Abnormal screening for gestational diabetes, maternal mood disorder, and preterm birth

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Abstract

Objective—Gestational diabetes (GDM) affects 7% of pregnant mothers and those with GDM have increased rates of perinatal complications. Major depressive disorder (MDD) and its pharmacologic treatments are associated with obesity and adverse pregnancy outcomes. In this prospective study, we investigated the relationship between abnormal GDM screens, maternal mood disorders, and adverse outcomes.

Methods—We examined mothers with MDD, bipolar disorder (BD), and healthy controls (HC) at 20, 30, and 36 weeks gestation and delivery. We obtained demographic data and pre-pregnancy body mass index (BMI), and confirmed diagnoses with the Structured Clinical Interview for DSM-IV. We evaluated smoking, alcohol, substance use, and medication treatments with the Longitudinal Interval Follow-up Evaluation interview. Mothers received the one-hour 50 g glucose challenge test (GCT) at 26–28 weeks gestation. Outcome variables were preterm birth, birth weight (BW) and peripartum events.

Results—We enrolled 62 HC, 50 BD, 41 past MDD, and 39 current MDD mother–infant pairs. Mean GCT levels and the frequency of abnormal GCT (> 140 mg/dL) did not differ across groups. Rates of smoking ($\chi^2 = 20.68$, df = 3, p < 0.001), substance use ($\chi^2 = 21.76$, df = 3, p < 0.001), and pre-pregnancy obesity [BMI 30 ($\chi^2 = 9.97$, df = 3, p = 0.019)] differed significantly across groups. Mothers with BD received medications associated with weight gain significantly more

often than others [13/45 (29%), p < 0.001]. After adjusting for group differences, GCT levels were associated significantly with increased odds for preterm birth (odds ratio = 1.29, 95% confidence interval: 1.0–1.7; p = 0.05) and increased perinatal events (beta = 0.11, p = 0.04) but not associated with BW.

Conclusions—In mothers with or without mood disorders, having increased GCT levels contributes to a higher likelihood for adverse pregnancy outcomes. Mothers with BD or current MDD can have additional risks for adverse outcomes and may benefit from early referral for high-risk services and supportive management in pregnancy.

Keywords

bipolar disorder; gestational diabetes; major depression; preterm birth

Diabetes mellitus is common in women of reproductive age. Gestational diabetes (GDM) affects 7% of pregnant women (200,000/year) (1). In low-income mothers, the risk for GDM or pre-pregnancy diabetes is twice as high in depressed (100/657 = 15.2%) versus non-depressed mothers (886/10,367 = 8.5%) [odds ratio (OR) = 1.85, 95% confidence interval (CI): 1.45–2.36] (2). Lack of medical intervention for GDM can increase depression risk. Compared to mothers who receive diabetes care (advice on nutrition, glucose monitoring, oral hypoglycemic agents or insulin, and specialty services), mothers who lack care have increased risk for postpartum depression (8% versus 17%) and poor functioning within three months of delivery (3).

In a large representative sampling of American women from all racial and ethnic groups, women of childbearing age (20–39 years) are frequently overweight or obese [body mass index (BMI) 25] (60%, n = 877) (4). Among non-Hispanic black mothers, the prevalence of being overweight or obese is even greater (78%, n = 191) (4). Gestational obesity not only increases the likelihood of GDM (5) but also of perinatal mood disorders. High pre-pregnancy BMI is strongly associated with major depression during pregnancy (6) and increased depression scores after delivery (7).

Risks for adverse outcomes are significantly increased with diabetes in pregnancy (8). Hyperglycemic mothers are more likely than non-affected mothers to develop preeclampsia, need for surgical delivery (8, 9), and delayed onset of diabetes later in life (10). Newborns have increased risk for congenital malformations by 3–4 fold (11), increased birth weight (> 90th percentile), hypoglycemia, and respiratory distress (8). *In utero* exposure to maternal hyperglycemia imprints lasting effects on the offspring resulting in childhood obesity and metabolic syndrome (12).

In this prospective observational study, we investigated the relationship between response to the 50 g glucose challenge test (GCT) at 28 weeks gestation (a routine screen for GDM) or having a maternal mood disorder and adverse pregnancy outcomes. We assessed mean GCT levels, frequency of abnormal GCT response (> 140 mg/dL) and pre-pregnancy BMI in mothers with major depressive disorder (MDD), bipolar disorder (BD), and healthy controls (HC). We examined differences among maternal diagnostic groups in sociodemographics, tobacco smoking, alcohol use, substance use, and antidepressant or mood-stabilizer

treatments. We explored the correlation between GCT levels and maternal obesity hypothesizing that increased mean GCT levels and having a maternal mood disorder would be associated with an increased rate of preterm birth, increased birth weight (BW), and greater frequency of perinatal events.

