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Title: The association between Gestational Diabetes Mellitus, Antipsychotics and Severe Mental Illness in pregnancy: a multicentre study

Short Title: Gestational Diabetes and Mental Illness

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Abstract

Background: There have been conflicting findings for severe mental illnesses (SMI) and risk for gestational diabetes mellitus (GDM). Outside of pregnancy both severe mental illnesses and specific antipsychotic medications have been associated with elevated risk for metabolic disorders including type 2 diabetes mellitus. Aims: This study will examine the risk of developing Gestational Diabetes Mellitus (GDM) in relation to mental disorder, psychotropic treatment, and co-morbid risk factors

Materials and Methods: A retrospective study of 539 pregnant women with mental disorders. Measures included GDM diagnosis, mental health diagnosis, psychotropic medication, body mass index, age, smoking, alcohol and illicit substance use.

Results: This study found women with psychotic disorders were found to have significantly elevated risk for GDM (20.9%) compared to women with non-psychotic SMI during pregnancy ($p = .023$) and nearly three times the expected population rate (8.3%). Furthermore, women using specific antipsychotic agent, risperidone ($p = .016$) clozapine ($p < .001$), and higher dose quetiapine ($p = .029$) also had a higher risk of developing GDM. After adjusting for maternal age, body mass index (BMI), women on these specific agents continued to have four times the risk of having GDM compared to women not taking these agents. Smoking, alcohol and illicit drug use was not associated with elevated GDM rate in women with mental disorders.

Conclusions: These findings support the need for early screening and closer surveillance of metabolic risk in pregnancy for women with psychotic disorders and for specific atypical antipsychotic agents.

Introduction

Gestational diabetes mellitus (GDM) is a serious medical complication of pregnancy with evidence suggesting rates are rising across the population [1, 2]. Identification and treatment has been shown to improve outcomes and those identified as high-risk for GDM, earlier screening than the standard 28 weeks gestation, is often recommended[3].

In non-pregnant women and men, severe mental illnesses (SMI), including both schizophrenia and bipolar disorder, have been associated with an increased prevalence of diabetes mellitus (DM)[4-7]. It has been suggested that individuals with SMI are two-to-three times more likely to develop type 2 DM [8]. Furthermore, the use of newer antipsychotic treatments for SMI may compound this risk with specific antipsychotics independently associated with an increased risk of obesity and type 2 DM[9, 10].

Given the evidence that type 2 DM risk is increased, it seems plausible that women with SMI are also at an increased risk of developing GDM in pregnancy. It should be noted that not all women that develop GDM develop type 2 diabetes mellitus. Hence understanding the specific risk of GDM for both antipsychotic medication use and SMI is important for both antenatal and mental health care of women in pregnancy and child outcomes including mental health [11-13].

Two small retrospective studies have suggested that women with SMI are at significantly higher risk of developing GDM. The first study of 138 women found GDM in women with SMI ranged 12.5%-20.5% compared to 4.4% in the local population over the same time period [14]. The second study of 112 women found a GDM rate of 12.7% for women with SMI compared the hospital rate of 6.4%, however numbers of women in each diagnostic group were small [15]. While these two retrospective studies in maternity settings in Australia have demonstrated significantly higher rates of GDM [15, 16], neither was able to adjust for important and potentially confounding variables, including maternal obesity and antipsychotic usage.

In contrast to these two studies, a larger population-based study did not find an association between schizophrenia and GDM; however, neither obesity nor the use of antipsychotic medication were included [17]. Another population-based study of atypical antipsychotic use in pregnancy found no association between exposure to atypical antipsychotics and GDM [18]; it should be noted, that the majority of those using atypical antipsychotics in pregnancy did not have schizophrenia or bipolar disorder, dosage was not available, and usage specifically in pregnancy was not verifiable. A third population-based study found GDM risk was elevated equally across all antipsychotic agents, but these elevated risks were no longer significant after BMI was added to the model [19]. The largest study to date using Medicaid data in the USA found a significant association between specific antipsychotics and GDM these included olanzapine and quetiapine [20]. They found no such relationship with risperidone, ziprasidone or aripiprazole and they did not include clozapine in their analysis. A limitation of this study was limited diagnostic and dosage information, no data on smoking and alcohol use and data on only part of the sample for obesity.

