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2013

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Katherine Bowers
Cincinnati Children's Hospital Medical Center

S. Katherine Laughon
National Institutes of Health

Sungduk Kim
National Institutes of Health

Sunni L. Mumford
National Institutes of Health

Jennifer Brite
CUNY School of Public Health

See next page for additional authors

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Authors

Katherine Bowers, S. Katherine Laughon, Sungduk Kim, Sunni L. Mumford, Jennifer Brite, Michele Kiely, and Cuilin Zhang

The Association between a Medical History of Depression and Gestational Diabetes in a Large Multi-ethnic Cohort in the United States

Katherine Bowers[a,b], **S. Katherine Laughon**[a], **Sungduk Kim**[a], **Sunni L. Mumford**[a], **Jennifer Brite**[c], **Michele Kiely**[a], and **Cuilin Zhang**[a]

[a]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

[b]Cincinnati Children's Hospital Medical Center, Division of Biostatistics and Epidemiology, Cincinnati, OH

[c]School of Public Health, City University of New York, New York, NY

Abstract

Background: Both major depression and gestational diabetes mellitus (GDM) are prevalent among women of reproductive age. Our objective was to determine whether a medical history of depression is related to subsequent development of GDM.

Methods: The Consortium on Safe Labor was a US retrospective cohort study of 228 562 births between 2002 and 2008. Exclusion criteria for the present analysis included multiple gestation pregnancies (*n* = 5059), pre-existing diabetes (*n* = 12 771), deliveries <24 weeks (*n* = 395), site GDM prevalence (<1%) (*n* = 20 721) and missing data on pre-pregnancy body mass index (BMI) (*n* = 61 321). Using generalised estimating equations, we estimated the association between a history of depression and a pregnancy complicated by GDM.

Results: The final analytic population included 121 260 women contributing 128 295 pregnancies, of which 5606 were affected by GDM. A history of depression was significantly associated with an increased risk of developing GDM (multivariate odds ratio [aOR] = 1.42 [95% confidence interval (CI) 1.26, 1.60]). Adjusting for pre-pregnancy BMI and weight gain during pregnancy attenuated the association, although it remained statistically significant (aOR = 1.17 [95% CI 1.03, 1.33]).

Conclusions: A history of depression was significantly associated with an increased GDM risk among a large multi-ethnic US cohort of women. If the association is confirmed, depression presents a potentially modifiable risk factor of GDM and provides additional clues to the underlying pathophysiology of GDM.

Keywords

depression; pregnancy; gestational diabetes

Gestational diabetes mellitus (GDM), a common pregnancy complication, affects approximately 7–14% of pregnancies in high-risk populations,[1] and as high as 18% according to recent recommendations from the International Association of Diabetes and Pregnancy Study Groups.[2] Over the past several years, the prevalence of GDM has been increasing.[3,4] A pregnancy complicated by GDM is at risk for further complications, such as preeclampsia, and GDM is related to elevated future risk of type 2 diabetes and cardiovascular diseases[1] after pregnancy. Outside of pregnancy, clinical depression has been associated with an increased risk for type 2 diabetes,[5,6] with evidence for a bidirectional relationship.[7] While few studies have evaluated the association between diabetes and the onset of perinatal depression,[8,9] and there is some evidence that treating GDM reduces the risk for postpartum depression,[10] it is unknown whether a history of depression is associated with an increased risk of GDM during pregnancy.

Both behavioural and biological theories exist to support the potential association between depression and GDM. Depression and depressive symptoms are associated with obesity and behaviours related to the development of type 2 diabetes and GDM, such as excessive caloric intake, physical inactivity and smoking.[11] There are also hypotheses that describe an underlying biological association between depression and diabetes. Depression can cause activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to enhanced and sustained cortisol secretion. Cortisol opposes the action of insulin, and can lead to visceral adiposity, insulin resistance and other risk precursors of diabetes.[11] Since depression is common among women of reproductive age,[12] it could represent an important and prevalent risk factor for targeted GDM prevention. We have, therefore, evaluated the association between a medical history of depression and GDM in the Consortium on Safe Labor (CSL), a large, multi-ethnic cohort representative of the US population.

Methods

Data for this study came from the CSL, a study initiated by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, in collaboration with 12 institutions across the US, and has been described in detail elsewhere.[13] In brief, this was a retrospective cohort study of births between 2002 and 2008 from 19 hospitals representing nine American College of Obstetrics and Gynecology (ACOG) districts. In total, data from 228 562 deliveries were abstracted from electronic medical records, including demographic data, medical history, labour and delivery information, as well as obstetrical, postpartum and neonatal outcomes. Maternal and newborn discharge International Classification of Diseases (ICD)-9 codes were collected for each delivery.

