ADA AWARD LECTURE

Diabetes in Pregnancy for Mothers and Offspring: Reflection on 30 Years of Clinical and Translational Research: The 2022 Norbert Freinkel Award Lecture

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Hyperglycemia during pregnancy is a double-edged sword, affecting both mothers and their offspring and creating a vicious cycle that can affect multiple generations. Research in this field over the past 30 years has greatly improved our understanding of this disease and formed the basis of improved strategies to improve the health of mothers and their babies. Despite this progress, gestational and preexisting diabetes continue to have significant effects on both short- and long-term health of mothers and their offspring. In this article, I provide an overview of the work that my colleagues and I have done to advance the knowledge base around diabetes and pregnancy in four areas: *1*) diabetes risk after gestational diabetes mellitus (GDM), including racial and ethnic disparities; *2*) the pathophysiology of GDM and subsequent diabetes in Hispanic women; *3*) diabetes prevention and β-cell preservation following GDM; and *4*) evidence for multiple potential developmental effects in offspring that vary according to the timing of exposure and severity of maternal diabetes during pregnancy. This research continues the legacy of Norbert Freinkel and the concepts that he contributed to the field of diabetes and pregnancy. With the epidemic of obesity, increasing rates of type 1 and type 2 diabetes in youth, and rising prevalence of GDM across all racial and ethnic groups, we have a lot more work to do to combat this disease to break the vicious cycle.

In his 1980 Banting Award lecture, "Of Pregnancy and Progeny" (1), Norbert Freinkel hypothesized that abnormal nutrient mixtures in the mother could disrupt fetal development and lead to long-range changes in offspring, including behavioral, anthropometric, and metabolic teratology—the concept of "fuel-mediated teratogenesis." Research over the ensuing 40 years has largely supported his original ideas, providing a wealth of specific information on the breadth and depth of long-term health effects related to maternal hyperglycemia and metabolic aberrations in pregnancy. Those effects mimic a double-edged sword, affecting both mothers and their offspring in a vicious cycle that can impact multiple generations. The growing body of knowledge in this field has helped to increase public health awareness of the associated risks and served as a base for development of strategies to improve maternal and child health.

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However, gestational and preexisting diabetes continue to impart significant morbidity to mothers and offspring, and rising rates of gestational diabetes mellitus (GDM), type 2 diabetes (T2D), and type 1 diabetes (T1D) in women of reproductive age amplify the impact of these conditions within and across generations. In this article, I provide an overview of work that my colleagues and I have done to better understand the health impacts of diabetes during pregnancy in four areas: *1*) future diabetes risk after pregnancies complicated by GDM, including racial and ethnic disparities; *2*) pathophysiology of GDM and subsequent diabetes in one racial and ethnic group, namely, Hispanic women; *3*) diabetes prevention and β-cell preservation following GDM; and *4*) multiple potential developmental effects of maternal diabetes on offspring that vary by the timing of exposure and severity of maternal diabetes during pregnancy.

