

ABSTRACT

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METFORMIN IN GESTATIONAL DIABETES MELLITUS

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Gestational diabetes mellitus (GDM) is a state of impaired glucose tolerance with onset or first recognized during pregnancy. Treatment of GDM is important, since adequate treatment reduces maternal and neonatal adverse effects. GDM is associated with an elevated risk of maternal blood pressure problems during pregnancy, cesarean deliveries and it raises the risk of type 2 diabetes later in life. The fetus has an increased risk of macrosomia, delivery complications and neonatal hypoglycemia. Medication is needed if adequate glycemic control is not achieved by diet. Insulin is the traditional medication for GDM but metformin as an oral drug has been suggested to be an alternative. Metformin crosses the placenta, but the transfer mechanism is not clear.

The main aim of this study was to compare the efficacy and safety of metformin and insulin in the treatment of GDM patients by evaluating the influence of medication on maternal and fetal outcomes in a retrospective and a randomized controlled trial (RCT). Predictors of the need for additional insulin with metformin to meet good glycemic control were evaluated.

The impact of metformin exposure on maternal and fetal outcomes was studied by assessment of metformin concentrations in maternal serum and umbilical cord serum. The mechanism of metformin placental transfer and the role of active organic cationic transporters (OCT) in metformin transfer were studied by *ex vivo* placental perfusion.

Measurements of metformin concentrations at birth indicated that there is a high degree of placental transfer of metformin from the mother to the fetus (96%). Metformin does not seem to accumulate in the fetus. The *ex vivo* placental perfusion study indicated that OCTs may not have a significant role on the placental transfer of metformin.

Metformin concentration levels were not related to fetal outcome. Higher metformin concentrations and a maximum clinical dose of metformin had a favorable effect on retarding maternal weight gain during pregnancy.

Compared to insulin, metformin did not increase the maternal, fetal or neonatal risks of adverse events, and the delivery modes were unaffected. Glycemic control evaluated by HbA1c and serum fructosamine levels was similar during metformin and insulin therapies. However, 21% of the metformin-treated patients needed additional insulin to obtain good glycemic control. High maternal age, performing the oral glucose tolerance test and initiation of medication early during pregnancy and high HbA1c and fructosamine values are associated with a need of additional insulin.

Key words: gestational diabetes, insulin, metformin, placental transfer, OCT