ORIGINAL ARTICLE

Antipsychotics During Pregnancy

Relation to Fetal and Maternal Metabolic Effects

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Context: Knowledge about the effects of exposure to the newer antipsychotics during pregnancy is limited.

Objective: To investigate the effects of maternal use of antipsychotics during pregnancy on gestational diabetes and fetal growth.

Design: Population-based cohort study comparing women exposed and not exposed to antipsychotics during pregnancy. Exposure was defined as prescriptions filled.

Setting: Swedish national health registers.

Participants: All women giving birth in Sweden from July 1, 2005, through December 31, 2009, grouped by filled prescriptions for (1) olanzapine and/or clozapine, the most obesogenic and diabetogenic antipsychotics (n=169), (2) other antipsychotics (n=338), or (3) no antipsychotics (n=357 696).

Main Outcome Measures: Odds ratios (ORs) with 95% CIs for gestational diabetes and being small for gestational age (SGA) and large for gestational age for birth weight, birth length, and head circumference.

Results: Exposure to other antipsychotics was associated with an increased risk of gestational diabetes (adjusted OR, 1.77 [95% CI, 1.04-3.03]). The risk increase with olanzapine and/or clozapine was of similar magnitude but not statistical significance (adjusted OR, 1.94 [95% CI, 0.97-3.91]). Infants exposed to either group of antipsychotics had increased risks of being SGA on birth weight, whereas only exposure to other antipsychotics yielded increased risks of being SGA for birth length and head circumference. None of the risks for SGA measurements remained significant after adjusting for maternal factors. There were no increased risks of being large for gestational age for birth weight or birth length after exposure to olanzapine and/or clozapine, but the risk increased for head circumference (OR, 3.02 [95% CI, 1.60-5.71]).

Conclusions: Women who used antipsychotics during pregnancy had increased risks of gestational diabetes. The increased risks of giving birth to an SGA infant seemed to be an effect of confounders, such as smoking. Except for macrocephaly, olanzapine and/or clozapine exposure was not associated with anabolic fetal growth.

Arch Gen Psychiatry. 2012;69(7):715-721

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SEVERE MENTAL ILLNESSES, SUCH as schizophrenia and bipolar disorder, are usually treated with continuous antipsychotic pharmacotherapy.[1,2] However, the evidence concerning use of antipsychotics during pregnancy is generally lacking or weak.[3] Guideline recommendations lend little support to the patients and their treating physicians in the difficult clinical risk-benefit analysis.[2,4] Observational studies in this field are limited in numbers and size. Associations between exposure to the older typical antipsychotics and preterm birth or low birth weight have been reported.[5-7] Several of the newer antipsychotics, such as olanzapine and clozapine, have been associated with substantial weight gain, hyperlipidemia, and increased insulin resistance.[8] Although the results from previous studies on the effects of exposure during pregnancy are ambiguous, with reports of growth restriction and escalation, concern remains that in particular olanzapine and clozapine may have anabolic fetal growth effects and increase the risk of gestational diabetes.[6,7,9-13]

The aim of the present study was to investigate the effects of maternal use of antipsychotics during pregnancy on gestational diabetes and fetal growth using data from national drug, patient, and birth registers. We hypothesized that pregnancy exposure to olanzapine and clozapine is associated with an increased risk of gestational diabetes and anabolic fetal growth, whereas other antipsychotics are associated with fetal growth restriction.

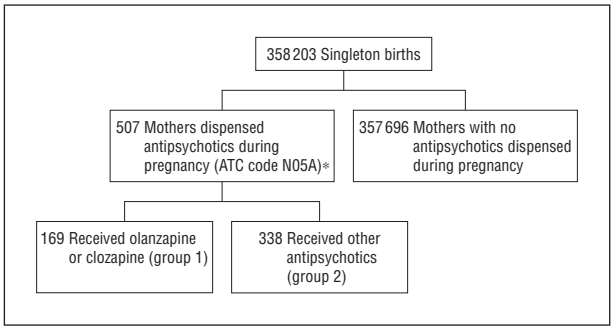

Figure. Flowchart of exposure groups. ATC indicates Anatomical Therapeutic Chemical. *Excludes lithium, prochlorperazine, levomepromazine, and melperone.

