Diabetes in Early Pregnancy: Getting to the Heart of the Matter

Jeffrey S. Gilbert,[1] Christopher T. Banek,[1] Sara A. Babcock,[2] and Hans C. Dreyer[1]

Pregnancy is a dynamic physiological stressor requiring numerous tightly choreographed alterations to the maternal physiological state. In addition to homeostatic regulation of maternal energy, fluid, and electrolyte balance, the needs of a rapidly developing fetus must also be satisfied. Indeed, contemporary literature is replete with evidence from clinical and experimental studies showing that alterations in the intrauterine environment have considerable impacts on fetal development and long-term health outcomes (1–7). Considering Centers for Disease Control and Prevention reports that the crude prevalence of diabetes has increased by 176% over the last three decades, the need for clinical and experimental interest in this particular health problem is increasing.

Gestational diabetes mellitus is widely recognized as a serious concern for expectant mothers and is routinely screened for in midpregnancy. However, the potential for undiagnosed or poorly controlled diabetes before pregnancy to generate significant embryonic and early fetal stress may be less obvious. Indeed, it is not standard clinical practice to evaluate women for glucose intolerance prior to 24 weeks of pregnancy unless obvious risk factors are present. While increased awareness and screening may provide some help in the early identification of diabetes in pregnancies, these will not capture a significant portion of potentially high-risk, diabetic pregnancies in which the pregnancy is not confirmed until a much later time, such as at 8–12 weeks of pregnancy. Thus, improved screening at the primary care level prior to pregnancy is needed to meet the needs of this diabetic patient population.

Despite the long observed deleterious relationships between diabetes and fetal cardiac development, the mechanisms underlying the role of hyperglycemia in early pregnancy on cardiogenesis remain unclear (8). Further complicating matters is the lack of specific malformation patterns in pregnancies affected by diabetes, a deficiency that has led to the suggestion that multiple teratogenic pathways are likely involved (8). To this end, new work by Scott-Dreschel et al. (9) in an article in this issue of *Diabetes* describes a novel model of hyperglycemia in the chick embryo.

From the [1]Department of Human Physiology, University of Oregon, Eugene, Oregon; and the [2]Department of Obstetrics, Gynecology & Women's Health, University of Minnesota Medical School, Minneapolis, Minnesota.
Corresponding author: Jeffrey S. Gilbert, jgilbe@uoregon.edu.
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In this study, the authors carefully developed and characterized two in vivo models of hyperglycemia during early embryonic development. These models mimic the conditions encountered in utero during early pregnancy in a gravida with undiagnosed or poorly controlled diabetes. The investigators chose the chick model for several reasons: *1*) it has similar cardiogenic pathways to humans, *2*) a short developmental period, *3*) reasonable costs, *4*) it is amenable to controlled manipulations, and *5*) it is easily observed across time points during the experiments. The authors evaluated glucose dose responses to identify the most appropriate concentrations for their experiments. They included both L- and D-glucose experiments, thus elegantly controlling for the effects of osmotic stress. The first model evaluated episodic hyperglycemia to mimic postprandial fluctuations in glucose levels, while the second model investigated chronically elevated glucose concentrations. Both models resulted in signs of embryonic stress and delayed embryonic growth and development, abnormalities that appear to be a highly conserved response to hyperglycemia across species.

The authors investigated several molecules and pathways that were altered in the setting of chronic hyperglycemia. Sustained hyperglycemia decreased expression of mRNA for glucose transporter 1 (GLUT1), a noninsulin regulated GLUT that is highly expressed in the developing avian heart. This is an intriguing and possibly counterintuitive finding because decreased GLUT1 may exacerbate extracellular hyperglycemia by decreasing glucose uptake thereby increasing the generation of advanced glycation end products (AGEs). Alternatively, decreased GLUT1 may be a cellular adaptation to mitigate increased intracellular production of reactive oxygen species (ROS) via the polyol pathway (10). Nevertheless, these observations raise several intriguing possibilities for further study.

