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EDITORIAL COMMENT

Mitochondrial Targeted Therapies to Prevent Maternal Diabetes–Induced Congenital Heart Defects*

Sushma Reddy, MD

The United States has the highest infant mortality rate among high-income countries at 5.4% per 1,000 live births. Birth defects are a major cause of infant mortality. Congenital heart defects (CHDs) are the most common type of birth defect and accounts for about 40% of birth defect-related mortalities in the United States and worldwide.[1] Most of these deaths occur during infancy, and this has not changed significantly in the past 2 decades despite the dramatic improvements seen in pediatric cardiology and cardiac surgery. At a systemic level, racial/ethnic disparities, access to quality care, insurance status, and socioeconomic status all play a key role in CHD-related deaths. Reducing the incidence of CHDs should therefore be factored into the overall solutions to reduce CHD-related mortality. The etiology of CHDs is likely multifactorial, with genetic (<10%) and noninherited risk factors. Environmental teratogens such as certain medications (thalidomide, isotretinoin, and lithium), viral infections such as maternal rubella, maternal exposure to smoking and alcohol, maternal malnutrition including folic acid and vitamin B_9 deficiency, and chronic diseases such as maternal diabetes and obesity contribute to the noninherited risk for developing CHDs and pose a potential solution to decreasing the incidence of CHDs.[2] Maternal pregestational diabetes mellitus is the only relatively prevalent population risk factor for CHDs, associated with a profoundly increased risk for CHDs in the fetus (adjusted relative risk: 4.0; 95% CI: 3.51-4.53).[3] Women with diabetes-related complications have a higher CHD risk than women with diabetes without complications (relative risk: 7.62 vs 3.49). Despite improvements in prenatal care and optimal diabetes control, the incidence of pregestational diabetes-related CHDs has not changed in many decades, highlighting the need to better understand the causal mechanisms.

Experimental data point to hyperglycemia during early embryogenesis altering gene expression in key cellular components of the developing heart, such as the outflow tracts. The mechanisms underlying altered gene expression are only now being unraveled. Diabetic animal models demonstrate the down-regulation of genes involved in metabolism, development, and proliferation of cardiac neural crest cells. This down-regulation of genes is mediated by hyperglycemia-induced oxidative stress, which then impairs paired box 3-mediated cardiac neural crest migration for outflow tract septation. In addition to hyperglycemia-induced oxidative stress, major reactive oxygen species (ROS) scavenging enzymes and antioxidant enzyme levels are also decreased in maternal diabetes, leading to cellular stress and damage during early embryogenesis, suggesting that the teratogenicity of glucose is mediated, in part, by oxidative stress. As mitochondria are the largest source and targets of oxidative stress, several groups have investigated the role of mitochondria in embryonic heart development. Balanced mitochondrial dynamics during embryonic development are critical to sustain the changes in heart metabolism, especially in energy-demanding cells such as cardiomyocytes. The mitochondrial fusion factors, mitofusin 2 (MFN2) and optic atrophy are essential for the differentiation

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From the Department of Pediatrics (Cardiology) and Cardiovascular Institute, Stanford University, Stanford, California, USA.

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of embryonic stem cells into cardiomyocytes, and activating fusion factors restores mitochondrial respiration and decreases oxidative stress and apoptosis.[4] Hyperglycemia reduces MFN2 expression and is now known to be a main player in diabetic mitochondrial dysfunction and in the progression of insulin resistance in animal models, with activation of mitochondrial fusion restoring mitochondrial function. These data suggest the need for more therapeutic strategies to target mitochondrial health in diabetes and reduce and/or delay disease progression and complications.

In this issue of *JACC: Basic to Translational Science*, Wang et al[5] report on the epigenetic mechanisms underlying maternal diabetes-induced CHDs. The investigators specifically assessed whether impaired mitochondrial fusion contributes to maternal diabetes-induced CHDs and if the fusion activators teriflunomide and echinacoside can reduce maternal diabetes-induced CHDs. They used a mouse diabetic embryopathy model induced by treatment with streptozotocin and transgenic overexpression models of micro-RNA (miR) 195 and miR-140. Using cardiomyocytes from the aforementioned embryonic mouse hearts, the investigators show that hyperglycemia activates the transcription factor FoxO3a, which up-regulates miR-195 and miR-140. miR-195 and miR-140 subsequently down-regulate the expression of mitochondrial fusion proteins Mfn1 and Mfn2 and, on time-lapse imaging, show decreased fusion. This was confirmed using a FoxO3a germline deletion in mice that abolished maternal diabetes-increased expression of miR-195 and miR-140, restored mitochondrial fusion and function, and reduced CHD development in maternal diabetes. The investigators confirmed that Mfn2 is a direct target of miR-195, whereas Mfn1 is a direct target of miR-140, and their cardiac-specific deletion rescues mitochondrial fusion, blocks hyperglycemia-induced teratogenicity, and reduces CHD development. Two mitochondrial fusion activators were effective in preventing CHDs in diabetic pregnancy, including teriflunomide, a U.S. Food and Drug Administration–approved drug for treating multiple sclerosis, which restored mitochondrial fusion by increasing mitofusins and decreased CHD formation. While providing mechanistic insight, the investigators raise a unique concept of altered mitochondrial dynamics driving cardiac dysmorphogenesis and demonstrate a role for targeting mitochondrial health to prevent the development of CHDs in maternal diabetes.

The growing number of women affected by pregestational diabetes is expected to increase the number of fetuses born with CHDs. In addition, there is a long-term cardiovascular risk in children born to mothers with diabetes, highlighting the crucial need to understand the mechanisms underlying the development of CHDs in this population. The present work by Wang et al[5] tackles this problem and also raises several more interesting questions. For instance, it remains to be determined what other essential regulatory checkpoints throughout multiple stages of cardiac development play a role in the development of maternal diabetes-induced CHDs. This would facilitate early and efficient additional interventions. Further studies should focus on delineating whether hyperglycemia acts directly to change gene expression or indirectly through oxidative stress and hypoxia. We do not know whether therapies used to rescue mitochondrial fusion in cell models and animal models would be safe and effective during human pregnancy and whether agents such as N-acetyl cysteine, a ROS scavenger, and zinc, a cofactor in ROS scavenging enzymes, which have been effective in animal models to reduce diabetes-induced CHDs, will reduce the incidence of maternal hyperglycemia-induced oxidative stress and the development of CHDs in humans. This work by Wang et al and future studies will hopefully pave the way toward developing specific strategies to prevent hyperglycemia-induced CHD development during early embryogenesis.

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ADDRESS FOR CORRESPONDENCE: Dr Sushma Reddy, Department of Pediatrics (Cardiology) and Cardiovascular Institute, Stanford University, 750 Welch Road, Suite 325, Stanford, California 94304, USA. E-mail: sureddy@stanford.edu.

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