Methods

Mothers and newborns were enrolled in the longitudinal prospective observational studies *Antidepressant use during pregnancy* [R01 MH60335, Principle Investigator (PI): KLW] (13) or *Antimanic use during pregnancy* (R01 MH 075921, PI: KLW). We recruited study participants from an urban obstetrical hospital (Magee Women's Hospital, University of Pittsburgh, Pittsburgh, PA, USA) and conducted study assessments at Women's Behavioral HealthCARE, a university-based research clinic with a focus on perinatal mood disorders. Subjects provided written informed consent. The University of Pittsburgh Institutional Review Board approved study protocols.

Maternal subjects

Pregnant women without mental illness (HC) and mothers with past or current MDD or BD type I, BD type II, or BD not otherwise specified confirmed with the Structured Clinical Interview for DSM-IV (SCID) (14) were enrolled. At intake, we recorded age, race, marital status, level of education completed, employment status, pre-pregnancy BMI, and medical history. Enrolled women were 18–45 years of age. Subjects with alcohol or substance abuse or dependence (as indicated by the SCID, urine drug screen, or substance use treatment, e.g., methadone) or medical conditions that could affect outcomes (twin gestation or pre-pregnancy diabetes) were excluded. Since marijuana use is common in many groups, we did not exclude mothers who used marijuana.

Procedures

At 20-, 30-, and 36-weeks gestation and delivery, we assessed maternal weight, antidepressant and antimanic drug treatment and doses, cigarette smoking, alcohol and substance use, and concomitant medication treatments for each gestational week with the Timeline Technique (15). At study visits we evaluated the course of illness and identified new mood episodes with the Longitudinal Interval Follow-up Evaluation (LIFE) (16). At 26–28 weeks gestation, mothers received the one-hour 50 g GCT. With a cutoff point of 140 mg/dL, the GCT has a sensitivity of 80% and false positive rate of 13% (17). Subjects provided signed release of information forms which allowed investigators to have access to obstetrical and hospital records including GCT results.

Infants

Newborns with antidepressant or antimanic medication exposure may develop clinical signs within days of birth. A standardized instrument to evaluate neonates with *in utero* medication exposure has not been published. Because of this, study team members with obstetrical expertise (nursing doctorate, and obstetrician/ gynecologist) who were blind to the hypotheses, performed a systematic record review of obstetrical, birth and infant hospital charts to retrieve all possible newborn outcomes data. Newborn data from the extensive

review were used to complete the Peripartum Events Scale (PES) (18). A second expert confirmed the positive findings. O'Hara et al (18) developed the PES instrument to index stressful events in the peripartum period experienced by the mother but not necessarily considered as obstetrical or postnatal complications. The psychometric properties, e.g., high inter-rater reliability (Pearson's correlation coefficient $r = 0.92$, p < 0.001), acceptable level of internal consistency (Cronbach's coefficient alpha = 0.7) and proven construct validity (significant correlations with depressive symptoms from repeated measurements with the Beck Depression Inventory in mothers with postpartum depression) (18) provided evidence the PES was an appropriate tool to quantify (count) events related to delivery. With the PES, we evaluated the following 14 items: gestational weeks, birth weight, Apgar scores, neonatal complications (need for ph correction, volume correction, need for transfusion or plasma exchange, hypoglycemia, hypocalcemia, hyperbilirubinemia, treatment for sepsis, meconium aspiration pneumonitis, other, other serious event, special care admission, and any treatment to alleviate distress).