GDM: DIABETES RISK AND RACIAL AND ETHNIC DISPARITIES

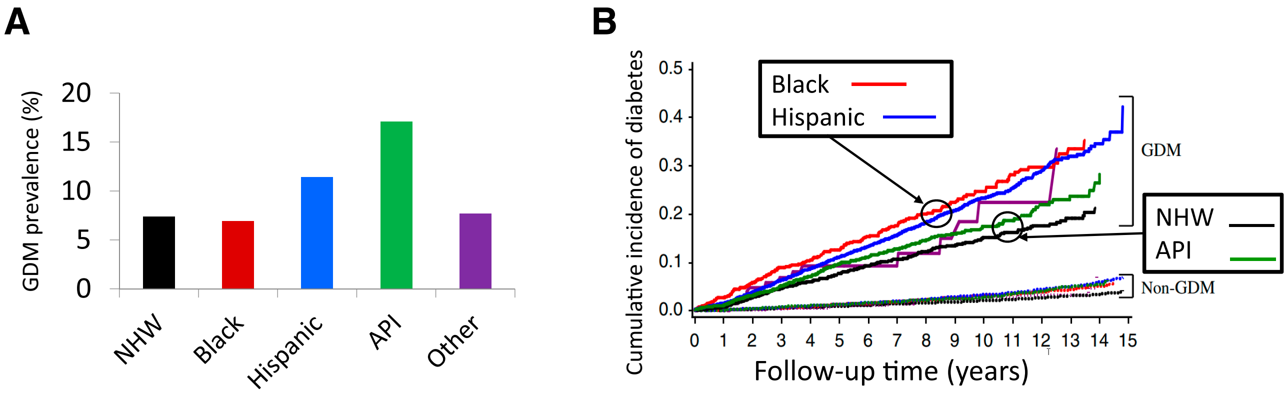
My work in the field of GDM research started in the 1990s while working closely with two pioneers of GDM research, Dr. Thomas Buchanan and Dr. Siri Kjos, at the University of Southern California (USC). Together we made several novel findings by analyzing data collected by Dr. Kjos from a clinical cohort of high-risk pregnancies at the Los Angeles County/USC Medical Center. A large majority of the patients were Hispanic, and GDM was diagnosed by National Diabetes Data Group criteria (2). We found that these women had almost 50% risk of developing diabetes within 5 years after the index pregnancy. Elevated glucose levels during oral glucose tolerance tests in pregnancy or postpartum, along with a relatively early gestational age at diagnosis of GDM, predicted the highest risk of future diabetes (3,4). In addition, one subsequent pregnancy tripled the long-term diabetes risk and each 10 lb of weight gain during follow-up doubled the diabetes risk. These two effects were independent of each other and all other identified risk factors (5). Furthermore, progestin-only contraception while breastfeeding added additional risk, while combination hormonal contraceptives had no detrimental effects (6–8). These findings provided important information relevant to patient management. They also provided hints into the pathogenesis of diabetes after GDM. Greater hyperglycemia during and after pregnancy identified women who were already close to diabetes; relatively little deterioration was required to develop diabetes during follow-up. However, data for individuals with weight gain, individuals who used progestin-only contraception, and, in particular, individuals who had one additional pregnancy suggested that insulin resistance may be accelerating the decline in β-cell compensation that leads to diabetes. That suggestion was borne out in subsequent studies discussed below.

Meta-analysis conducted by others showed that women with GDM had an approximately sevenfold higher long-term diabetes risk than women without GDM (9). Moreover, GDM was known to be rising in frequency across all racial and ethnic groups (10), in parallel with the epidemic of obesity and increasing trend in T1D and T2D in children and adolescents (11). However, less was known about whether the long-term diabetes risks after GDM are the same across racial and ethnic groups. Using electronic medical records from Kaiser Permanente Southern California (KPSC), we found that 10.3% of the 139,334 singleton pregnancies delivered at KPSC between 1995 and 2008 had GDM by the Carpenter and Coustan criteria (12,13). The rate was highest for women who self-identified as Asian and Pacific Islander (17.1%), followed by self-identified Hispanic (11.4%), non-Hispanic White (NHW) (7.4%), and Black (6.9%) women (13) (Fig. 1*A*). We assessed incidence rates of diabetes by race and ethnicity for up to a decade after delivery of GDM pregnancies and age-matched and race- and ethnicity-matched control participants who delivered in the same year. As expected, all the GDM groups had a much higher rate of diabetes during follow-up than their counterparts who did not have GDM (Fig. 1*B*). However, the pattern of variation in long-term diabetes rates among racial and ethnic groups with GDM did not parallel the variation in their rates of GDM during pregnancy. Specifically, Black women had the lowest rate of GDM during pregnancy but the highest rate of diabetes over the next decade. Asian and Pacific Islander women had the opposite pattern, with the highest rate of GDM but the second lowest rate of subsequent diabetes. Hispanic women demonstrated the best concordance, with the second highest rate of GDM and the second highest rate of subsequent diabetes. NHW women had a GDM rate that was nearly as low as that of Black women combined with the lowest rate of diabetes during follow-up (Fig. 1*C*). Compared with counterparts who did not have GDM, the relative risks (95% CI) of developing diabetes associated with GDM were 9.9 (7.5–13.1) for Black, 7.7 (6.8–8.7) for Hispanic, 6.5 (5.2–8.0) for NHW, and 6.3 (5.0–7.9) for Asian and Pacific Islander women after adjusting for potential confounders. Adjusting for maternal obesity measured by prepregnancy BMI reduced the risk estimates associated with GDM for all racial and ethnic groups but did not explain the differences of future diabetes risk across racial and ethnic groups (13). Thus, this large observational study revealed important racial and ethnic differences between GDM risk and future diabetes risk. The discrepancies suggest different pathophysiologies among groups. Mechanistic studies are needed to understand the differences in more detail, along with influences of genetics, environment, lifestyle, and other factors that may contribute to these differences.