METHODS

Data for this cohort study were obtained from 3 Swedish national health registers (the Swedish Prescribed Drug Register, the Medical Birth Register, and the National Patient Register), all of which operate under the umbrella of the National Board of Health and Welfare. Data from the 2 former registers included the period from 2005 to 2009, whereas data from the latter included information from 1997 to 2009. The unique personal identification number assigned to each resident in Sweden enabled the linkage of information from these various sources.

The Swedish Prescribed Drug Register contains information on all prescriptions filled in Sweden, including the dispensed substances' Anatomical Therapeutic Chemical code and the amount, formulation, and dates the substance was prescribed and dispensed.[14] However, the register does not include drugs administered in hospitals. The Medical Birth Register contains data on almost all births in Sweden.[15] The information is obtained by midwives and attending physicians in connection with visits and hospitalizations from the antenatal visit through the neonatal period. The obtained data consists of maternal demographic variables, tobacco use, early pregnancy height and weight, and complications during pregnancy, delivery, and the neonatal period. Furthermore, offspring anthropometrics on birth weight, birth length, and head circumference are recorded in the register. Gestational age is primarily based on prenatal ultrasonographic estimation of the last menstrual period if present; otherwise, it is estimated on the recorded date of the first day of the last menstrual period. Ultrasonography for determination of gestational length has been offered to all pregnant women in Sweden since 1990 (95% of whom accept it).[16] The National Patient Register contains information on diagnoses from all specialized inpatient and outpatient care in Sweden (excluding primary care facilities). The diagnoses have been coded according to *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*), since 1997. All women (n = 358 203) with a singleton birth from July 1, 2005, through December 31, 2009, were identified in the Medical Birth Register.

MEASURES

Exposure was defined as filling a prescription for an antipsychotic (Anatomical Therapeutic Chemical code N05A) from last menstrual period to parturition. We excluded prochlorperazine, levomepromazine, and melperone prescriptions because these drugs are mainly used as antiemetics or anxiolytics with low and intermittently administrated doses. Lithium, which also belongs to the Anatomical Therapeutic Chemical category N05A, was excluded because of its different pharmacological action and placental passage compared with the other compounds in the N05A group and because it is mainly used to treat bipolar disorder. We divided the antipsychotics into 2 groups according to their obesogenic and diabetogenic potential[8]; highly anabolic drugs (group 1) included olanzapine and clozapine, and less anabolic drugs (group 2) included the remaining antipsychotics. Women using olanzapine or clozapine alone or together with any other antipsychotic during their pregnancy were included in group 1. A flowchart of the exposure groups is depicted in the **Figure**.

Gestational diabetes was defined as a recorded diagnosis with *ICD-10* code O24 during pregnancy in the Medical Birth Register. Preterm birth was defined as before 37 weeks of gestation. Being small for gestational age (SGA) or large for gestational age (LGA) on birth weight, birth length, and head circumference was defined as a measurement at the 2.3rd percentile or less and the 97.7th percentile or more, respectively, of the total population by infant sex.[17,18] As potential confounders, we included maternal country of origin, smoking, height, and cohabitation status at the first antenatal visit; maternal age when giving birth; and birth order of the infant. The study was approved by the regional ethical board at the Faculty of Medicine, Uppsala University (approval No. 2008/305).

STATISTICAL ANALYSIS

The 2 exposure groups (groups 1 and 2) were compared with the total population of unexposed pregnancies one-by-one in separate models. We analyzed the data in several steps. All outcomes were analyzed using univariate logistic regression models.

