Name of journal: *World Journal of Diabetes*
ESPS Manuscript NO: 13691
Columns: MINIREVIEW

Birth defects in pregestational diabetes: defect range, glycemic threshold and pathogenesis

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Abstract

Currently, 60 million women of reproductive age (18-44 years old) worldwide, and approximately 3 million American women have diabetes mellitus, and it has been estimated that this number will double by 2030. Pregestational diabetes mellitus (PGD) is a significant public health problem that increases the risk for structural birth defects affecting both maternal and neonatal pregnancy outcome. The most common types of human structural birth defects associated with PGD are congenital heart defects and central nervous system defects. However, diabetes can induce birth defects in any other fetal organ. In general, the rate of birth defects increases linearly with the degree of maternal hyperglycemia, which is the major factor that mediates teratogenicity of PGD. Stringent prenatal care and glycemic control are effective means to reduce birth defects in PGD pregnancies, but cannot reduce the incidence of birth defects to the rate of that is seen in the nondiabetic population. Studies in animal models have revealed that PGD induces oxidative stress, which activates cellular stress signalling leading to dysregulation of gene expression and excess apoptosis in the target organs, including the neural tube and embryonic heart. Activation of the Apoptosis signal-regulating kinase 1 (ASK1)-Forkhead transcription factor 3a (FoxO3a)-caspase 8 pathway caus apoptosis in the developing neural tube leading to neural tube defects (NTDs). ASK1 activates the c-Jun-N-Terminal kinase 1/2 (JNK1/2), which leads to activation of the unfolded protein response and endoplasmic reticulum (ER) stress. Deletion of the *Ask1* gene, the *Jnk1* gene, or the *Jnk2* gene, or inhibition of ER stress by 4-Phenylbutyric acid (4-PBA) abrogates diabetes-induced apoptosis and reduces the formation of NTDs. Antioxidants, such as thioredoxin, which inhibits the ASK1-FoxO3a-caspase 8 pathway or ER stress inhibitors, may prevent PGD-induced birth defects.

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