Women contributed up to four pregnancies over the course of the study. Exclusion criteria for the present analyses included multiple gestation pregnancies (*n* = 5059), missing or positive medical history of preexisting diabetes (*n* = 12 771), and deliveries <24 weeks (*n* =

395). We excluded one site due to an unrealistic GDM prevalence of <1% (*n* = 20 725), as well as participants whose pre-pregnancy body mass index (BMI) data were missing (*n* = 61 321).

All exposure and outcome data were abstracted from two sources within the electronic medical records, including the medical chart and discharge record ICD9 codes. ICD9 codes for depression included 296.2 (major depression, single episode), 296.3 (major depression, recurrent), 311 (depressive disorder, not otherwise classified), and ICD9 codes for GDM included 648.8. Both sources of data were combined to assess depression and GDM status (Figure 1). For example, 2623 cases of GDM were unique to the medical chart, 1109 cases were unique to the discharge record and 1874 were identified from both sources, for a total of *n* = 5606 GDM cases. For medical history of depression, 4230 were unique to the medical chart, 465 unique to the discharge records and 1120 were identified from both sources, for a total of *n* = 5815 instances of depression. A majority of depression cases were acquired from the medical chart, which did not distinguish between types of depression or whether the depression was accompanied by other psychiatric conditions. Therefore, we did not make any distinctions in the analyses. Data on treatment for depression were not available for the majority of the participants, and all cases were included regardless of treatment.

Means with standard deviations for continuous baseline characteristics, and the number and proportions for categorical characteristics, were compared between women with and without history of depression. Due to the large sample size, statistical differences were not tested as minor, and clinically irrelevant differences would be statistically significant. In multivariate analyses, the unit of analysis was pregnancy. To account for multiple pregnancies per woman, generalised estimating equations were employed to estimate the odds ratio (OR) for GDM, comparing women with and without a history of depression and accounting for multiple pregnancies per woman. Models adjusted for potential confounding factors that were selected a priori and included risk factors for depression and GDM, and not in the causal pathway. These variables included age, race/ethnicity, study site, insurance, parity, continuous BMI and gestational weight gain (calculated by subtracting the pre-pregnancy weight from the hospital admission weight). Effect modification was evaluated for age (<25, 25–<30, 30–35 and >35), BMI (<25, 25–29.9 or >30 kg/m^2), parity (0, 1, 2, 3 or more) and race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, multiracial/other/unknown) by fitting multiplicative interaction terms of these factors with depression in multivariate models, and by stratified analyses to determine whether the depression–GDM association varied across strata of these risk factors. Given the wide range of the prevalence of depression by study site, we performed additional analyses with subgroups of sites reporting low (<1–2%) and high (12–17%) prevalence of depression. Sensitivity analyses were conducted to estimate the bias arising from missing data on BMI. Specifically, baseline characteristics and age and multivariate ORs describing the association between depression and GDM were estimated for women with missing and no missing data on BMI. In addition, to strengthen the temporality assumption, we examined the association limiting the assessment of depression to the data available in the medical history which was experienced prior to the current GDM-affected pregnancy. Moreover, we conducted sensitivity analyses to differentiate the effect history of major depression from that of postpartum depression by

restricting the analysis to nulliparous women. All statistical analyses were performed using SAS 9.1 (Cary, NC, USA).

Results

The final analytic population included 121 260 women including 128 295 pregnancies, of which 5606 were cases of GDM. The age range of women included in the study was 12–58 years. Women with history of depression were heavier [pre-pregnancy BMI (26.9 vs. 25.1 kg/m^2)] and were more likely to have GDM (5.4% vs. 4.3%). They gained slightly less weight during pregnancy than women with no reported history of depression (13.8 vs. 14.2 kg) (Table 1). Non-Hispanic White women reported the highest frequency of depression (5.8%) compared with non-Hispanic Black (3.9%), Hispanic (3.0%), Asian (0.8%) and multiracial/other/unknown race women (2.6%). The frequency of reported depression also increased with increasing parity (from 3.4% for nulliparous women to 6.2% for women with three or more pregnancies). In addition, no significant differences on distributions of major baseline characteristics in the entire analytical population were observed from those with missing data on pre-pregnancy BMI.

The age-adjusted OR for GDM comparing women with a medical history of depression to women without a medical history of depression was 1.30 [95% CI 1.16, 1.47] (Table 2). Controlling for age, study site, race/ethnicity and parity, as well as the type of medical insurance (to address socio-economic differences among women, and as a proxy for access to psychiatric and prenatal care), strengthened the association, aOR = 1.42 [95% CI 1.26, 1.60]. However, adjusting for continuous pre-pregnancy BMI and gestational weight gain attenuated the results, although they remained significant, aOR = 1.17 [95% CI 1.03, 1.33]. Moreover, the association persisted across sites with high vs. low prevalence of depression, and between nulliparous and multiparous women. Moreover, when the analysis was limited to depression abstracted only from medical record where depression was experienced prior to the current GDM-affected pregnancy, the results were comparable (Table 2).