We also performed multivariate analyses adjusting for potential confounders. Because we regarded body mass index (BMI) as a potential effect mediator and confounder, we made additional analyses that included early pregnancy BMI in a second model for the analyses of gestational diabetes and preterm birth. For those infants SGA or LGA regarding the anthropometric measures, we adjusted for birth order and maternal age, country of origin, cohabitation, smoking, and height. We performed a sensitivity analysis to address the issue of potential misclassification of women with a severe mental illness treated as inpatients and administered antipsychotics at the hospital. After excluding patients with bipolar disorder who had filled a prescription for a mood stabilizer during pregnancy, we identified women not exposed to antipsychotics who were admitted to a psychiatric department for more than 28 days with a nonaffective psychosis (*ICD-10* codes F20-F29) or with bipolar disorder (*ICD-10* codes F30-F31). We calculated the number of potentially misclassified women who developed gestational diabetes and potentially misclassified infants born SGA or LGA. In a second sensitivity analysis we included risperidone and quetiapine fumarate in the highly anabolic drug group (group 1). Furthermore, in a post hoc investigation, we sought to determine whether the infants exposed to olanzapine and/or clozapine who had a large head circumference also had a hydrocephalus diagnosis recorded. To adjust for the effect of more than 1 child of the same mother, estimates in all logistic regression models were calculated using the generalized estimating equation method and determined with the use of commercially available statistical software (GENMOD procedure in SAS software, version 9.2; SAS Institute, Inc). Relative risks are presented as odds ratios (ORs) with 95% CIs.

RESULTS

DESCRIPTIVE DATA

Two (0.4%) children of the 507 mothers using antipsychotics were stillborn and 1 (0.2%) died during the neonatal period 4 weeks post partum. The corresponding figures for those in the total population not receiving

Table 1. Maternal Sociodemographic and Clinical Characteristics

Characteristic	Drug Group, No. (%) of Births		
	Group 1: Olanzapine and/or Clozapine (n = 169)	Group 2: Other Antipsychotic (n = 338)	No Antipsychotic (n = 357 696)
Mother born in Sweden	103 (60.9)	226 (66.9)	279 837 (78.2)
Maternal age at parturition, y			
<25	27 (16.0)	57 (16.9)	52 132 (14.6)
25-34	85 (50.3)	185 (54.7)	227 937 (63.7)
≥35	57 (33.7)	96 (28.4)	77 627 (21.7)
Birth order			
1	73 (43.2)	150 (44.4)	161 354 (45.1)
2 or 3	67 (39.6)	147 (43.5)	176 348 (49.3)
≥4	29 (17.2)	41 (12.1)	19 994 (5.6)
Maternal cohabitation[a]			
With father of child	122 (72.2)	259 (76.6)	320 429 (89.6)
Single	17 (10.1)	37 (10.9)	5902 (1.7)
Other forms of cohabitation	22 (13.0)	28 (8.3)	13 690 (3.8)
Maternal smoking in early pregnancy[a]	38 (22.5)	107 (31.7)	24 007 (6.7)
Maternal early pregnancy BMI[b]			
<18.5	5 (3.0)	7 (2.1)	7850 (2.2)
18.5-24.9	67 (39.6)	137 (40.5)	199 247 (55.7)
25.0-29.9	59 (34.9)	85 (25.1)	80 248 (22.4)
≥30.0	24 (14.2)	79 (23.4)	38 333 (10.7)
Clinical psychiatric history (*ICD-10* code)			
Previous psychiatric hospitalization	135 (79.9)	226 (66.9)	9881 (2.8)
Any psychiatric diagnosis (F10-F99)[c]	158 (93.5)	300 (88.8)	30 966 (8.7)
Schizophrenia (F20, F25)	42 (24.9)	64 (18.9)	117 (0.03)
Other nonaffective psychosis (F21-F29, excluding F25)	34 (20.1)	55 (16.3)	459 (0.1)
Bipolar disorder (F30-F31)	20 (11.8)	37 (10.9)	749 (0.2)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); *ICD-10*, *International Statistical Classification of Diseases, 10th Revision*.
[a] Data were missing for 4.9%.
[b] Data were missing for 9.0%. $P = .03$ with χ^2 test.
[c] Indicates inpatient or outpatient diagnoses since 1997.

antipsychotics (n=357 696) were 1289 stillbirths (0.4%) and 630 neonatal deaths (0.2%). Maternal sociodemographic and clinical characteristics are summarized in **Table 1**. Compared with the total population, women who used antipsychotics during pregnancy were generally older, smoked more often, had a higher BMI, and were more likely to be born outside Sweden. Furthermore, they had given birth to more children and were more often not living with the father of the child. Most of the women in the antipsychotic use groups had a recorded psychiatric diagnosis before or during pregnancy and about half had a psychotic disorder. Compared with women using other antipsychotics, women in group 1 were less often smokers, had a lower BMI, and had more previous psychiatric hospitalizations.