Outcome measures and statistical analysis

The outcome measures were preterm birth (< 37weeks gestation), BW, and perinatal events (PES total score, dichotomized PES 1 and PES 2). To investigate possible differences among diagnostic groups (HC, current MDD, past MDD, and BD) across baseline measures, we used analysis of variance (ANOVA) for continuous measures, Pearson's chi-square test and Fisher's Exact test for categorical measures. We examined associations between the outcome measures and GCT, maternal diagnosis and the interaction of GCT and diagnosis. We used logistic regression models for outcomes of preterm birth and dichotomized PES 1 and PES 2; and linear regression models for BW and PES total scores. Since PES total scores did not distribute normally (most PES total scores were zero), we assumed a Poisson distribution. In the statistical analyses we examined unadjusted models and to correct for group differences, models adjusted for socio-demographics (age, race, education, employment, marital status), pre-pregnancy BMI, tobacco, substance (primarily marijuana) use, any psychiatric drug treatment (serotonin reuptake inhibitors-SRI and other agents), medications which could induce weight gain (19), diabetes or impaired glucose tolerance (1, 20, 21). We explored correlations between pre-pregnancy BMI or pre-pregnancy BMI 30 and mean GCT or abnormal GCT (> 140 mg/dL) with Spearman correlation coefficients. We corrected for repeated testing with the Bonferroni method.

Results

Sample characteristics (Tables 1 and 2)

We enrolled 192 mother–infant pairs (62 HC, 50 BD, 41 past MDD, and 39 current MDD) with complete infant outcome data; 186 mothers (61 HC, 45 BD, 41 past MDD, and 39 current MDD) provided complete demographic and GCT data. Maternal age differed across diagnostic groups ($F = 3.48$; df = 3,182; p = 0.017). Mothers with BD (26.2 ±6 years) were significantly younger than HC (30 ±6 years, p = 0.005) or mothers with prior MDD (30 ±5 years, p = 0.008) (Table 1). The proportion of African Americans, who represented 23% (43/186) of all of the patients, did not differ significantly across diagnostic groups. Rates of completing college differed significantly with diagnosis ($\chi^2 = 41.58$, df = 3, p < 0.001;

mothers with BD had significantly lower rates of college completion (6/45 = 13%) compared to mothers in other groups (44–73%). The frequency of employment was significantly different across groups (χ^2 = 21.07, df = 3, p < 0.001). Mothers without mental illness (43/61 = 72%) were employed significantly more frequently than mothers with BD (11/45 = 26%; p < 0.001) or mothers with current depression (18/39 = 46%; p = 0.01). Marriage rates differed significantly by diagnosis (χ^2 = 17.08, df = 3, p < 0.001). Mothers with BD were married less often (17/45 = 38%) than HC (45/61 = 74%; p < 0.001) or mothers with prior MDD (30/41 = 73%; p < 0.001).

Rates of cigarette smoking (χ^2 = 20.68, df = 3, p < 0.001) and substance use (χ^2 = 21.76, df = 3, p < 0.001) differed significantly across groups (Table 1). Smoking was significantly more common in mothers with BD (16/45 = 36%) compared to HC (3/61 = 5%; p < 0.001) or mothers who had prior MDD (4/41 = 10%; p = 0.004). Mothers with BD used substances including marijuana significantly more frequently (14/45 = 33%) than HC (4/61 = 6.6%; p < 0.001) or mothers with prior MDD (1/41 = 2.4%; p < 0.001). Across groups, the frequency of alcohol use did not differ significantly.

Mothers with BD and with prior and current MDD received antidepressants (citalopram, escitalopram, fluoxetine, sertraline, and nortriptyline) at similar rates (27–36%) (Table 1). More than one-fifth of mothers with mood disorders (29/125 = 23%) received medications which were associated with diabetes or glucose intolerance (olanzapine, quetiapine, risperidone, prednisone, sertraline, venlafaxine, and nortriptyline) and 11% (14/125) received medications which promoted weight gain (lithium, olanzapine, quetiapine, risperidone, and prednisone) (Table 1). Mothers who had BD received medications associated with weight gain significantly more often (13/45 = 29%) than mothers with prior MDD (1/41 = 2%; p < 0.001) or current MDD (n = 0; p < 0.001).

The mean GCT level was 100 ±25.0 mg/dL and the rate of abnormal GCT response (> 140 mg/dL) was 7.0% (13/186) (Table 1); GCT levels and the rate of abnormal GCT response did not differ significantly across groups. Of the 13 patients with abnormal GCT response: (n = 3) were confirmed with GDM, i.e., two or more abnormal values on the 75 g or 100 g oral glucose challenge test (OGTT); (n = 3) had single abnormal OGTT values; (n = 2) had normal OGTT values; and (n = 5) did not complete the follow-up OGTT. Before pregnancy, enrolled mothers were on average overweight (mean pre-pregnancy BMI = 27.1 ±7.6) and frequently obese (BMI 30) (50/186 = 29%) (Table 1). The frequency of obesity differed by diagnosis (χ^2 = 9.97, df = 3, p = 0.019). Obesity was significantly more common in mothers with current MDD compared to HC (17/39 = 44% versus 9/61 = 16%; p = 0.003). Pre-pregnancy BMI was significantly (albeit weakly) correlated with GCT (Spearman's rho = 0.284, p = 0.0002) and GCT > 140 mg/dL (Spearman's rho = 0.221, p = 0.005).