PATHOPHYSIOLOGY OF GDM AND DIABETES DEVELOPMENT IN HISPANIC WOMEN

Pregnancy is normally attended by progressive insulin resistance that begins near midpregnancy and progresses through the third trimester due to increased maternal adiposity and the insulin-desensitizing effects of hormonal products of the placenta (14). This is a normal pathophysiologic response of pregnancy that is thought to ensure adequate nutrient supply from the mother to meet the needs of a growing fetus (15).

To understand the pathophysiology of GDM and future diabetes risk, our group designed a detailed study of glucose regulation in Hispanic women with GDM diagnosed by using the criteria of the Third International Workshop Conference on GDM (16). We recruited 175 Hispanic women during the third trimester of pregnancy, 150 with GDM and 25 without GDM, and they were frequency matched on age, prepregnancy BMI, and gestational age to the GDM group. All women had a 100-g oral glucose tolerance test, euglycemic clamp at physiologic hyperinsulinemia,



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GDM and Subsequent Diabetes		
Rate of GDM or Diabetes	GDM Prevalence	Diabetes Incidence
High	API	Black
Intermediate	Hispanic	Hispanic
Low	NHW and Black	NHW and API

Figure 1—GDM and subsequent diabetes risk by race and ethnicity. *A*: GDM prevalence, including 139,334 singleton pregnancies between 1995 and 2008, with GDM by the Carpenter and Coustan criteria. *B*: Diabetes cumulative incidence after GDM. Both panels *A* and *B* were adapted with permission from Xiang et al. (13). *C*: Rank order of GDM prevalence and diabetes cumulative incidence by race and ethnicity. Red and green circles highlight discordance between GDM prevalence and diabetes incidence in Asian Pacific Islander (API) (red circles) and Black (green circles) groups, respectively.

and frequently sampled intravenous glucose tolerance tests (IVGTT) between 28 and 34 weeks gestation. Compared with their non-GDM counterparts, women with GDM had significantly lower glucose clearance, higher glucose production, higher levels of free fatty acids at baseline of the clamp, and less stimulation of glucose clearance and suppression of glucose production and fatty acid levels compared with controls (17). The GDM group also had a marked reduction in the disposition index from the IVGTTs, a measure of acute β-cell compensation for the degree of insulin resistance (17). These results demonstrate that GDM in Hispanic women is characterized by all the major defects in glucose regulation, i.e., insulin resistance in muscles, liver, and fat and reduced β-cell compensation, observed in patients with T2D, albeit to a lesser degree. Testing of a large subset of these women ∼6 months after pregnancy revealed that their defect in β-cell compensation was similar to that observed during the third trimester (−69% vs. −62%, respectively) (14). Similar patterns were observed for Black women (18) and White women (19). Thus, GDM in large part represents the detection of preexisting defects in β-cell compensation for chronic insulin resistance in relatively young women.