It appears that there was a significant interaction between pre-pregnancy BMI and depression ($P = 0.02$). Across categories of BMI, the OR associating depression and GDM was 20 kg/m^2: aOR = 1.48 (0.85, 2.55); 20–24.9 kg/m^2: 1.11 (0.86, 1.44); 25–30 kg/m^2: 1.32 (1.05, 1.66); and >30: 1.11 (0.92, 1.33). No significant interactions between depression and age or race were identified ($P > 0.05$).

Comment

In this large, population-based, multi-ethnic cohort of US population, sampled from each of the nine ACOG districts, we identified a significantly increased odds of GDM associated with a medical history of depression. The association remained significant even after adjustment for pre-pregnancy BMI and was robust to several sensitivity analyses. Although BMI remains the strongest risk factor for identifying women at high risk for GDM, depression may represent an independent and novel risk factor for identifying women at high risk and help us further understand the underlying pathophysiology.

We are unaware of prior studies evaluating the association between depression and the onset of GDM. However, our results are in line with several studies that have evaluated the association between depression and type 2 diabetes.[5–7] While there is evidence for a bidirectional association, the effect appears to be larger for the risk of diabetes following depression (pooled relative risk across 13 studies was 1.60 [95% CI 1.37, 1.88]).[6]

Depression is a prevalent public health issue with significant medical, emotional and economic burden. It affects 2.3–4.9% of the population at any given time[14] and 13.3–17.1% of individuals over a lifetime.[14] Women are disproportionately affected, having around two times the lifetime prevalence of major depression compared with men,[15] and the onset of symptoms often occurs during the reproductive years.[16] There is evidence that up to 25% of women experience depression or depressive symptoms during pregnancy.[17] If depression leads to GDM, it could represent an important and prevalent risk factor for targeted prevention strategies. In addition, depression may be associated with other metabolic conditions, such as obesity,[18] the major risk factor for GDM, as well as metabolic syndrome.[19]

Several biologically plausible pathways have been suggested to describe the association between depression and glucose intolerance.[11] Depression has long been implicated in elevating cortisol following activation of the HPA axis.[20,21] Cortisol is a counter-regulatory hormone, which is a hormone that opposes the action of insulin. Prolonged exposure to cortisol can, therefore, lead to visceral adiposity, insulin resistance, dyslipidemia and hypertension,[11] each implicated in the pathology of GDM. During the course of pregnancy, urinary cortisol levels increase along with the upregulation of the maternal HPA axis,[22] and may in fact regulate metabolic changes, such as increases in body weight and metabolic rate, that lead to insulin resistance in pregnancy.[23] Exacerbating these high cortisol levels could, in turn, increase the metabolic consequences that contribute to GDM pathogenesis. Additional pathways include catecholamine release due to an enhanced sympathetic nervous system response or an inflammatory response, which also contributes to insulin resistance.[11]

There are several strengths to this study. It utilises a large cohort, representative of multiple race/ethnicities of women throughout the US. In addition, we were able to establish a reasonable assumption of temporality by conducting sensitivity analyses, limiting the assessment of depression to data available in the medical history where depression was experienced prior to the current GDM-affected pregnancy. There are also potential limitations. First, the temporal relationship between pre-pregnancy BMI and depression is not clear in this dataset so that we are unable to conclusively determine whether BMI is a confounder (common cause of depression and GDM), mediator (caused by depression and a cause of GDM), effect modifier or a combination. For the analyses, we made the assumption that pre-pregnancy BMI represents a lifetime weight burden and would predate depression, and therefore present models adjusted for BMI. Nonetheless, even if BMI is a mediator, the importance of identifying depression and the subsequent metabolic consequences remains. Although determining the exact causal relationship is beyond the scope of the CSL data, depression may work through direct pathways, or indirectly through BMI, and remains an important avenue for identification of women at risk for GDM.

Although a validation study determined that mapping data from electronic medical records to an analytic dataset was a highly valid process comparable to abstraction undertaken by hand,[13] data on medical history of depression and GDM were not explicitly validated. We observed that the depression prevalence varied across sites. However, regardless of the level of reporting, the significant association between depression and GDM remained. Third, for a large per cent of participants, data on pre-pregnancy BMI were missing; however, the prevalence of a history of depression, race, type of insurance coverage, parity or GDM did not vary appreciably between women with and without missing data. Therefore, reporting of BMI was not dependent on risk factors for either depression or GDM, and we believe it is unlikely to have biased our results. We did not have information on potentially important covariates, including physical activity, smoking and dietary factors, or treatment of depression.