Preterm birth

Although rates of preterm birth were not significantly different across diagnostic groups, preterm birth rate was lowest in HC (4/62 = 6.5%) and increased for mothers with BD and past or current MDD (7/50 = 14%, 6/41 = 15%, and 6/39 = 15%, respectively) (Table 2). In the unadjusted model having increased GCT levels was not associated with preterm birth. Adjusted models indicated the presence of increased GCT levels was associated

significantly with increased odds for preterm birth (OR = 1.3, 95% CI: 1.0–1.7; p = 0.05).
Maternal diagnosis and the interaction of GCT levels with maternal diagnosis were not
significantly associated with increased odds for preterm birth in unadjusted and adjusted
models (Table 3).

Birth weight

Mean BW differed with maternal diagnosis (F = 4.74; df = 3,182; p = 0.012) (Table 2).
Mothers with BD delivered newborns who had significantly reduced BW (3229 g ±569 g)
compared to HC mothers (3604 g ±555 g; p < 0.001). Because the majority of infants with
low BW (< 2500 g) (n = 11) were born prematurely (8/11 = 73%) we did not explore
differences in low BW across groups. Neither GCT levels nor maternal diagnosis was
associated with BW in unadjusted and adjusted models.

Perinatal events

Overall, 26% (49/192) of mother–infant pairs had any perinatal event (PES   1) and 7.0%
(13/192) had increased perinatal events (PES   2) (Table 2). Perinatal events included
preterm births and complications such as preeclampsia, neonatal care admissions, transient
respiratory distress, feeding difficulty and low Apgar scores at one and five minutes. Mean
PES scores and rates of any or increased perinatal events were not significantly different
across groups. In unadjusted models, GCT levels, maternal diagnosis and the interaction of
GCT level with diagnosis were not significantly associated with PES scores, any or
increased perinatal events. With adjusted models, we only detected a significant association
between increased GCT levels and higher PES scores (beta = 0.11, 95% CI: 0.004–0.21; p =
0.04) (Table 3).

Discussion

The presence of increased GCT levels (> 140 mg/dL) suggests altered glucose metabolism
and possible risk for GDM or maternal hyperglycemia. Having increased GCT levels was
significantly associated with adverse outcomes including preterm birth and perinatal events,
similar to findings reported by others (8). The odds of preterm birth was significantly
increased with higher GCT levels (adjusted models; OR = 1.3, 95% CI: 1.0–1.7; p = 0.05)
(Table 2). Concordantly, having increased GCT levels was significantly associated with
increased perinatal events (adjusted models; beta = 0.11, p = 0.04) from preterm delivery
plus other complications (18). Poor glycemic control is associated with various pregnancy-
related complications (22) (preterm labor, intrauterine infection, eclampsia, fetal distress)
which result in preterm birth (23). The findings reaffirm that mothers (with and without
mood disorders) with increased risk for GDM or gestational hyperglycemia are more likely
to experience preterm birth.

We hypothesized that having a maternal mood disorder would be associated with increased
adverse outcomes. Although preterm birth was more common in mothers with past or
current MDD or BD (14–15%) versus HC (6.5%, p = 0.389) (Table 2), maternal diagnosis
was not associated with preterm birth, birth weight or perinatal events (Table 3) contrary to
published reports (24, 25). On the other hand, health risk behaviors such as cigarette

smoking and substance use, which also contribute to adverse outcomes such as preterm birth (25), differed significantly across diagnostic groups. Mothers with BD smoked cigarettes (16/45 = 36%) and used substances including marijuana (14/45 = 33%) significantly more often than HC (3/61 = 4.9% and 4/61 = 6.6%) (Table 1). Maternal marijuana use and cigarette smoking usually co-occur. The effects of exposure to marijuana on neonatal adaptation (26) and ongoing neurodevelopment of the offspring (27) are likely additive to the effects of maternal smoking. Furthermore, smoking and substance use may alter stress responses in patients with mood disorders and provoke an inappropriate release of counter-regulatory hormones, e.g., cortisol (28) and accelerated production of inflammatory markers (29). Increased maternal-fetal circulation of cortisol may lead to abnormal fetal arousal, placental dysfunction (30) and exaggerated risks for preterm delivery and neonatal distress (31). Although we did not detect a significant association between maternal diagnosis and adverse outcomes, it is possible mood disorders in pregnancy could result in adverse outcomes from indirect or direct effects of health risk behaviors and activated stress pathways.