The filled prescriptions of antipsychotics are listed in **Table 2**. Of all women who used antipsychotics, 87.9% used only 1 antipsychotic drug throughout the whole pregnancy. The corresponding proportion among women in group 1 was 80.5%. Distributions of birth weight, birth length, head circumference, gestational age, and maternal BMI by exposure are summarized in **Table 3**.

Table 2. Maternal Prescriptions for Antipsychotics Filled During Pregnancy

Antipsychotic	No. (%) of Subjects[a]
Olanzapine	159 (31.4)
Clozapine	11 (2.2)
Other antipsychotics	338 (66.7)
Quetiapine fumarate	90 (17.8)
Risperidone	72 (14.2)
Flupentixol	58 (11.4)
Haloperidol	52 (10.3)
Aripiprazole	38 (7.5)
Perphenazine	35 (6.9)
Zuclopenthixol	30 (5.9)
Ziprasidone hydrochloride	18 (3.6)
Chlorprothixene	9 (1.8)
Fluphenazine	2 (0.4)
Pimozide	1 (0.2)

[a] Percentages sum to more than 100% because some of the antipsychotics are used concomitantly.

MAIN RESULTS

Gestational diabetes was more than twice as common in mothers who used antipsychotics (7 mothers [4.1%] for group 1 and 15 [4.4%] for group 2) than in the total population of pregnant women (5970 [1.7%]). The unadjusted ORs were of similar magnitude in antipsychotic user groups 1 and 2 (2.44 [95% CI, 1.14-4.24] and 2.53 [1.48-4.34], respectively). The ORs remained similar af-

Table 3. Birth Characteristics and Maternal BMI by Maternal Use of Antipsychotics During Pregnancy[a]

	Drug Group		
	No Antipsychotic	Group 1: Olanzapine or Clozapine	Group 2: Other Antipsychotic
Anthropometrics			
Weight, g	3528 (567)	3427 (591)	3475 (587)
Length, cm	50.4 (2.6)	50.1 (2.7)	49.9 (2.6)
Head circumference, cm	34.9 (1.7)	34.7 (1.9)	34.8 (1.7)
Gestational age, d	278 (13)	276 (14)	276 (13)
Maternal BMI	24.6 (4.6)	25.8 (4.1)	27.1 (5.8)
Median (IQR)	23.6 (5.2)	25.3 (5.2)	25.8 (7.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.
[a]Unless otherwise indicated, data are expressed as mean (SD).

ter adjusting for potential confounders of birth order and maternal age, country of birth, cohabitation, smoking, and height (1.94 [95% CI, 0.97-3.91] and 1.77 [1.04-3.03], respectively). After including early pregnancy BMI in the model, the ORs were slightly attenuated and no longer statistically significant (1.71 [95% CI, 0.82-3.56] and 1.46 [0.84-2.53], respectively). Subjects with missing data in the adjusted models were excluded from the unadjusted model.

Of all unexposed infants, 5.1% were born preterm. The corresponding figure for infants exposed to olanzapine and/or clozapine was 8.0%, whereas it was 9.5% for other antipsychotics. In comparison with unexposed births, the ORs for being born preterm were 1.58 (95% CI, 0.91-2.73) for group 1 infants and 1.94 (95% CI, 1.37-2.77) for group 2 infants.

Birth anthropometric outcomes are summarized in **Table 4**. Infants exposed to antipsychotics had a more-than-doubled risk of being SGA regardless of group. For group 2 infants, similar risk increases were found for being SGA for head circumference and birth length. Group 1 infants had a more-than-doubled risk of being LGA with respect to head circumference. After adjusting for maternal factors, the risk estimates on SGA were attenuated and were no longer statistically significant. For group 1 infants, the risk of being LGA for head circumference increased after the adjustments (OR, 3.02 [95% CI, 1.60-5.71]).

OTHER ANALYSES

In a post hoc investigation we assessed whether the increased risks of being LGA for head circumference among group 1 infants could be explained by hydrocephalus being more frequent among infants exposed to the drugs. However, none of the neonates had a hydrocephalus diagnosis.