Understanding whether women with SMI are at heightened risk of GDM is important for developing specific recommendations for antenatal care. Currently these women are not identified as high risk for GDM. In part this is due to the current limitations in the research available on GDM and SMI.

The aim of this study is firstly to address the question of whether the rate of GDM differs between psychotic disorders, bipolar disorder and other SMIs. Secondly, whether particular antipsychotic and mood stabilizer agents associated with higher rates of GDM than other agents. Finally, birth outcomes associated with SMI and GDM.

Methods

Sample

The sample comprised 539 women from two tertiary obstetric hospitals: Mercy Hospital for Women in Melbourne, Victoria (n = 127) and King Edward Memorial Hospital in Perth, Western Australia (n = 412). Authors extracted data from the hospital records. Five women were excluded from the analyses due to having comorbid diagnoses associated with GDM; these were pre-existing diabetes (n = 2) and bulimia nervosa (n = 3).

Ethics Approval

Ethics approvals were acquired from Mercy Hospital for Women Human Research Ethics Committee (R11/55) and from King Edward Memorial Human Research Ethics Committee (2016128EW).

Measures

Demographics

Demographic data included maternal age, Body Mass Index (BMI) and parity at the first antenatal appointment and was used to produce a binary variable, where BMI < 25 was coded as 0 (Healthy Weight) and BMI ≥ 25 was coded 1 (Overweight or Obese). Women's current smoking status (0 = Non-smoker, 1 = Smoker), alcohol consumption (0 = No, 1 = Yes) and current substance abuse status (0 = No, 1 = Yes) was also extracted.

Maternal Mental Health

Severe mental illness (SMI) was coded on the primary mental health diagnosis recorded on the patients' files. Both clinics have experienced perinatal psychiatrists who assign diagnoses following a comprehensive assessment. Three diagnostic groups were coded: psychotic disorders (including schizophrenia, schizoaffective and related psychotic disorders), bipolar disorder, and non-psychotic SMIs. Non-Psychotic SMIs include major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, anorexia and bulimia nervosa.

GDM

GDM was coded from the hospital records as no GDM (coded 0) and GDM (coded 1). GDM in both centres is diagnosed at 28 weeks gestation using the full 75g two-hour glucose tolerance test (GTT) as part of universal screening policy for pregnant women. Criteria for GDM in Australia changed during this study period. Prior to September 2015, a positive GTT

was recorded if fasting glucose ≥ 5.5 mmol/L, and the two-hour value ≥ 8 mmol/L. After this time period, GDM was diagnosed if fasting glucose ≥ 5.1 mmol/L, one-hour glucose ≥ 10 mmol/L or two-hour glucose ≥ 8.5 mmol/L [21]. Very few women in our sample (KEMH = 7, Mercy Hospital for Women = 5) were tested for GDM post-September, 2015.

Psychotropic Medication

Specific medications and dose were extracted from hospital records. For analysis, psychotropic exposure covered exposure during any trimester. Psychotropic agents were grouped as atypical antipsychotics (quetiapine, olanzapine, risperidone, clozapine, aripiprazole, ziprasidone and asenapine), typical antipsychotics (low potency and high potency) and mood stabilizers (lithium, and sodium valproate, lamotrigine, carbamazepine, gabapentin). In addition, some analyses used individual agents. Other psychotropic agents were recorded, including antidepressants, hypnotics and anxiolytics.

Statistical Analysis

Analyses were conducted using SPSS 24 [22], unless specified. A log-binomial regression was used to calculate the unadjusted relative risk (RR) of GDM. Next, a series of unadjusted relative risk statistics were calculated, with associated 95% confidence intervals, using Medcalc for Windows, version 18.6 [23], quantifying the risk between GDM for exposures to specific agents. Attributable risk (AR) was also reported. In these set of analyses, we excluded any woman with exposure to any other antipsychotic or mood stabilizer, and we only compared the rates of specific agents when more than 10 women reported exposure. We then conducted a log-binomial regression model to compare the adjusted relative risk (aRR) of GDM for women with exposure to specific antipsychotics associated with higher risk of diabetes with women exposed to other antipsychotics, after accounting for maternal age, BMI and diagnosis.