In the study, mothers with BD used marijuana more frequently than healthy mothers or mothers with past MDD (14/45 = 33%, 4/61 = 6.6%, and 1/41 = 2.4%, respectively; p < 0.001). Newborns of mothers who use marijuana can have increased tremors, exaggerated startles and repeated hand to mouth activity (26) which may contribute to a higher PES score. Even so, we did not detect increased rates of neurobehavioral symptoms or other adverse birth outcomes in the neonates of mothers with BD and we did not find associations between diagnosis and adverse birth outcomes in the unadjusted and adjusted models. Endogenous cannabinoids and their receptors likely have an integral role in neural development (32, 33). Increased amounts of maternal marijuana intake are associated with abnormal fetal and offspring brain function, e.g., decreased dopamine-2 receptor gene expression in the fetal amygdala (34) plus reduced verbal reasoning and short-term memory in children as early as ages three, four, and six years (26, 27). The reports suggest prenatal cannabis exposure may alter fetal neural development and impair the neural systems for cognition and emotion regulation. Because the study was not designed to explore outcomes of *in utero* marijuana exposure, the effect of maternal marijuana use on newborn outcomes was not clear. Regardless, additional research is critical to examine the potential relationship between substance use in mothers with mood disorders and adverse effects on the offspring.

The overall rate of preterm birth (23/192 = 12%) (Table 2) was comparable to national trends which indicate the rate of preterm singleton births is 10.6% (35). Despite medical advances and efforts to improve obstetrical care, the frequency of preterm delivery remains substantially increased, especially in African Americans versus Whites (16.2% and 9.4%, respectively) (23). Preterm birth is an important adverse outcome. Birth before 37-weeks gestation is a strong predictor of perinatal death (36). Lives of infants with preterm birth often are complicated by recurrent respiratory illnesses, ophthalmologic diseases, neurological disabilities including delayed psychomotor development, and problems with behavior and academic performance during school-age years (37). To more fully appreciate the impact of maternal hyperglycemia and mood disorders on offspring, assessment times must be extended to cover infancy, toddler and childhood stages of development.

Having MDD or BD introduces medical burden and the risk for diabetes can increase substantially. Patients with MDD have a two-fold increased risk for diabetes compared to general patients (38). We did not detect differences in GCT levels or the frequency of abnormal GCT response between HC and mothers with mood disorders. This finding was surprising because mothers with BD or current depression had some risk factors for diabetes (exposure to medications which induce weight gain or pre-pregnancy obesity). On the other hand, the medical burden from mood disorders may be related to age. Because mothers of childbearing age were younger, the accumulative effects of chronic obesity or treatment with drugs which alter metabolism were not observable yet.

One of the strengths of the investigation was that clinical follow-up did not impact study results. The outcome measures—preterm birth, birth weight and perinatal events—were obtained directly from perinatal reviews of maternal obstetrical, hospital and birth records (we did not rely on study patients to provide reports of their newborn's health status). Of concern, more than 40% (5/13) of participants with abnormal GCT results did not return for clinical follow-up and high-risk services, e.g., ongoing glucose monitoring, education on nutrition, and lifestyle changes for diabetes, plus assertive management of maternal hyperglycemia, obesity, and weight gain to lessen pregnancy risks. Prompt treatment of maternal hyperglycemia can effectively reduce adverse outcomes (39). The problem with incomplete clinical testing and lack of follow-up care suggested delivery of health services was not accessible to some urban mothers who were receiving care in a high volume obstetrical referral center and likely were contending with multiple stressors in pregnancy— high acuity symptoms, other diseases, reduced supports, low income and limited education (40).