In conclusion, we identified a significant association between a medical history of depression and the onset of GDM in a large, population-based, multi-ethnic cohort of US women. Depression is a common condition among women of reproductive age. If confirmed in future studies, this may represent a novel risk factor for identifying women at high risk and to potentially provide novel clues to the underlying pathophysiology of GDM.

Acknowledgments

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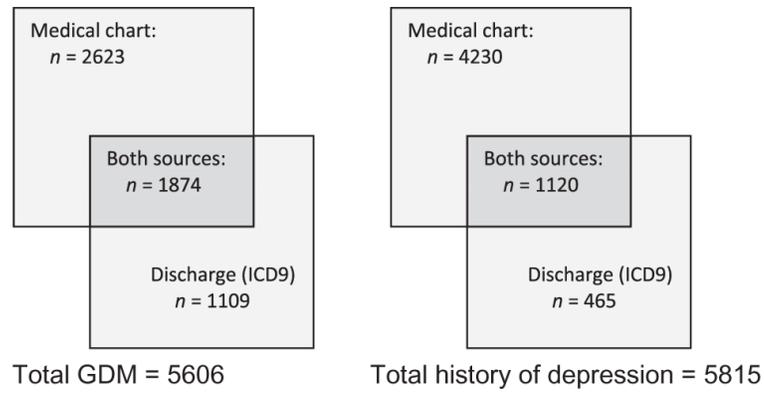
Total GDM = 5606   Total history of depression = 5815

Figure 1.
Assessment of depression and gestational diabetes mellitus (GDM) from the medical chart and the discharge records.

Table 1

Maternal baseline characteristics[a] of individuals with and without a medical history of depression among 128 295 pregnancies in the Consortium for Safe Labor delivered between 2002 and 2008

	Medical history of depression (*n* = 5815)	No medical history of depression (*n* = 122 480)
Gestational diabetes	313 (5.4)	5293 (4.3)
Maternal age, years	27.6 (6.1)	27.8 (6.1)
Height, m	1.6 (0.1)	1.6 (0.1)
Pre-pregnancy weight, kg	72.3 (20.0)	67.3 (16.9)
Weight gain, lbs	13.8 (7.8)	14.2 (6.6)
BMI, kg/m^2	26.9 (7.0)	25.1 (6.0)
<25 (%)	2820 (48.5)	74 015 (60.4)
25 and <30 (%)	1438 (24.7)	27 353 (22.3)
30 (%)	1557 (26.8)	21 112 (17.2)
Race (%)		
Non-Hispanic White	4000 (68.8)	65 459 (53.4)
Non-Hispanic Black	858 (14.8)	21 317 (17.4)
Hispanic	721 (12.4)	23 594 (19.3)
Asian/Pacific Islander	36 (0.6)	4596 (3.8)
Multiracial/other/unknown	200 (3.4)	7513 (6.1)
Parity (%)		
0	1730 (29.9)	49 817 (40.7)
1	1803 (31.0)	36 674 (29.9)
2	1209 (30.8)	20 002 (16.3)
3 or more	1064 (18.3)	15 987 (13.1)
Insurance (%)		
Private	3252 (55.9)	67 323 (55.0)
Public	2291 (39.4)	33 584 (27.4)
Self-pay	90 (1.6)	1139 (0.9)
Other/unknown	182 (3.1)	20 434 (16.7)

[a]Data presented in the table are mean (standard deviation) unless otherwise specified.

Table 2

Age- and multivariate-adjusted odds ratios (OR) and 95% confidence intervals (CI) describing the association between a history of depression and GDM

	Full cohort	Medical history of depression	Sites reporting high prevalence of depression	Sites reporting a low prevalence of depression
n	5606	5098	860	2317
N	128 295	111 952	16 072	47 297
Unadjusted	1.26 [1.12, 1.42]	1.23 [1.10, 1.40]	1.23 [1.00, 1.45]	1.53 [1.05, 2.24]
[a]aOR I [95% CI]	1.30 [1.16, 1.47]	1.21 [1.07, 1.36]	1.23 [1.02, 1.48]	1.55 [1.05, 2.27]
[b]aOR II [95% CI]	1.42 [1.26, 1.60]	1.36 [1.20, 1.54]	1.27 [1.05, 1.53]	1.58 [1.07, 2.34]
[c]aOR III [95% CI]	1.17 [1.03, 1.33]	1.15 [1.01, 1.31]	1.21 [0.98, 1.49]	1.28 [0.85, 1.94]

[a]aOR I: adjusts for age.

[b]aOR II: additionally adjusts for race/ethnicity, study site, insurance, parity.

[c]aOR III: additionally adjusts for pre-pregnancy BMI (continuous) and gestational weight gain.