Although the authors identify that p21 and cyclin D1 expression are altered by hyperglycemia, the exact role of these molecules in this experimental paradigm remains unclear. Both the decrease in the cell cycle promoter cyclin D1 as well as the increase in the cell cycle inhibitor p21 are consistent with the hypothesis that hyperglycemia slows cell cycle progression and decreases the rate of embryonic and cardiac development (summarized in Fig. 1). However, it remains unclear whether the observed effects are dependent on decreased cyclin D1, increased p21, or a synergistic combination of the two. Moreover, the intermediate signaling molecules in this pathway remain to be identified. The figure illustrates several of these possibilities by synthesizing data from the current study with previous literature (11–13). Earlier work has shown AGE activates p21 on endothelial cells via the receptor for AGEs (RAGE) (13) and decreases cyclin D1 in renal proximal tubule cells (11). The current work by Scott-Dreschel et al.

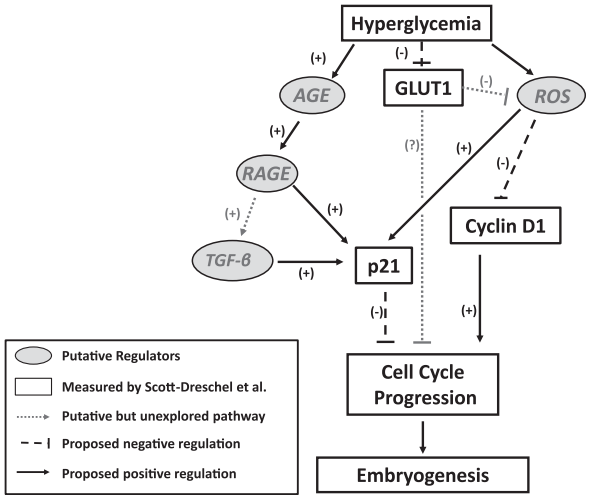

FIG. 1. A brief summary of several putative mechanisms of hyperglycemia-induced developmental delay and disrupted embryonic cardiogenesis relevant to the work of Scott-Dreschel et al. (9). Observations reported in the current study are noted by open rectangles. Gray ovals denote putative regulators not measured in the current study but reported elsewhere. Dashed lines denote possible negative regulatory signals. Solid lines illustrate positive regulatory pathways. TGF-β, transforming growth factor-β.

(9) is consistent with previous studies, identifies specific hyperglycemia-regulated molecules, and characterizes an additional model system for future hypothesis-driven mechanistic experiments. Moreover, further RAGE signaling research may also provide insights regarding the elevated incidence of preeclampsia in patients with diabetes (14).

Another consideration regarding the observation that embryonic stage and weight were decreased in this study is the possibility that the biological sex of the embryo could play a role such that the exact mechanism may vary between male and female fetuses. It is well known that male embryos develop more rapidly than female embryos, and sex-based size differences continue through fetal life with male babies growing larger than females by mid-pregnancy (3). The authors addressed this by measuring randomly selected male and female chick embryos. While this approach minimizes the chances that biological sex plays a role in the stage and size differences associated with hyperglycemia, it does not eliminate the possibility that biological sex may play an important role in how the embryonic heart develops when exposed to chronically elevated glucose concentrations.

While the findings of the current study are intriguing, many stones remain unturned. Studies using specific pharmacological or genetic instruments for blocking or activating relevant pathways as well as testing clinically relevant and easy to implement interventions such as folic acid or antioxidants (5,6,10) would provide significant insights regarding the exact molecular mechanisms underlying hyperglycemia-induced defects in cardiogenesis. It also remains unclear if there are any long-term effects on cardiac function or whether there is reduced cardiomyocyte number and function, and/or decreased capacity to tolerate physiological or pathological stressors such as exercise or infarction in later life. The answers to these questions are complex and may be difficult to answer using any single experimental model; thus, continued refinement of physiological modeling and experimental paradigms will be essential to elucidate the exact mechanisms of hyperglycemia-induced embryopathies, identify efficacious targets for intervention, and provide therapeutic options for pregnancies that escape early identification of diabetes.

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