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Gestational diabetes: Linking epidemiology, excessive gestational weight gain, adverse pregnancy outcomes, and future metabolic syndrome

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ABSTRACT

Gestational diabetes (GDM) affects up to 200,000 deliveries in the United States each year. With the growing obesity epidemic, delayed childbearing, and multiple gestations, the diagnosis of GDM is expected to continue to rise. GDM unmasks a beta-cell defect that persists after pregnancy and typically worsens over time imparting the increased risk of type 2 diabetes mellitus after the index pregnancy. In addition, coexisting obesity and progressive weight gain are additive factors for progression to type 2 DM. Obstetricians play an integral role in informing GDM women about their lifelong risk of type 2 diabetes (T2DM) and can help bridge the care to primary care physicians, as it relates to recommended screening and long-term follow-up.

Gestational diabetes is one of the most common medical complications of pregnancy, affecting up to 7–8% of pregnancies. Until recently, the focus of GDM management has been on prevention of pregnancy complications. Institution of strict glycemic control reduces neonatal morbidity and mortality, including macrosomia and stillbirth.[1,2] Maternal benefits of GDM treatment have also been demonstrated. In the NICHD Maternal Fetal Medicine Units randomized control trial of Treatment of Mild GDM, women treated for GDM had lower rates of hypertensive disorders of pregnancy, cesarean delivery, and less weight gain.[3] Despite this short-term benefit, a diagnosis of GDM has far reaching implications for long-term maternal health.

Gestational diabetes as a pathway to type 2 diabetes

The original criteria for diagnosis of GDM derived by O'Sullivan and Mahan[4] based on the oral glucose tolerance test were set to identify those women who were at risk for the development of type 2 diabetes in the future. Intuitively, a diagnosis of GDM increases the risk for progression to type 2 DM. Women with gestational diabetes have a sevenfold increased risk of developing type 2 diabetes in their lifetime.[5] Approximately half of these women develop diabetes in the 1st 5–10 years after the index pregnancy. The cumulative incidence rate of type 2 diabetes increases markedly in the 1st 5 years and appears to plateau after 10 years.[6] The rate of conversion to type 2 DM can vary, with ranges reported from 2.6% to 70% over a period from 6 weeks to 26 years from the index pregnancy.[6] GDM is more prevalent in women of certain ethnicities including Hispanic, African American, Native American, and Asian and Pacific Islander than in Caucasians.[7] Racial and ethnic disparities also persist in the risk of development of type 2 diabetes after a diagnosis of GDM. In a large retrospective cohort study conducted in the Kaiser Permanente Health System, women diagnosed with GDM were evaluated to determine the incidence of type 2 diabetes

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Table 1 – Diabetes incidence rates and rate ratios associated with GDM in a matched cohort (cite).

Race/ethnicity	Prior GDM (N = 12,855)			Non-GDM (N = 63,978)			Rate ratio (95% CI)
	Women (*n*)	Diabetes cases (*n*)	Incidence/1000 person-years (95% CI)	Women (*n*)	Diabetes cases (*n*)	Incidence/1000 person-years (95% CI)	
Black	1184	195	29.0 (25.2, 33.4)	5890	114	3.2 (2.6, 3.8)	9.2 (7.2, 11.7)
Hispanic	6673	849	24.6 (23.0, 26.3)	33,242	615	3.3 (3.1, 3.6)	7.4 (6.6, 8.2)
Non-Hispanic White	2902	261	15.8 (14.0, 7.8)	14,498	198	2.3 (2.0, 2.6)	7.0 (5.8, 8.4)
Asian Pacific Islander	2096	219	18.9 (16.6, 21.6)	10,345	184	3.1 (2.7, 3.5)	6.2 (5.1, 7.6)

Adapted from Xiang et al.[8]

after the index pregnancy.[8] Women with GDM were matched (1:5 ratio) with non-GDM women based on maternal age at delivery, race/ethnicity, and year of delivery. Black women had the highest risk of developing type 2 diabetes after a GDM pregnancy (Table 1). After adjustment for prepregnancy BMI, the overall risk of type 2 DM decreased for each group but did not negate the differences seen across ethnicities.

