, congenital malformations, maternal hypoglycaemia, caesarean section, hypertension, and pre-eclampsia. Subgroup analyses were conducted based on (1) timing of insulin initiation in M+I and (2) T2DM versus GDM populations. The GRADE framework was used to assess the quality of evidence.

Results

Nine RCTs (1,673 participants) were included. Moderate-quality evidence suggested that M+I was associated with a reduced risk of stillbirth (RR 0.36, 95% CI 0.14–0.90). Low-quality evidence indicated that M+I was linked to lower risks of gestational hypertension (RR 0.68, 95% CI 0.48–0.97) and neonatal hypoglycaemia (RR 0.49, 95% CI 0.30–0.80) compared to insulin alone. For other outcomes, the quality of evidence was low or very low, primarily due to imprecision and inconsistency, with no significant differences observed between groups. Subgroup analyses did not resolve the inconsistencies in some outcomes.

Conclusions: Combining metformin with insulin in pregnant women with T2DM or GDM may reduce the risk of stillbirth, gestational hypertension, and neonatal hypoglycaemia compared to insulin alone. However, the certainty of the evidence remains low to very low for most outcomes. Further high-quality RCTs are needed to confirm these findings. The observed benefits of M+I align with previous reviews comparing metformin alone with insulin alone.

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