New Concepts in Diabetic Embryopathy

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KEYWORDS

• Diabetic embryopathy • Birth defects • Hyperglycemia • Apoptosis
• Cell proliferation • Metabolism • Intracellular stress • Intervention

KEY POINTS

- Diabetes mellitus in early pregnancy increases the risk of birth defects in infants.
- High glucose induces intracellular stress, increases programmed cell death (apoptosis), and decreases cell proliferation in the embryo.
- Reduction of the risk includes preconceptional and early gestational glycemic control.
- Interventions via dietary supplementation remain to be developed.
- Preconceptional counseling and planned pregnancy are encouraged for physicians and patients.

INTRODUCTION

Diabetes mellitus is a metabolic disease, primarily caused by high concentrations of glucose in the circulation.[1] Hyperglycemia interrupts normal cellular metabolism and signaling and causes organ dysfunction.[2,3] Nearly 2 centuries after diabetes was first recognized,[4] its association with congenital birth defects and fetal mortality in pregnancy was recognized and referred to as diabetic embryopathy.[4,5] Before the introduction of insulin, diabetes-associated fetal and maternal mortality were nearly 70% and 40%, respectively.[6,7] Since the administration of insulin to control glycemia in pregnant women, this mortality has decreased dramatically to nearly 12%.[8–15] In addition to the control of glycemia with insulin, aggressive perinatal care and neonatal management also contributed to the decline of maternal and fetal mortality.[10,16–19]

The present birth defect rate in diabetic pregnancies (about 10%) is still higher than that in the general population (3%) and seems to be on the increase.[7,12,13,15,20–25] The reasons for this increase in birth defect rates are complex. One reason is that there has been a rapid increase in diabetic patients in the population, which includes women of childbearing age.[26] It is estimated that approximately 8000 babies in the United States

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Clin Lab Med 33 (2013) 207–233
http://dx.doi.org/10.1016/j.cll.2013.03.017 **labmed.theclinics.com**
0272-2712/13/$ – see front matter

are born each year with maternal diabetes-associated congenital malformations. The incidence of these malformations also has risen to near-epidemic level in developing countries.

Tackling this issue involves battles on several fronts: diagnosing fetal anomalies must be improved; technologies that can recognize developmental malformations as early as the embryogenesis period are needed; and better prenatal and planned pregnancy consultations should be implemented to help reduce diabetes-associated birth defects. These remain ongoing challenges for perinatal care providers.

An important goal in eliminating birth defects is to develop therapeutic interventions that can protect embryos from hyperglycemic insult. This goal can be achieved only by understanding the cellular and molecular mechanisms underlying diabetic embryopathy. Basic research using animal models has contributed a considerable amount of information about the manifestations of fetal abnormalities, but more work is still needed.

Pregestational and Gestational Diabetes

Diabetes mellitus is a chronic disease manifested by hyperglycemia and its associated metabolic factors. This condition is usually diagnosed by measuring the levels of plasma glucose, expressed as mg/dL or mM, and glycosylated hemoglobin A (HbA_{1c}), indexed as percentage of total hemoglobin A.[27–29] Manifestation of diabetes can be the result of insulin deficiency (type 1) or insulin resistance (type 2).

- Type 1 diabetes, or insulin-dependent diabetes, is caused by autoimmune destruction of insulin-producing β-cells in the pancreas.[30,31]
- Type 2 diabetes, or non–insulin-dependent diabetes, is caused by failure in insulin signaling to regulate cellular glucose uptake.[32–34]

Diabetes mellitus, either type 1 or type 2, diagnosed in women before pregnancy is referred to as pregestational diabetes.[20,35–37] When hyperglycemia is detected after the onset of pregnancy, usually in the third trimester (24–28 weeks), the pregnant woman is considered to have gestational diabetes mellitus (GDM).[38–42] According to guidelines from the International Association of Diabetes in Pregnancy Study Group, women who have a fasting plasma glucose of 126 mg/dL or greater and HbA_{1c} of 6.5% or greater are diagnosed as having GDM.[43]

Congenital birth defects in infants of diabetic mothers have been found to be associated with pregestational diabetes that is uncontrolled in the first trimester of pregnancy.[44–48] Although a few cases have suggested a link between GDM and birth defects, this association remains unclear and lacks strong supporting evidence.[49,50] One possible reason for the controversy is that some women with early-onset type 2 diabetes are misdiagnosed as having GDM when first screened in the second trimester.[39,51] Nevertheless, it is well established that GDM can lead to many adverse fetal outcomes, including macrosomia, hypoglycemia, hypocalcemia, and hyperbilirubinemia.[51–53]

High Glucose as a Major Teratogenic Factor

Human studies have shown a strong link between maternal glycemic level, as indicated by the association of plasma glucose and HbA_{1c} levels[54,55] with the incidence of congenital malformations in offspring.[19,55–59] Other adverse metabolic factors produced in diabetes mellitus, such as ketone bodies, advanced glycation end products, and branched chain amino acids, may have synergetic effects with glucose on disrupting normal embryonic development.[60–64] The putative teratogenic effects of hyperglycemia are supported by studies that show a reduction in the incidence of birth