To avoid relapse and alleviate highly impairing symptoms, pregnant mothers with BD or MDD are choosing to continue or begin treatments for mood disorders (41, 42). Many of the psycho-pharmacologic treatments are associated with adverse metabolic profiles. Greater than one-tenth (14/125 = 11%) of mothers with BD, prior or current MDD received drugs which promote weight gain and 23% (29/125) received drugs which alter glucose metabolism (Table 1) (19-21). Moreover, mothers with mood disorders frequently were practicing health risk behaviors such as smoking and starting to develop physical diseases such as obesity which increase future risks for cardiovascular disease, metabolic syndrome and irreversible medical complications. Because of the specialized needs of mothers with MDD or BD (and obese mothers), early referral for medical and mental health services could be offered and made more accessible through a hybrid model in which psychiatric and high risk obstetrical care are combined and integrated within the urban community. This potential solution—to widen the availability of effective care for mothers with mood disorders with an integrated care model—merits further investigation (43).

Acknowledgments

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Table 1

Mother demographic and clinical measures by diagnostic group at baseline

Measure	Diagnostic group					Analyses								
	All (N = 186)	HC (n = 61)	BD (n = 45)	PRI-MDD (n = 41)	CURR-MDD (n = 39)	Test statistic	df	p-value	HC vs. BD	HC vs. PRI-MDD	HC vs. CURR-MDD	BD vs. PRI-MDD	BD vs. CURR-MDD	PRI-MDD vs. CURR-MDD
Age, years, mean ± SD	28.7 ± 6.0	29.5 ± 5.7	26.2 ± 6.0	29.6 ± 5.3	29.3 ± 6.7	F = 3.48	3,182	0.017	0.005[e]	0.986	0.852	0.008[e]	0.029	0.851
Race, n (%)						$p < 0.0001$		0.114						
White	136 (73.1)	45 (73.8)	29 (64.4)	36 (87.8)	26 (66.7)									
Black	43 (23.1)	14 (23.0)	15 (33.3)	4 (9.8)	10 (25.6)									
Other	7 (3.8)	2 (3.3)	1 (2.2)	1 (2.4)	3 (7.7)									
White race, n (%)	136 (73.1)	45 (73.8)	29 (64.4)	36 (87.8)	26 (66.7)	χ^2 = 7.06	3	0.070						0.067
Educational level, n (%)						$p < 0.0001$		< 0.001	< 0.001[e]	0.385	0.016	< 0.001[e]	0.004[e]	
< High school	19 (10.3)	5 (8.2)	8 (17.8)	1 (2.5)	5 (12.8)									
High school	32 (17.3)	10 (16.4)	13 (28.9)	4 (10.0)	5 (12.8)									
Some college	40 (21.6)	4 (6.6)	18 (40.0)	6 (15.0)	12 (30.8)									
College	54 (29.2)	22 (36.1)	6 (13.3)	18 (45.0)	8 (20.5)									
Graduate school	40 (21.6)	20 (32.8)	0 (0)	11 (27.5)	9 (23.1)									
Completed college, n (%)	94 (50.8)	42 (68.9)	6 (13.3)	29 (72.5)	17 (43.6)	χ^2 = 41.58	3	< 0.001	< 0.001[e]	0.695	0.012[e]	< 0.001[e]	0.002[e]	0.009[e]
Employed, n (%)	94 (51.6)	43 (71.7)	11 (26.2)	22 (53.7)	18 (46.2)	χ^2 = 21.07	3	< 0.001	< 0.001[e]	0.064	0.011[e]	0.011[e]	0.061	0.502
Marital status, n (%)						$p < 0.0001$		0.003	< 0.001[e]	1.000	0.251	0.001[e]	0.096	0.448
Single	65 (34.9)	15 (24.6)	26 (57.8)	10 (24.4)	14 (35.9)									
Married/cohabiting	115 (61.8)	45 (73.8)	17 (37.8)	30 (73.2)	23 (59.0)									
Divorced/separated	5 (2.7)	1 (1.6)	1 (2.2)	1 (2.4)	2 (5.1)									
Widowed	1 (0.5)	0 (0)	1 (2.2)	0 (0)	0 (0.0)									
Married/cohabiting, n (%)	115 (61.8)	45 (73.8)	17 (37.8)	30 (73.2)	23 (59.0)	χ^2 = 17.08	3	< 0.001	< 0.001[e]	0.946	0.122	< 0.001[e]	0.052	0.180
Pre-pregnancy BMI, mean ± SD	27.1 ± 7.6	25.4 ± 5.4	27.8 ± 8.1	25.6 ± 5.4	30.6 ± 10.3	H = 0.07	3	0.068						0.069
Pre-pregnancy BMI ≥ 30, n (%)	50 (28.6)	9 (16.1)	14 (35.9)	10 (24.4)	17 (43.6)	χ^2 = 9.97	3	0.019	0.026	0.308	0.003[e]	0.262	0.488	0.069
Tobacco use, n (%)	29 (15.7)	3 (4.9)	16 (36.4)	4 (9.8)	6 (15.4)	χ^2 = 20.68	3	< 0.001	< 0.001[e]	0.435	0.148	0.004[e]	0.031	0.513
Alcohol use, n (%)	44 (23.8)	11 (18.0)	7 (15.9)	14 (34.1)	12 (30.8)	χ^2 = 6.10	3	0.107						
Illicit drug use, n (%)	23 (12.5)	4 (6.6)	14 (32.6)	1 (2.4)	4 (10.3)	χ^2 = 21.76	3	< 0.001	< 0.001[e]	0.646	0.708	< 0.001[e]	0.015	0.195
Glucose challenge test, mean ± SD	100 ± 25.0	99.4 ± 22.6	96.7 ± 27.2	103 ± 24.3	103 ± 26.8	F = 0.68	3,182	0.564						
Glucose challenge test > 140, n (%)	13 (7.0)	4 (6.6)	3 (6.7)	3 (7.3)	3 (7.7)	p = 0.02		1.000						
Any psychiatric medication, n (%)[a]	56 (44.8)		23 (51.1)	16 (39.0)	17 (43.6)	χ^2 = 1.30	2	0.522						