Results

Table 1 displays demographic information and rates of GDM by SMI groups. Using the whole sample, there were no associations between GDM and smoking (GDM = 42.9% versus no GDM = 44.8%, p = .796), alcohol consumption (GDM = 6.8% versus no GDM = 14.6%, p = .096), and illicit drug use (GDM = 17.3% versus no GDM = 20.5%, p = .541). Table 2 displays frequencies for specific antipsychotic and mood stabilizer medications. There was no significant association found in our sample for parity and GDM.

INSERT TABLE 1 and 2

SMI and GDM

The rate of GDM was highest in women with psychotic disorders (20.9%) compared to bipolar disorders (12.0%) and those with non-psychotic SMI (11.3%). Using data from the national perinatal collection [24], the prevalence of GDM in the Australian population in 2014 was 8.3%. While the prevalence of GDM was only marginally higher than national prevalence for women with bipolar disorder and non-psychotic SMI, GDM was nearly triple the prevalence in women with psychotic disorders. In our data, women in the psychotic disorders group demonstrated a higher attributable risk of having GDM compared to women in the non-psychotic SMI groups (RR = 1.86 [95% CI: 1.09, 3.17], AR = 8.9%). There was no difference in the attributable GDM risk between women with bipolar disorder and women in the non-psychotic SMI groups (RR = 1.07 [95% CI: .61, 1.87], AR = 0.7%).

Psychotropic Medication and GDM

There was no increased risk of GDM for women exposed to typical antipsychotics (7.1%) versus women not exposed (14.7%; RR = .49 [95% CI: .13, 1.88], AR = -7.6%), and for women exposed to mood stabilizers (18.7%) versus no exposure (13.0%, RR = 1.44 [95% CI: .92, 2.25], AR = 5.7%). The rate of GDM was significantly higher in women exposed to atypical antipsychotics (17.3%) compared to women not exposed (10.7%; RR = 1.62 [95% CI: 1.04, 2.52], AR = 6.6%).

Table 3 displays dose for specific psychotropic agents by GDM groups, and the rates of GDM by psychotropic agent exposures, attributable risk and unadjusted relative risk of GDM for each psychotropic agent compared to the comparison group. Exposure to atypical antipsychotics, olanzapine, quetiapine and aripiprazole, were each not associated with increased GDM rates, although for olanzapine this approached significance. Lithium and lamotrigine were also not associated with increased rates of GDM. Atypical antipsychotics, risperidone and clozapine, were each associated with higher risk of GDM. Within these comparisons, 91.4% of women taking quetiapine continued on the agent throughout pregnancy, 89.1% continued on olanzapine, 85% continued on risperidone, 100% continued on clozapine, 49.7% continued on aripiprazole, 82.4% continued on lithium, and 78.9% remained on lamotrigine. Interestingly, one patient commenced quetiapine in the third trimester.

As low dose quetiapine is used typically to treat anxiety and sleep disorders rather than psychotic or bipolar disorders, we investigated quetiapine dose on GDM rates compared to the control group. We split the quetiapine sample into low dose (< 300, n = 75) and those within therapeutic range (≥ 300, n = 21) to test if GDM rates are related to quetiapine dose. Although lower dose quetiapine was not associated with increased GDM rates compared to the control group, women taking higher dose quetiapine were at significantly higher relative risk of having GDM (see Table 3). In addition, women taking a higher dose range of quetiapine (23.8%) had significantly greater risk of having GDM compared to women in the lower dose group (6.7%; RR = 3.57 [95% CI: 1.14, 11.18], AR = 17.1%). Throughout pregnancy, 93.1% continued taking lower dose quetiapine and 85.7% continued taking higher dose quetiapine.