In the sensitivity analysis concerning potential misclassification of exposure, we identified 56 women who had been treated as inpatients for more than 28 days with a nonaffective psychosis or with bipolar disorder. Among these women, 5 gave birth to infants who were SGA for birth weight; 4, for birth length; and 3, for head circumference. None of the infants was born LGA and none of the women developed gestational diabetes.

By including risperidone and quetiapine in group 1 with olanzapine and clozapine, the risk of macrocephaly was no longer significant (unadjusted OR, 1.53 [95% CI, 0.84-2.77]; adjusted OR, 1.77 [95% CI, 0.98-3.22]). Risks of gestational diabetes and deviant fetal growth (other than macrocephaly) were essentially unchanged (data not shown).

COMMENT

To our knowledge, no other population-based study has investigated maternal and fetal metabolic effects for different antipsychotics during pregnancy. We have 2 major findings. First, we observed an increased risk of gestational diabetes for women filling prescriptions for antipsychotics during pregnancy, even after adjusting for maternal factors. However, similar risk increases occurred for the more obesogenic and diabetogenic antipsychotics clozapine and olanzapine as for other antipsychotics, which suggest similar effects. Second, women using antipsychotics had an increased risk of giving birth to an SGA infant but, after adjusting for maternal factors, the risk was no longer statistically significant. Contrary to our hypothesis, no increased risk of being born LGA was associated with antipsychotic use except for macrocephaly.

The major strengths of our study include the large sample size and the population-based design. The study design, in combination with minimal loss to follow-up, should make the results highly generalizable. Moreover, because drug exposure was based on prescription fills, recall bias could be precluded. In contrast to a previous study,[19] which used information on drug use recorded in the Swedish Medical Birth Register, we obtained this information from the Prescribed Drug Register. The coverage of drug use is poor for late pregnancy in the Medical Birth Register and is based on self-report, which may result in several types of bias and underreporting.[20] In contrast, obtaining information on drug use from the Prescribed Drug Register ensures coverage throughout the pregnancy except in cases of hospitalization, during which a drug might be administered without an individual prescription. However, we consider the issue of not covering antipsychotics administered at hospitals a minor problem because only 56 women not recorded as having filled a prescription with an antipsychotic were admitted to the hospital for more than 28 days during pregnancy because of a nonaffective psychosis or bipolar disorder.

The most obvious source of potential confounding is the indication for which the drug is used; that is, a severe mental illness may in itself be associated with adverse pregnancy and neonatal outcomes,[6] as are associated lifestyle and comorbidity factors.[21] For example, clozapine is generally used for treatment-resistant schizophrenia. Patients with this type of schizophrenia differ from other schizophrenic patients considered for antipsychotic treatment. However, the clozapine-treated

Table 4. Odds of Being SGA or LGA Associated With Maternal Use of Antipsychotics During Pregnancy Compared With the Total Population of Births

Measurement by Antipsychotic (No. of Births)	SGA[a]			LGA[b]		
	% of Births	OR (95% CI)		% of Births	OR (95% CI)	
		Unadjusted[c]	Adjusted[d]		Unadjusted[c]	Adjusted[d]
Birth weight[e]						
Group 1: olanzapine and/or clozapine (187)	5.4	2.63 (1.35-5.14)	1.82 (0.91-3.61)	1.2	0.46 (0.12-1.74)	0.55 (0.14-2.11)
Group 2: other antipsychotic (354)	4.8	2.02 (1.19-3.43)	1.24 (0.72-2.15)	3.0	1.13 (0.57-2.25)	1.37 (0.69-2.75)
Birth length[f]						
Group 1: olanzapine and/or clozapine (186)	3.6	1.70 (0.75-3.84)	1.17 (0.54-2.55)	3.6	1.71 (0.76-3.81)	1.94 (0.87-4.34)
Group 2: other antipsychotic (350)	5.2	2.17 (1.29-3.64)	1.35 (0.79-2.28)	1.8	0.72 (0.3-1.72)	0.96 (0.40-2.29)
Head circumference[f]						
Group 1: olanzapine and/or clozapine (186)	2.4	0.76 (0.24-2.44)	0.62 (0.19-2.01)	6.0	2.79 (1.48-5.25)	3.02 (1.60-5.71)
Group 2: other antipsychotic (340)	5.0	2.07 (1.21-3.54)	1.64 (0.97-2.77)	1.6	0.57 (0.22-1.49)	0.67 (0.25-1.76)