In a recent study of 843 Asian women with GDM, women were divided into those with early conversion to T2DM, within the 1st 2 months postpartum, and those with late conversion, at least 1-year after delivery.[9] In this report, 12.5% of women were diagnosed with type 2 DM in the 1st 2 months postpartum. Of the 370 remaining women, an additional 23.8% were late converters. The median time from index pregnancy to diagnosis was 8.0 years (95% CI: 7.2, 8.9) with an annual incidence of 6.8% per year. Risk factors associated with early conversion were higher prepregnancy body mass index (BMI), a higher glucose area under the curve (AUC) on the antepartum oral glucose tolerance test, a lower fasting insulin concentration, and decreased beta-cell function. Both higher prepregnancy BMI and higher glucose AUC were also associated with late conversion. These findings confirm the beta-cell dysfunction that persists after the index pregnancy, and that maternal weight is a strong contributor to long-term metabolic dysfunction.

Buchanan identifies two metabolic factors that influence a woman's risk for the development of type 2 DM after a GDM pregnancy. The first is related to the level of metabolic dysregulation that exists both during the pregnancy and immediately thereafter. The second is related to the ongoing rate of decline in beta-cell function.[10] Both higher glucose concentrations and lower insulin levels during the oral glucose tolerance signify a more significant impairment of beta-cell function.[9] Clinically, this is seen in women diagnosed with GDM early in pregnancy, those women who require insulin during pregnancy to achieve euglycemia and those with impaired glucose tolerance at the time of the postpartum 2 h 75 g oral glucose tolerance test. Because of the underlying impairment in beta-cell dysfunction that already exists, it takes very little further decrease in beta-cell secretion for a formal diagnosis of T2DM. One of the biggest factors that influences beta-cell deterioration and insulin sensitivity in the body is successive weight gain and obesity. Weight gain in successive pregnancies without returning to a normal BMI increases a woman's risk of obesity. Obesity has been shown to be associated with an increased risk of type 2 DM after a GDM pregnancy.[6,11] Both GDM and T2DM share a similar mechanism for metabolic dysregulation; decreased insulin sensitivity in addition to an inadequate insulin response.[12]

It is likely that a woman's genetic predisposition for the development of T2DM may also play a role in future risk after a GDM pregnancy. There have been more than 60 T2DM-associated genetic risk loci identified by large-scale genomic studies (GWAS). Of these, a total of 21 genetic variants in 10 known T2DM-associated genes were genotyped in a subset of GDM women. Of total, 69 early converters and 70 late converters along with an independent cohort of elderly non-diabetic controls ($n = 632$) were analyzed.[9] Early converters were more likely to have variants in CDKN2A/2B and HHEX, while late converters were more likely to have variants in CDKAL1. Both of these variants have been identified by GWAS to be associated with type 2 DM. Variants in both CDKN2A/2B and HHEX have been associated with a reduction in 30-min insulin secretion at the time of glucose challenge in addition to decreased beta-cell sensitivity.

Identification of impaired glucose tolerance after a GDM pregnancy

Despite the well-established increased risk of developing type 2 DM with a prior GDM pregnancy, rates of postpartum screening are dismal, averaging approximately 30–50%. In the National Diabetes Education Program call to action, the case for postpartum screening is convincing. If all 200,000 women diagnosed with GDM annually completed the recommended postpartum screening, 8000 women with frank diabetes and an additional 30,000 women with impaired glucose tolerance would be identified.[13] Women with T2DM would undergo immediate referral for long-term diabetes management, and women with impaired glucose tolerance would benefit from referral for diabetes prevention efforts that have been shown to delay the progression to type 2 DM.

Once we identify women with impaired glucose tolerance, we can offer interventions to delay the progression to type 2 DM. The Diabetes Prevention Program (DPP) was a multicenter NIH trial designed to study an intervention to delay