Finally, using only those women with psychotic disorders (n = 153), we fitted a log-binomial regression model to test the effect of those antipsychotic agents that have been previously associated with an increased risk of type 2 diabetes outside of pregnancy, controlling for BMI and maternal age. These antipsychotics included quetiapine (dose ≥ 300), olanzapine, risperidone or clozapine. In this model, women taking these specific antipsychotics (n = 69) were compared to women exposed to mood stabilizers, antidepressants, stimulants or anxiolytics, other antipsychotics not associated with increased type 2 diabetes risk and low-dose quetiapine (n = 71). The model was a parsimonious fit to the data (Deviance/d.f. = .79) and was a significant improvement on the intercept-only model (Likelihood Ratio $\chi^2(3) = 26.28$, $p < .001$). Exposure to antipsychotics previously associated with increased type 2 diabetes risk were associated with significantly higher risk of GDM (aRR = 4.39 [95% CI: 1.80, 10.69]). Controlling for maternal age (aRR = 1.08 [95% CI: 1.03, 1.14]) and maternal BMI (aRR = 1.31 [95% CI: .61, 2.78]), women taking either quetiapine (dose ≥ 300), olanzapine, risperidone or clozapine remained at a fourfold risk of GDM compared to women not exposed to other antipsychotics.

INSERT TABLE 3

SMI, GDM and Birth Outcomes.

Table 4 displays descriptive statistics for birth outcomes. Women with bipolar disorder and GDM had babies born with a significantly smaller head circumference and those with GDM, regardless of disorder, had babies born earlier compared to those without GDM.

INSERT TABLE 4

Sensitivity Analysis

There were 75 (13.9%) women in the sample whose ethnic backgrounds are associated with an increased risk of Type 2 diabetes and GDM. In this sample, these included women identifying as Aboriginal and Torres Strait Islander, Chinese, South-East Asian, Pacific Islander, Middle-Eastern, South American, and African. As we only had ethnicity of part of the sample, we conducted a sensitivity analysis by omitting these women and rerunning all analyses. First, when comparing the rate of GDM between this at-risk sample (16%) and the rest of the sample (14.2%), there was no increased risk of GDM associated with the at-risk ethnicities (RR = 1.13 [95% CIs: .64, 1.98]). In the sensitivity analysis omitting the at-risk sample, there were no substantive differences to the findings reported above.

Discussion

This study found 20.9% of women with psychotic disorders developed GDM, nearly three times the Australian population rate of 8.3%. We also confirmed that atypical antipsychotic agents known to have a metabolic effect including risperidone, clozapine and higher dose quetiapine were associated with higher rates of GDM in contrast with non-exposure to these agents and elevated above population GDM rates and olanzapine approached significance. This finding for olanzapine may reflect the dose range which was at the lower end for this medication. When we examined women with psychotic disorders, after controlling for maternal age and obesity, those on those specific antipsychotic agents continued to have an increased risk of GDM at four times those not on these agents. This suggests these four agents do potentially increase the risk for GDM above the risk from a psychotic disorder, age or BMI.

Park et al. drawing on Medicaid data in the USA also found a significant association between specific antipsychotics and GDM these included olanzapine and quetiapine [20]. Taken together this current study and Park et al. would suggest there is a likelihood that specific antipsychotic medications may increase the risk of Gestational Diabetes Mellitus and as such needs consideration in clinical care of women in pregnancy. However, what this current study also adds is the importance of also consideration of risk associated with mental health diagnosis and common co-morbidities including obesity.

Treating SMI in pregnancy is an important and challenging area for both obstetrics and psychiatry; these pregnancies carry elevated risk and ideally are managed through co-ordinated care supporting her pregnancy, physical and mental health[16, 25]. A common

dilemma in managing SMIs in pregnancy is which agent to use. While our study highlighted differences across the agents this information should be placed within the broader rubric for deciding on clinical care for women in pregnancy. Mental disorders, including SMI, continue to be the leading indirect cause of maternal mortality across several countries and when women are undertreated and unwell, the associated impairment of parenting may increase the risk of removal of a child from their care [26-28]. These serious adverse effects highlight the importance of careful individualised shared decisions by clinicians and women [29].