Abbreviations: LGA, large for gestational age; OR, odds ratio; SGA, small for gestational age.
[a] Defined as being in the 2.3rd percentile or less of the total population in our cohort.
[b] Defined as being in the 97.7th percentile or more of the total population in our cohort.
[c] Subjects with missing data in the adjusted models have been excluded from the unadjusted models.
[d] Adjusted for birth order and maternal age, country of origin, cohabitation, smoking, and height.
[e] Growth references are from Marsál et al.[17]
[f] Growth references are from Niklasson et al.[18]

mothers constituted only a small fraction of the combined group of mothers using olanzapine or clozapine. Also, clinicians might be less likely to prescribe olanzapine and clozapine to overweight women, which could be an explanation for the observed lower BMI in group 1 during early pregnancy. A selection process such as this could have concealed a pharmacological effect that increased the risk of gestational diabetes. Our findings of an attenuation of the association between exposure to antipsychotics and being born SGA when adjusting for maternal factors suggest a combined effect of sociodemographic factors, disorder, and medication rather than a direct pharmacological effect. The infants of the potentially misclassified women hospitalized for more than 28 days during pregnancy because of a diagnosis of nonaffective psychosis or bipolar disorder were to a higher degree born SGA on weight (5 of 56 with uncertain exposure status compared with approximately 5% for the exposed infants). Thus, the findings of increased SGA risk might be slightly underestimated, whereas our findings concerning LGA would be sustained because none of the infants with uncertain exposure were born LGA. Nevertheless, filling a prescription is not equal to taking the medication. If the patients do not take the medication, an underestimation of a potential pharmacological effect might result. Our hypothesis of a pharmacological effect, however, was supported by the increased risk of gestational diabetes being almost unaffected after adjusting for maternal factors. The difficulties in measuring a newborn infant's length with precision and the small biological variation in head circumference measurements make us confident in the other results for birth weight and gestational diabetes.

The classification of antipsychotics into first and second generation or typical and atypical, which has been used in several studies, is probably less useful when assessing metabolic outcomes.[6,7,10,11] Accordingly, and based on the lack of homogeneity within the classes, it has been proposed to divide antipsychotics according to their adverse effects, such as the propensity to cause weight gain and metabolic syndrome.[22] Olanzapine and clozapine are the 2 most notorious agents associated with substantial weight gain and increased insulin resistance.[8] Thus, in contrast to previous studies, the groups in our study are formed on a potentially more rational ground given the actual research question on anabolic growth effects.[6,7,10] We did not include quetiapine in our group of highly anabolic drugs, which consisted of olanzapine and clozapine. This decision was based on the equivocal evidence concerning quetiapine's metabolic profile[8] and the reported low placental passage ratio of 23% compared with 72% for olanzapine.[11] Knowledge concerning placental passage of clozapine is limited, with only 1 case report documenting fetal accumulation.[23] Because quetiapine and risperidone might be considered to have high liability to induce glucose-related adverse events,[24] we made additional analyses including those 2 antipsychotics in the high anabolic risk group. Except for attenuating the risk of macrocephaly, the main results were not substantially different using this alternative grouping.

When we compared all pregnancies, we found higher risks of gestational diabetes in association with the use of olanzapine and/or clozapine and with the use of other antipsychotics. The risks were only partly attenuated after adjustment for the potentially confounding effects of maternal factors. When we adjusted for early pregnancy BMI, the risk estimates were further attenuated and no longer significant. Previous research has shown that gestational diabetes leads to a higher risk of the offspring being LGA for birth weight alone and on both birth weight and length.[25] The increased risk of being born LGA associated with gestational diabetes has been explained by the lack of insulin resistance in the fetus (in contrast to the mother). As a result, the fetus grows in a hyperinsulinemic and hyper-