Measure	Diagnostic group					Test statistic	df	p-value	Analyses					
	All (N = 186)	HC (n = 61)	BD (n = 45)	PRI-MDD (n = 41)	CURR-MDD (n = 39)				HC vs. BD	HC vs. PRI-MDD	HC vs. CURR-MDD	BD vs. PRI-MDD	BD vs. CURR-MDD	PRI-MDD vs. CURR-MDD
SRI[b]	39 (31.2)		12 (26.7)	13 (31.7)	14 (35.9)	$\chi^2 = 0.84$	2	0.658						
Other	17 (13.6)		11 (24.4)	3 (7.3)	3 (7.7)	$\chi^2 = 7.04$	2	0.030				0.032	0.040	1.000
Any metabolism-altering medication, n (%)[a]	34 (27.2)		16 (35.6)	10 (24.4)	8 (20.5)	$\chi^2 = 2.63$	2	0.268						
Diabetogenic[c]	29 (23.2)		11 (24.4)	10 (24.4)	8 (20.5)	$\chi^2 = 0.23$	2	0.891						
Weight-inducing[d]	14 (11.2)		13 (28.9)	1 (2.4)	0 (0)	$\chi^2 = 22.24$	2	< 0.001				< 0.001[e]	< 0.001[e]	1.000

SD = standard deviation; BMI = body mass index; SRI = serotonin reuptake inhibitors; HC = healthy control; BD = bipolar disorder; PRI-MDD = prior major depressive disorder; CURR-MDD = current major depressive disorder.

[a] n = 186 − 61 = 125.

[b] SRI included sertraline (n = 23), citalopram (n = 6), escitalopram (n =5), and fluoxetine (n = 14).

[c] Medications associated with hyperglycemia included quetiapine (n = 5), risperidone (n = 2), olanzapine (n =1), prednisone (n = 2), sertraline (n = 23), venlafaxine (n = 6), and nortriptyline (n = 1).

[d] Medications associated with weight gain included quetiapine (n = 5), lithium (n = 2), risperidone (n = 2), olanzapine (n = 1), and prednisone (n = 2).

[e] Significant after Bonferroni correction.

