Are insulin sensitivity and β-cell function associated with adverse pregnancy outcomes among women with gestational diabetes?

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Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy, is a common pregnancy outcome.[1] GDM carries risks for the mothers, and fetus, neonate, and childhood in the offspring. Women with GDM may increase risks of high blood pressure and preeclampsia during pregnancy, primary cesarean section, and future obesity, hypertension, dyslipidemia, metabolic syndrome, and cardiovascular disease.[2-6] About 20–50% of women with prior GDM will develop type 2 diabetes within 3–5 years of pregnancy, and 70% will develop type 2 diabetes if followed ≥10 years.[7-9] More alarming, children exposed to GDM *in utero* have a series of adverse pregnancy outcomes at birth including preterm delivery, excessive birth weight, and low blood sugar, and also have higher risks of obesity,[10] impaired glucose tolerance and type 2 diabetes,[10] high blood pressure,[11] and dyslipidemia later in life.[12] Thus, GDM likely contributes to the vicious intergenerational cycle of obesity and type 2 diabetes.[13]

The prevalence of GDM varies greatly due to the variation in screening strategies and diagnostic criteria used in identifying GDM cases [Table 1]. GDM can be diagnosed by either of these two strategies. (1) One-step approach performs a diagnostic 2-h 75-g oral glucose tolerance test (OGTT) at 24–28 weeks of gestation. The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded: fasting glucose ≥5.1 mmol/L, 1-h glucose ≥10.0 mmol/L, or 2-h glucose ≥8.5 mmol/L.[14-16] (2) The two-step approach first performs a 50-g non-fasting oral glucose challenge test at 24–28 weeks of gestation. If the plasma glucose level is ≥7.8 mmol/L, followed by a 2-h 75-g OGTT or a 3-h 100-g OGTT. The diagnosis of GDM is made when any of the following plasma glucose values are met or exceeded: fasting glucose ≥7.0 mmol/L, or 2-h glucose ≥7.8 mmol/L based on a 2-h 75-g OGTT in the 1999 World Health Organization (WHO) criteria.[17] The diagnosis of GDM in the US is made when at least two of the following four plasma glucose values are met or exceeded: fasting glucose ≥5.3 mmol/L, 1-h glucose ≥10.0 mmol/L, 2-h glucose ≥8.6 mmol/L, and 3-h glucose ≥7.8 mmol/L based on a 3-h 100-g OGTT in the American Diabetes Association criteria.[14] The one-step approach has resulted about 1.7–3.0 times higher prevalence of GDM than the two-step approach.[14] In China, GDM has increased from 2.4% in 1999 to 8.1% in 2012 by using the 1999 WHO criteria of the two-step approach.[18,19] Several recent studies in China found that the prevalence of GDM was over 20% by using the one-step approach.[20] It has been shown an overall increase in β-cell mass during normal pregnancy.[21] β-cell mass returns to normal levels within 10 days after birth through increased β-cell apoptosis, decreased proliferation, and reduced β-cell size.[22] One recent review concluded that the balance between β-cell growth and loss is tightly regulated and functional β-cell mass normally compensates for increased insulin resistance (IR) during pregnancy.[23] However, if this equilibrium is skewed improperly away from normal induction of β-cell growth and survival during β-cell expansion, β-cell compensation can fail, resulting in GDM.[23] One human glucose clamp study supported this conclusion and found that women with GDM had a 67% reduction in pancreatic β-cell compensation for IR at the late stage of pregnancy compared with normal pregnant women.[24] Thus, the pathogenesis of GDM is usually considered as IR, glucose intolerance, and decreased β-cell function during pregnancy.[24-26] Several studies have assessed the association of maternal glucose and IR during pregnancy with the risk of adverse pregnancy outcomes among women with GDM. However, very few studies have assessed β-cell dysfunction during pregnancy with the risk of adverse pregnancy outcomes in women with GDM. The Hyperglycemia and Adverse Pregnancy Outcome study including 25,505 pregnant women at 15 centers in nine countries who underwent 2-h 75-g OGTT at 24–32 weeks of gestation indicated strong, continuous associations of maternal glucose levels at fasting, 1-h and 2-h below or higher than those diagnostic of GDM with increased risk of adverse pregnancy outcomes.[27] Two Chinese studies also found that increasing IR in the late second trimester might be

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Table 1: Diagnostic criteria for GDM.