glycemic environment that leads to macrosomia and thus a higher risk of being born LGA.[26] However, in our study, antipsychotic use was associated with higher risks of gestational diabetes and of being SGA for birth weight instead. This counterintuitive observation may be the result of a more direct pharmacological insulin resistance–promoting effect by the antipsychotics. Such direct effects have been observed in animal models and clinical studies and could cause the fetus to become insulin resistant and unable to cope with the hyperinsulinemic and hyperglycemic environment.[27-29] Although studies investigating the effects of olanzapine or clozapine specifically on insulin resistance and fetal growth are lacking, there are reports on chlorpromazine hydrochloride and intrauterine growth restriction in rats.[12] Chlorpromazine was the first available low-potency antipsychotic and has also been associated with substantial weight gain and diabetogenic potential, effects similar to those reported for olanzapine and clozapine.[8,30] These similarities lend support to a growth-restrictive effect that is due to induced insulin resistance in the fetus. However, a direct pharmacological effect may also be caused by other nonmetabolic factors (eg, vascular toxic effects), leading to poor placental function.

In our study, the increased risks of being born SGA were no longer significant after adjusting for potential confounders. The findings reported in previous studies are ambiguous, with reports on growth restriction and escalation.[6,7,9-11,19] The discrepancy in findings across studies are likely due to different patient-selection criteria, limited numbers of exposed infants, and different drug selection and grouping, things that further underline the problems related to grouping of antipsychotics. Another important difference between our study and previous studies is that we had access to information on important confounding factors, such as smoking. The increased risk of giving birth to a macrocephalic infant among women exposed to olanzapine and/or clozapine was surprising, and we do not know the potential mechanism underlying this observation.

In conclusion, maternal use of antipsychotics during pregnancy, regardless of the drug group, is associated with an increased risk of gestational diabetes. The increased risk of giving birth to an SGA infant observed among women treated with antipsychotics during pregnancy is probably an effect of confounding factors, such as smoking. Olanzapine and/or clozapine exposure during pregnancy is not associated with infants being born LGA, except regarding head circumference. This observation deserves to be investigated in future research. Pregnant women treated with antipsychotics should be closely monitored for gestational diabetes and deviating fetal growth.

Submitted for Publication: October 12, 2011; accepted November 13, 2011.
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Author Contributions: Dr Bodén had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Financial Disclosure: None reported.
Funding/Support: This study was supported by unrestricted grants from the Lennander's Foundation and Gillbergska Foundation.
Role of the Sponsor: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Additional Contributions: Morten Andersen, MD, PhD, Karolinska Institutet, provided intellectual input during the project.

REFERENCES

1. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, Himelhoch S, Fang B, Peterson E, Aquino PR, Keller W; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 Schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):71-93.
2. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, MacQueen G, McIntyre RS, Sharma V, Ravindran A, Young LT, Young AH, Alda M, Milev R, Vieta E, Calabrese JR, Berk M, Ha K, Kapczinski F. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord*. 2009;11(3):225-255.
3. Webb RT, Howard LM, Abel KM. Antipsychotic drugs for non-affective psychosis during pregnancy and postpartum. *Cochrane Database Syst Rev*. 2004;(2):CD004411.
4. ACOG Committee on Practice Bulletins–Obstetrics. ACOG Practice Bulletin: clinical management guidelines for obstetrician-gynecologists number 92, April 2008 (replaces practice bulletin number 87, November 2007): use of psychiatric medications during pregnancy and lactation. *Obstet Gynecol*. 2008;111(4):1001-1020.
5. Diav-Citrin O, Shechtman S, Ornoy S, Arnon J, Schaefer C, Garbis H, Clementi M, Ornoy A. Safety of haloperidol and penfluridol in pregnancy: a multicenter, prospective, controlled study. *J Clin Psychiatry*. 2005;66(3):317-322.
6. Lin HC, Chen IJ, Chen YH, Lee HC, Wu FJ. Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference? *Schizophr Res*. 2010;116(1):55-60.
7. Newham JJ, Thomas SH, MacRitchie K, McElhatton PR, McAllister-Williams RH. Birth weight of infants after maternal exposure to typical and atypical antipsychotics: prospective comparison study. *Br J Psychiatry*. 2008;192(5):333-337.
8. Newcomer JW. Antipsychotic medications: metabolic and cardiovascular risk. *J Clin Psychiatry*. 2007;68(suppl 4):8-13.
9. Babu GN, Desai G, Tippeswamy H, Chandra PS. Birth weight and use of olanzapine in pregnancy: a prospective comparative study. *J Clin Psychopharmacol*. 2010;30(3):331-332.
10. McKenna K, Koren G, Tetelbaum M, Wilton L, Shakir S, Diav-Citrin O, Levinson A, Zipursky RB, Einarson A. Pregnancy outcome of women using atypical antipsychotic drugs: a prospective comparative study. *J Clin Psychiatry*. 2005;66(4):444-449, 546.
11. Newport DJ, Calamaras MR, DeVane CL, Donovan J, Beach AJ, Winn S, Knight BT, Gibson BB, Viguera AC, Owens MJ, Nemeroff CB, Stowe ZN. Atypical antipsychotic administration during late pregnancy: placental passage and obstetrical outcomes. *Am J Psychiatry*. 2007;164(8):1214-1220.
12. Singh S, Padmanabhan R. Growth retardation in rat fetuses induced by chlorpromazine hydrochloride (CPZ). *Anat Anz*. 1979;145(4):327-337.
13. Gentile S. Clinical utilization of atypical antipsychotics in pregnancy and lactation. *Ann Pharmacother*. 2004;38(7-8):1265-1271.
14. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, Persson I, Sundström A, Westerholm B, Rosén M. The new Swedish Prescribed Drug Register: opportunities for pharmacoepidemiological research and experience from the first six months [published correction appears in *Pharmacoepidemiol Drug Saf*. 2008;17(5):533]. *Pharmacoepidemiol Drug Saf*. 2007;16(7):726-735.
15. Cnattingius S, Ericson A, Gunnarskog J, Källén B. A quality study of a medical birth registry. *Scand J Soc Med*. 1990;18(2):143-148.