Table 2

Infant demographic and birth outcome measures by diagnostic group

Measure	All (N = 192)	Diagnostic group				Test statistic	df	p-value	Analyses					
		HC (n = 62)	BD (n = 50)	PRI-MDD (n = 41)	CURR-MDD (n = 39)				HC vs. BD	HC vs. PRI-MDD	HC vs. CURR-MDD	BD vs. PRI-MDD	BD vs. CURR-MDD	PRI-MDD vs. CURR-MDD
Pre-term, n (%)	23 (12.0)	4 (6.5)	7 (14.0)	6 (14.6)	6 (15.4)	p = 0.003		0.389						
Sex, n (%)						$\chi^2 = 8.74$	3	0.033	0.114	0.097	0.004^a	0.875	0.164	0.235
Male	95 (49.5)	39 (62.9)	24 (48.0)	19 (46.3)	13 (33.3)									
Female	97 (50.5)	23 (37.1)	26 (52.0)	22 (53.7)	26 (66.7)									
Weight, g, mean ± SD	3407 ± 615	3604 ± 555	3229 ± 569	3343 ± 667	3381 ± 645	$F = 3.74$	3,182	0.012	$<0.001^a$	0.038	0.069	0.395	0.245	0.798
PES Total, mean ± SD	0.38 ± 0.76	0.31 ± 0.62	0.26 ± 0.57	0.60 ± 1.1	0.39 ± 0.68	$H = 0.42$	3	0.417						
PES 1, n (%)	49 (26.3)	15 (24.6)	9 (19.1)	13 (32.5)	12 (31.6)	$\chi^2 = 2.67$	3	0.446						
PES 2, n (%)	13 (7.0)	3 (4.9)	3 (6.4)	5 (12.5)	2 (5.3)	p = 0.008		0.522						

SD = standard deviation; HC = healthy control; BD = bipolar disorder; PRI-MDD = prior major depressive disorder; CURR-MDD = current major depressive disorder; PES = peripartum events scale.

^{a}Significant after Bonferroni correction.

Table 3

Parameter estimates and probability values from models of birth outcomes[a]

Parameter	Pre-term birth			Birth weight (g)			Peripartum events scale			Peripartum events scale 1			Peripartum events scale 2		
	OR	95% CI	p-value	β	95% CI	p-value	β	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
GCT, unadjusted	0.986	0.826–1.176	0.8715	19.6	-16.2 to 55.4	0.2839	0.084	-0.004 to 0.172	0.0610	1.017	0.893–1.158	0.7993	1.150	0.932–1.419	0.1938
GCT, adjusted[b]	1.290	1.001–1.661	0.0488	-28.5	-68.3 to 11.3	0.1608	0.107	0.004–0.210	0.0420	1.040	0.884–1.223	0.6355	1.250	0.931–1.680	0.1382
GCT[a] diagnosis, unadjusted			0.2424			0.3566			0.1330			0.4735			0.4389
Healthy control	0.785	0.452–1.361	0.3879	32.8	-34.9 to 100	0.3429	0.089	-0.099 to 0.278	0.3529	1.034	0.801–1.336	0.7965	1.196	0.741–1.929	0.4642
Bipolar disorder	0.817	0.537–2.020	0.9048	33.6	-91.3 to 93.1	0.9854	-0.181	-0.594 to 0.053	0.1006	0.805	0.509–1.189	0.2463	0.811	0.327–1.410	0.2987
Prior MDD	1.295	0.854–3.192	0.1363	-47.2	-185 to 25.1	0.1359	0.140	-0.195 to 0.296	0.6851	1.073	0.714–1.507	0.8487	1.280	0.580–1.979	0.8266
Current MDD	1.018	0.684–2.460	0.4260	38.3	-91.8 to 103	0.9118	0.135	-0.210 to 0.300	0.7287	1.080	0.728–1.497	0.8157	1.344	0.568–2.227	0.7362
GCT[a] diagnosis, adjusted[b]			0.3248			0.3530			0.2498			0.6144			0.3342
Healthy control	1.021	0.577–1.805	0.9434	-3.2	-71.2 to 64.7	0.9259	0.121	-0.086 to 0.327	0.2513	1.004	0.751–1.343	0.9787	1.529	0.893–2.617	0.1218
Bipolar disorder	1.025	0.486–2.072	0.9922	-16.7	-108 to 80.8	0.7796	-0.181	-0.703 to 0.100	0.1406	0.839	0.506–1.379	0.4820	0.543	0.085–1.491	0.1574
Prior MDD	1.714	0.829–3.401	0.1502	-90.7	-190 to 15.3	0.0953	0.177	-0.204 to 0.316	0.6733	1.135	0.752–1.700	0.5555	1.351	0.442–1.765	0.7261
Current MDD	1.261	0.622–2.453	0.5457	-13.1	-106 to 86.7	0.8415	0.088	-0.313 to 0.247	0.8167	1.096	0.734–1.623	0.6656	1.048	0.293–1.604	0.3840

OR = odds ratio; CI = confidence interval; GCT = glucose challenge test; MDD = major depressive disorder.

[a] GCT modeled in increments of 10.

[b] Adjusted for age, education, employment, marital status, pre-pregnancy body mass index, tobacco, illicit drug use, psychiatric and, metabolism-changing medications.