Limitations of this study include the lack of a standardised mental health diagnostic measure, past history of GDM, family history of either type 2 diabetes or GDM were not recorded and ethnicity was not recorded across the whole sample. There was no control group of untreated women without a mental disorder.

Understanding the association between GDM and SMI allows early identification through consideration of targeted earlier screening and closer surveillance of women with multiple risk factors for GDM. Earlier screening for this population could be considered in week 16-18 of pregnancy rather than waiting until week 28 for routine screening. Future research could examine both the ideal screening and management for this population and also further explore the different findings for women with psychotic and bipolar disorder. Identifying GDM earlier, developing strategies that are acceptable to this population for management of GDM, has the potential to benefit lifelong health and wellbeing. Pregnancy is an ideal opportunity for mental and physical health interventions with women having regular contact with health services. These findings highlight an important opportunity to improve health within maternity and mental health care.

References

1 Abouzeid M, Versace VL, Janus ED*, et al.* A population-based observational study of diabetes during pregnancy in Victoria, Australia, 1999–2008*.* *BMJ Open*. 2014; **4**.

2 Lavery JA, Friedman AM, Keyes KM, Wright JD, Ananth CV. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010*.* *BJOG*. 2017; **124**: 804-13.

3 Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes*.* *N Engl J Med*. 2005; **352**: 2477-86.

4 Bushe C, Holt R. Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia. *Br J Psychiatry*. 2004; **184**: s67-s71.

5 Ryan MC, Collins P, Thakore JH. Impaired fasting glucose tolerance in first-episode, drug-naive patients with schizophrenia. *Am J Psych*. 2003; **160**: 284-9.

6 Mcintyre RS, Konarski JZ, Misener VL, Kennedy SH. Bipolar disorder and diabetes mellitus: epidemiology, etiology, and treatment implications. *Ann Clin Psychiatry*. 2005; **17**: 83-93.

7 Garcia-Rizo C, Kirkpatrick B, Fernandez-Egea E, Oliveira C, Bernardo M. Abnormal glycemic homeostasis at the onset of serious mental illnesses: a common pathway. *Psychoneuroendocrinology*. 2016; **67**: 70-5.

8 Stubbs B, Vancampfort D, De Hert M, Mitchell A. The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. *Acta Psychiatr Scand*. 2015; **132**: 144-57.

9 Association AD. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes care*. 2004; **27**: 596-601.

10 Lambert TJ, Chapman LH. Diabetes, psychotic disorders and antipsychotic therapy: a consensus statement. *Medical Journal of Australia*. 2004; **181**: 544.

11 Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *The Lancet*. 2009; **373**: 1773-9.

12 Van Lieshout RJ, Voruganti LP. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. *J Psychiatry Neurosci*. 2008; **33**: 395.

13 Malcolm J. Through the looking glass: gestational diabetes as a predictor of maternal and offspring long-term health. *Diabetes/metabolism research and reviews*. 2012; **28**: 307-11.

14 Nguyen TN, Faulkner D, Frayne JS, *et al.* Obstetric and neonatal outcomes of pregnant women with severe mental illness at a specialist antenatal clinic. *Med J Aust*. 2013; **199**: 26-9.

15 Judd F, Komiti A, Sheehan P, Newman L, Castle D, Everall I. Adverse obstetric and neonatal outcomes in women with severe mental illness: To what extent can they be prevented? *Schizophr Res*. 2014; **157**: 305-9.

16 Nguyen TN, Faulkner D, Frayne JS, *et al.* Obstetric and neonatal outcomes of pregnant women with severe mental illness at a specialist antenatal clinic. *The Medical journal of Australia*. 2013; **199**: S26-9.

17 Vigod S, Kurdyak P, Dennis C, *et al.* Maternal and newborn outcomes among women with schizophrenia: a retrospective population-based cohort study. *BJOG*. 2014; **121**: 566-74.