Diagnostic criteria	One-step or two-step strategy	Diagnosis	Fasting glucose (mmol/L)	1-h glucose (mmol/L)	2-h glucose (mmol/L)	3-h glucose (mmol/L)
ADA/Carpenter-Coustan[14]	Two-step	Any two	≥5.3	≥10.0	≥8.6	≥7.8
WHO Consultation[17]	Two-step	Any one	≥7.0	–	≥7.8	–
IADPSG/ADA[14,15]	One-step	Any one	≥5.1	≥10.0	≥8.5	–
WHO[16]	One-step	Any one	≥5.1	≥10.0	≥8.5	–

ADA: American Diabetes Association; GDM: Gestational diabetes mellitus; IADPSG: International Association of Diabetes and Pregnancy Study Groups; WHO: World Health Organization; –: Not applicable.

associated with an increased risk of adverse pregnancy outcomes in women with GDM.[28,29]

In this issue of the *Chinese Medical Journal*, the study by Shen *et al*[30] assessed the association of β-cell function and insulin sensitivity with the risk of adverse pregnancy outcomes among Chinese women with GDM, and also evaluated the potential impact of different pathophysiologic patterns on adverse pregnancy outcomes of GDM. This observational study included 482 Chinese women diagnosed with GDM. A one-step 2-h 75-g OGTT was used to diagnose GDM at 24–28 weeks of gestation. Indices of β-cell secretory function (the homeostatic model assessment for β-cell function [HOMA-β]) and IR (HOMA-IR) were calculated using measures obtained at fasting, 30-min, 1-h, and 2-h glucose and insulin during 24–28 weeks of gestation. The major adverse pregnancy outcomes were maternal outcomes including primary cesarean section, preeclampsia, and postpartum hemorrhage, and neonatal outcomes including large for gestational age, small for gestational age, macrosomia, and preterm delivery. This study indicated that β-cell function at 24–28 weeks of gestation was inversely and HOMA-IR during pregnancy was positively associated with the risk of adverse pregnancy outcomes among women with GDM. Each 1-unit increase in HOMA-β decreased 43% risk of adverse pregnancy outcomes and each 1-unit increase in HOMA-IR increased 34% risk of adverse pregnancy outcomes among women with GDM. However, other indices of insulin sensitivity (insulin sensitivity index) or differences in insulin 30 min during pregnancy were not associated with the risk of adverse pregnancy outcomes among women with GDM. HOMA-β could represent a reduced β-cell function per β-cell, or a reduced β-cell mass in women with GDM. During pregnancy, the β-cell mass in women increases up to two-fold more than that in women without pregnancy. This remains one of the unknown questions that how much is due to an inability of β-cell mass to increase *vs.* how much is a functional deficit in β-cells in terms of glucose-stimulated insulin secretion (GSIS). This might be worthy of further investigations. However, it is always hard to quantify β-cell mass *in vivo*.

It has been suggested a potential link between GDM and type 2 diabetes because GDM shares several risk factors with type 2 diabetes. Several studies have indicated that Asian women, compared with other racial/ethnic groups in the US or Europe, have a very high risk for GDM although Asians are more likely to be thin than other racial/ethnic groups.[31-33] It has been hypothesized that Asians have higher adiposity per unit body mass index (BMI) compared with other racial/ethnic groups, leading to an increased risk of GDM or type 2 diabetes at a lower BMI.[34] A recent Chinese study found that β-cell dysfunction had a more pronounced contribution to type 2 diabetes among non-obese subjects, whereas IR contributed more to type 2 diabetes among obese subjects.[35] A genetic study sampled from a Chinese national survey also showed that patients with type 2 diabetes with a higher genetic risk score were leaner or had a worse β-cell function.[36] Thus, more studies are needed to assess joint associations of pre-pregnancy BMI, β-cell function, and IR during pregnancy with the risk of adverse pregnancy outcomes among women with GDM.

Several unhealthy lifestyle factors, such as pre-pregnancy overweight or obesity, physical inactivity, excessive weight gain during pregnancy, increase GDM risk. Modification of lifestyle factors is therefore an important strategy for reducing adverse pregnancy outcomes among women with GDM. Several randomized clinical trials in China, the US, and Australia have demonstrated that treatment effective lifestyle intervention strategies (dietary modification, enhanced physical activity, self-monitoring of blood glucose, and insulin therapy) of GDM reduced the rate of serious perinatal complications.[37-39] However, these randomized controlled trials (RCTs) found that intensive lifestyle intervention during pregnancy did not reduce the risk of postpartum diabetes among women with GDM and did not modify the growth of offspring born to GDM.[40,41] In addition, the traditional puerperal practices in China (like Zuoyuezi, or sitting the month, postpartum confinement) may specifically affect postpartum cardiometabolic measurements. Diets with energy surplus and lack of exercise contribute a lot to cardiometabolic diseases postpartum, which should be of great caution, especially among overweight or obese women.

Overall, this study found that β-cell function at 24–28 weeks of gestation was inversely and HOMA-IR at 24–28 weeks of gestation was positively associated with the risk of adverse pregnancy outcomes among women with GDM. An effective lifestyle intervention strategy of GDM during pregnancy can reduce the rate of serious perinatal complications. We need more studies to assess whether an effective lifestyle intervention strategy before pregnancy or from the prenatal to early postpartum can greatly improve adverse pregnancy outcomes and later cardiometabolic risk factors in both mothers with GDM and their children.

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