We continued following these women with oral glucose tolerance tests and IVGTT at 12−15-month intervals for up to 12 years after the index pregnancy unless their fasting glucose reached 140 mg/dL or they were lost to follow-up. Forty-three percent developed diabetes, with an average annual incidence rate of 7.2% (20). Body weight and fasting and postchallenge glucose increased significantly; β-cell compensation measured by disposition index declined significantly (20,21). The strongest factor associated with falling β-cell compensation was weight gain, an association explained statistically by a combination of increasing insulin resistance (40%), falling adiponectin, and rising C-reactive protein (31% combined effect) (21). This study also revealed that low insulin sensitivity and β-cell function at baseline and the rate of their deterioration during follow-up contributed to the risk of T2D development (20). In addition, high habitual daily caloric intake was associated with worsening insulin resistance, falling β-cell compensation, and rising glucose levels independent of weight gain (22). This study provides the longest follow-up of which we are aware, and it uses detailed physiological measurements to characterize the natural history of glucose regulation following pregnancies complicated by GDM. It provides evidence that obesity and related metabolic changes may be important drivers of the β-cell decline that leads to diabetes. Interventions to increase exercise and reduce body weight should reduce diabetes risk, as was demonstrated in the Diabetes Prevention Program (23).

An important observation from this longitudinal study is that the relationship between changes in circulating glucose levels and changes in β-cell function is nonlinear (24). Both fasting and 2h glucose rise slowly with the decline in β-cell compensation over many years (Fig. 2 in Xiang et al. [24]), followed by more rapid increase in glucose per change in β-cell compensation when compensation gets very low (∼10% of normal). These findings define a pathogenesis for T2D in Hispanic women with prior GDM that is characterized by a relatively long-term decline in acute β-cell compensation for chronic insulin resistance, attended initially by slowly rising glucose levels. Only relatively late in this process do glucose levels rise rapidly and

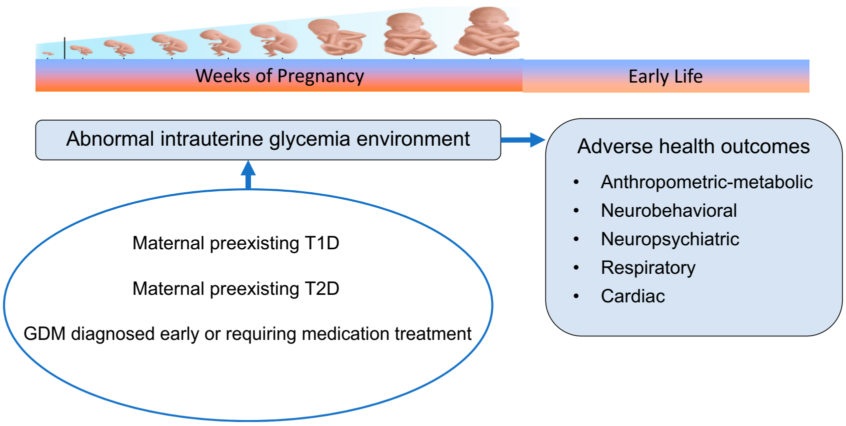

Figure 4—Potential long-range effects on offspring caused by different types of diabetes during pregnancy.

behavioral, anthropometric, and metabolic teratology (1).

FUTURE RESEARCH

Despite much progress over the past 40 years, many unknowns remain at the intersection of diabetes and pregnancy. Three areas where gains in knowledge could have important implications for the personal care of diabetes during pregnancy should be highlighted. First, we need to understand racial and ethnic differences in the pathophysiology of GDM and subsequent diabetes development, such that targeted approaches specific to each racial and ethnic group can be developed to mitigate the risk. Second, more studies are needed to understand the relative contributions of maternal factors such as obesity, weight gain, hyperglycemia, and hyperlipidemia (15) to perinatal and long-term risks in offspring of mothers with diabetes. Such understanding could have important implications for antenatal management to mitigate risk. Third, much work is needed to understand mechanisms, timing of exposure, and severity of maternal diabetes that predisposes to neurocognitive disorders in children, so that clinical approaches to early detection and treatment (53) can be developed and tested to help women at high risk manage their glucose levels (54) to minimize both short- and long-term impacts to the offspring.

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