18 Vigod SN, Gomes T, Wilton AS, Taylor VH, Ray JG. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. *BMJ*. 2015; **350**: h2298.

19 Boden R, Lundgren M, Brandt L, Reutfors J, Kieler H. Antipsychotics during pregnancy: relation to fetal and maternal metabolic effects. *Arch Gen Psychiatry*. 2012; **69**: 715-21.

20 Park Y, Hernandez-Diaz S, Bateman BT*, et al.* Continuation of Atypical Antipsychotic Medication During Early Pregnancy and the Risk of Gestational Diabetes. *American Journal of Psychiatry*. 2018; **175**: 564-74.

21 Women's Health Committee. Diagnosis of Gestational Diabetes Mellitus (GDM) and Diabetes Mellitus in Pregnancy. Melbourne, Victoria: The Royal Australian and New Zealand College of Obstetricians and Gynaecologists; 2017.

22 IBM Corp. IBM SPSS Statistics for Windows, 24 edn. Armonk, NY: IBM Cop.; 2016.

23 MedCalc Software. MedCalc for Windows, version 15.0. Ostend, Belgium: MedCalc Software.

24 Australian Institute of Health and Welfare. Australia's mothers and babies 2014—in brief. Perinatal statistics Canberra, ACT: AIHW; 2016.

25 Galbally M, Snellen M, Walker S, Permezel M. Management of antipsychotic and mood stabilizer medication in pregnancy: recommendations for antenatal care. *Aust N Z J Psychiatry*. 2010; **44**: 99-108.

26 Austin MP, Kildea S, Sullivan E. Maternal mortality and psychiatric morbidity in the perinatal period: challenges and opportunities for prevention in the Australian setting. *Med J Aust*. 2007; **186**: 364-7.

27 Oates M. Perinatal psychiatric disorders: a leading cause of maternal morbidity and mortality. *Br Med Bull*. 2003; **67**: 219-29.

28 Howard LM, Goss C, Leese M, Appleby L, Thornicroft G. The psychosocial outcome of pregnancy in women with psychotic disorders. *Schizophr Res*. 2004; **71**: 49-60.

29 Galbally M, Snellen M, Lewis A, Psychopharmacology and Pregnancy: Springer; 2014.

Table 1

Demographic Statistics by SMI Group (N = 539)

	Psychotic disorders (n = 153)		Bipolar Disorder (n = 217)		Non-Psychotic SMI (n = 160)		
	M	SD	M	SD	M	SD	p-value
Maternal Age	30.93_a	5.90	29.89_a	5.90	28.31_b	5.78	< .001
	n	%	n	%	n	%	
Overweight or Obese BMI (≥ 25)	111_a	78.2	139_b	65.6	102_b	65.0	.019
Smoking	74_a	54.4	76_b	41.3	58_b	40.6	.030
Alcohol Use	31_a	21.7	20_b	9.2	18_b	11.3	.003
Illicit Drug Use	43_a	29.1	$40_{a, b}$	18.5	23_b	14.5	.004

Note. Subscript letters denote cell statistics that differ significantly in pairwise comparisons between SMI groups. Non-Psychotic SMI comprises: major depression (n = 64), borderline personality disorder (n = 48), generalised anxiety disorder (n = 14), non-psychotic SMI NOS (n = 14), post-traumatic stress disorder (n = 5), substance-induced psychosis (n = 4), anorexia nervosa (n = 3), attention-deficit hyperactivity disorder (n = 2), panic disorder (n = 1), eating disorder NOS (n = 1), obsessive compulsive disorder (n = 1), and major depression with psychosis (n = 1).

Table 2

Sample Frequency Statistics for Antipsychotic, Mood Stabilizing and Antiepileptic Agents (N = 539)

	n	%
Atypical Antipsychotics		
Quetiapine	169	31.4
Olanzapine	88	16.3
Clozapine	16	3.0
Risperidone	22	4.1
Aripiprazole	26	4.8
Ziprasidone	3	0.6
Asenapine	2	0.4
Typical Antipsychotics		
Low Potency	4	0.7
High Potency	25	4.6
Mood Stabilizers		
Lithium	49	9.1
Sodium valproate	20	3.7
Carbamazepine	11	2.0
Lamotrigine	48	8.9
Gabapentin	3	0.6

Table 3

Median (Mdn) and Interquartile Range (IQR) for Agent Dose by GDM Group, and The Rates, Attributable Risk and Unadjusted Relative Risk Estimates with 95% Confidence Intervals of GDM For Women Exposed to Specific Psychotropic Agents Compared to a No Exposure Group.

