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Onset of T2DM after gestational diabetes: What the prevention paradox tells us about risk

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ABSTRACT

This study investigates the effect of severity of gestational diabetes (GDM) on likelihood of post-delivery glucose testing and early onset Type 2 diabetes (T2DM). We asked if clinical focus on relative risk (RR), i.e. greater probability of T2DM onset in a higher-severity group, contributes to missed opportunities for prevention among women with lower-severity GDM. A sample of 12,622 continuously-insured women with GDM (2006–2015) was drawn from a large national dataset (OptumLabs® Data Warehouse) and followed for 3-years post-delivery. Higher-severity GDM was defined as addition of hypoglycemic therapy to standard of care for GDM. We found that women with higher-severity (n = 2627) were twice as likely as lower-severity women (n = 9995) to obtain glucose testing post-delivery. Moreover, 357 (13.6%) of the higher-severity women developed T2DM by year-3 vs. 600 (6.0%) lower-severity women. In an analysis of the population attributable fraction (PAF), defined as the contribution of excess risk to population prevalence, lower-severity women contributed more cases to diabetes rates than higher-risk women (PAF 79% vs. 21%), despite an increased RR in the higher-severity group (13.6% vs. 6.0%, RR 2.26, 95%CI 2.00, 2.56). Projecting out to the 327,950 U.S. deliveries in 2014, we estimate that 9277 higher-severity women (13.6%) and 15,584 lower-severity women (6.0%), will have developed T2DM by 2018. These data demonstrate that lower-severity GDM contributes substantially to the diabetes epidemic. Greater awareness of clinical and cost implications of gaps in follow-up for lower-severity GDM may strengthen the likelihood of post-delivery testing and primary care referral, and thus reinforce the path to prevention.

1. Background

Gestational diabetes (GDM) offers an instructive window on women's health over the life course and their future risk of chronic illness, illuminating a 60% chance of developing type 2 diabetes (T2DM) within the following decade (Kim et al., 2002). Nevertheless most women with GDM are not tested after delivery (McCloskey et al., 2014; Carson et al., 2013) and do not transition to primary care in time to prevent, delay, or treat T2DM. (Shaw et al., 2010; Hajjaj et al., 2010; Bernstein et al., 2016) Both the American Diabetes Association and the American Congress of Obstetricians and Gynecologists have issued clear, population focused guidelines requiring postpartum glucose monitoring and referral to primary care for preventive measures (American Diabetes Association, 2014; American Congress of Obstetricians and Gynecologists, 2017). However these guidelines have not been widely adopted in clinical practice despite the national concern about the increasing prevalence and cost of diabetes,(Manuel et al., 2010) and availability of evidence-based measures for T2DM prevention (Chasan-Taber, 2015). This gap in the bridge from obstetric complication to comprehensive prevention may be an example of a missed opportunity—a prevention paradox in action.

The prevention paradox argues that determinants of disease and prevention strategies differ according to whether the focus is on sick individuals rather than sick populations. If we focus narrowly on women with the most severe presentation (sick individuals), we will correctly identify the subset with the highest probability of developing disease later in life, but we are less likely to continue to monitor those who have a less severe presentation, and will thus miss those who make up the largest proportion of patients who go on to develop chronic illness (Manuel et al., 2010). The number of lower-risk women with less severe GDM who are not followed, perhaps because they themselves and their clinicians think they are less likely to develop disease, as documented in interviews with both patients and physicians, (Bernstein et al., 2016) may contribute significantly to the diabetes epidemic in

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the U.S. (Shaw et al., 2010).

The potential effects of this prevention paradox have been worked out for the link from obesity to diabetes,(Chasan-Taber, 2015) but not yet for the link between GDM and T2DM. For example, people who are overweight are estimated to contribute 712,000 new cases of diabetes, compared to those who are obese (456,000 cases) or very obese (247,000 cases), even though the risk of diabetes for the very obese is three times the risk for those who are overweight. In the case of GDM, testing after delivery is known to be a hard sell for women with a new baby and competing responsibilities.

Risk can be calculated in two very different ways. Clinical risk is usually assessed as relative risk (RR), the ratio of the probability of an event occurring in an exposed group (higher severity women) compared to the probability of the event occurring in a comparison group (lower-severity women). Population risk is usually analyzed by determining the population attributable fraction (PAF), the proportional reduction in population disease that would occur if exposure to a risk factor among higher-severity women were reduced to an alternative ideal exposure.

Clinical decision-making driven by relative risk rather than by attributable fraction may also add to the diabetes prevalence, but this possibility has not yet been investigated among women with GDM.