		Dose (mg)[a]				
		No GDM	GDM		GDM	GDM Relative
		Mdn	Mdn	GDM Rate	Attributable	Risk
Agent	n	[IQR]	[IQR]	(%)	Risk (%)	[95% CI]
No Exposure[b]	181	-	-	8.8	-	-
Quetiapine	96	100	225	10.4	1.6	1.18
		[50 - 200]	[68 - 580]			[.56, 2.50]
Low-dose quetiapine	75	75	75	6.7	-2.1	.71
		[25 - 150]	[38 - 150]			[.27, 1.86]
High-dose quetiapine	21	425	525	23.8	15	2.69
		[300 - 600]	[300 - 775]			[1.10, 6.60]
Olanzapine	49	5	10	18.4	9.6	2.08
		[5 - 10]	[5 - 11]			[.98, 4.41]
Risperidone	14	2	2	28.6	19.8	3.23
		[1 - 4]	[.50 - 29]			[1.25, 8.37]
Clozapine	11	375	250	72.7	8.23	8.23
		[100 - 375]	[200 - 300]			[4.55, 14.86]
Aripiprazole	14	15	30[c]	7.1	-1.7	.81
		[5 - 20]				[.01, 5.66]

Lithium	17	900 [500 - 1000]	1350 [1350 - 1350]	11.8	3.0	1.33 [.33, 5.31]
Lamotrigine	19	200 [150 - 325]	250 [200 - 250]	10.5	1.7	1.19 [.30, 4.79]

[a]No significant difference for specific agent between GDM groups using Mann-Whitney U Test. [b]Comparison group for each Relative Risk estimate [c]Only one patient with GDM, no Mann-Whitney U Test conducted.

Table 4

Univariate Birth Outcome Descriptive Statistics (Main Effects and Interactions) by SMI and GDM for the Factorial Multivariate Analysis of Variance (n = 496)

	Psychotic Disorders (n = 141)		Bipolar Disorder (n = 201)		Non-Psychotic SMI (n = 154)		Main Effect $_{GDM}$	
	EMM	SE	EMM	SE	EMM	SE	EMM	SE
Gestation at Birth								
No GDM (n = 422)	38.50	0.22	38.33	0.17	38.50	0.20	38.44	0.11
GDM (n = 74)	38.20	0.41	36.87	0.46	37.46	0.54	37.51	0.27
Infant Birth Weight								
No GDM	3266.26	61.51	3263.56	48.63	3244.23	55.32	3258.15	31.99
GDM	3404.65	115.87	3021.32	129.02	3298.50	152.06	3241.49	76.88
Infant Birth Length								
No GDM	49.56	0.34	49.13	0.27	49.36	0.30	49.35	0.18
GDM	49.34	0.63	48.80	0.71	49.94	0.83	49.36	0.42
Infant Head Circumference								
No GDM	33.98	0.21	34.05	0.17	34.02	0.19	34.02	0.11
GDM	34.55	0.39	33.00	0.44	34.31	0.52	33.95	0.26
Main Effects $_{SMI}$								

Gestation at Birth	38.35	0.23	37.59	0.24	37.98	0.29
Infant Birth Weight	3340.38	64.63	3144.75	68.75	3271.36	80.90
Infant Birth Length	49.48	0.35	48.97	0.38	49.65	0.44
Infant Head Circumference	34.29	0.22	33.53	0.23	34.17	0.28

Note. SMI = serious mental illness, GDM = gestational diabetes mellitus, EMM = estimated marginal mean, SE = standard error. Cases with missing data were handled using case-wise deletion.