1.1. Objective

We investigated the influence of GDM severity on outcomes of postpartum glucose testing and glucose testing of any type by one year and three years, to determine the risk of early T2DM onset and the volume of early T2DM cases by severity of GDM presentation, and estimate what results of different methods of risk calculation (RR vs. PAF) might suggest for the contribution of GDM to U.S. diabetes prevalence.

2. Methods

2.1. Sample

This analysis is a secondary inquiry from a larger investigation of predictors of follow-up after GDM, (Bernstein et al., 2017) using national data from OptumLabs® Data Warehouse (OLDW), a comprehensive, longitudinal, de-identified datasystem derived from insurance claims, electronic medical record data assigned both encounter and enrollment codes, survey results and enrollment assessments. This multi-source national data set is available as a package to academic researchers through academic partnerships. Coding allows all data points to be assigned to unique individuals across episodes of care. Claims data are available for all of these episodes; electronic medical information is much less complete. The details of sample selection are available from the original publication in print and in online Supplementary material.

First we identified all unique women with delivery of a livebirth between 1/31/06–9/30/12, as represented by single or multiple claims for pregnancy, delivery and/or postpartum care, using the International Classification of Diseases, 9th revision (ICD-9). We then characterized the first GDM-affected livebirth in the system (ICD-9 GDM code 648.8×), excluding women who had an ICD-9 code or history of standard hypoglycemic therapy suggestive of pre-existing T2DM, either prior to the 28th week of the index pregnancy or immediately postpartum. We also excluded women who did not have continuous insurance coverage from 1-year pre-pregnancy to 3-years post-delivery, because our unit of analysis was adequacy of follow-up after GDM in women who had limited financial barriers to seeking care.

We also excluded women who lacked comprehensive validated demographic data or information about service providers and delivery institutions, because demographic and institutional factors have been shown to affect adequacy of follow-up care. These exclusions were large (see Fig. 1), but necessary to achieve analytic goals. We assessed generalizability of the reduced sample through comparisons of excluded with included women, and proceeded with analyses only after comparability was determined. Included and excluded samples were similar on all key variables listed in Table 1. Findings from these comparability analyses are summarized in the Results section, and available in online Supplementary material associated with the original publication (Bernstein et al., 2017).

2.2. Protection of human subjects

This study was determined to be “not human research” by the Boston University Institutional Review Board because extensive, regularly monitored de-identification processes are in place.

2.3. Variable construction

We defined a GDM diagnosis conservatively as either one inpatient or two outpatient ICD-9 codes of 648.8, excluding cases with evidence for pre-existing T2DM as described above. Outcome variables include: glucose testing within the recommended period of 56–84 days postdelivery by fasting blood glucose, oral glucose tolerance test, or hemoglobin A1C within six months of delivery, and any of these tests at one year and three years post-delivery. These time periods were additive—e.g. any postpartum test counted as testing at one year and also at three years. Women who had any second pregnancy within the three year follow-up period were excluded, because their opportunity for follow-up was limited by that pregnancy, and glucose testing during a second pregnancy would confound the outcome of follow-up testing. Diagnosis of T2DM in the period from 12 weeks postpartum to three years after an index GDM delivery was based on the same combination of claims history and medication records that was used to identify pre-existing T2DM.

2.4. Analytic measures

We conducted descriptive analyses to determine the prevalence of 1) higher severity (defined as use of hypoglycemic medication for GDM) vs. lower severity (standard of care, usually consisting of diet and counseling only during a GDM pregnancy), 2) rates of glucose testing during the postpartum period and by one and three years following delivery, 3) the proportion in each category with onset of T2DM within three years after delivery, 4) the relative risk (RR) and 95%CI for T2DM onset by level of severity, and 5) analysis of the population attributable fraction (PAF) to determine the comparative contributions of lower and higher severity groups to the prevalence of T2DM. SAS 9.4 (Cary, NC) was used for these analyses. PAFs and their 95% confidence intervals were calculated using proc. stdrate in SAS. Calculation of national estimates of early T2DM onset were based on a GDM rate of 9.2% (DeSisto et al., 2014).

3. Results

Our sampling method yielded an analytic sample of 12,622 continuously insured women who had no prior evidence of T2DM on claims history or record of medications prescribed (see Fig. 1: Strobe Diagram). The GDM rate of 8.2% that we found in our sample is roughly comparable to the national rate of 9.2% estimated by DeSisto et al. at the CDC, based on 2014 prevalence (DeSisto et al., 2014).

3.1. Continuity of enrollment

Women with continuity of enrollment (n = 280,933) were generally similar to those excluded for enrollment gaps (1,004,376), although statistical differences were present ($p < 0.001$), magnified due to large sample size. For example, those with continuous coverage were on average 31.6 years old (s.d. 5.3) compared to 30.0 (s.d. 5.7) for non-