16. Høgberg U, Larsson N. Early dating by ultrasound and perinatal outcome: a cohort study. *Acta Obstet Gynecol Scand*. 1997;76(10):907-912.
17. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996; 85(7):843-848.
18. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). *Acta Paediatr Scand*. 1991;80 (8-9):756-762.
19. Reis M, Källén B. Maternal use of antipsychotics in early pregnancy and delivery outcome. *J Clin Psychopharmacol*. 2008;28(3):279-288.
20. Stephansson O, Granath F, Svensson T, Haglund B, Ekbom A, Kieler H. Drug use during pregnancy in Sweden: assessed by the Prescribed Drug Register and the Medical Birth Register. *Clin Epidemiol*. February 2011;3:43-50.
21. Bennedsen BE. Adverse pregnancy outcome in schizophrenic women: occurrence and risk factors. *Schizophr Res*. 1998;33(1-2):1-26.
22. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373(9657):31-41.
23. Barnas C, Bergant A, Hummer M, Saria A, Fleischhacker WW. Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk [comment]. *Am J Psychiatry*. 1994;151(6):945.
24. Guo Z, L'italien GJ, Jing Y, Baker RA, Forbes RA, Hebden T, Kim E. A real-world data analysis of dose effect of second-generation antipsychotic therapy on hemoglobin A1C level. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35 (5):1326-1332.
25. Ahlsson F, Lundgren M, Tuvemo T, Gustafsson J, Haglund B. Gestational diabetes and offspring body disproportion. *Acta Paediatr*. 2010;99(1):89-93.
26. Baird JD. Some aspects of carbohydrate metabolism in pregnancy with special reference to the energy metabolism and hormonal status of the infant of the diabetic woman and the diabetogenic effect of pregnancy. *J Endocrinol*. 1969; 44(1):139-172.
27. Boyda HN, Tse L, Procyshyn RM, Wong D, Wu TK, Pang CC, Barr AM. A parametric study of the acute effects of antipsychotic drugs on glucose sensitivity in an animal model. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(6): 945-954.
28. Henderson DC, Cagliero E, Copeland PM, Borba CP, Evins E, Hayden D, Weber MT, Anderson EJ, Allison DB, Daley TB, Schoenfeld D, Goff DC. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *Arch Gen Psychiatry*. 2005;62(1):19-28.
29. Henderson DC, Copeland PM, Borba CP, Daley TB, Nguyen DD, Cagliero E, Evins AE, Zhang H, Hayden DL, Freudenreich O, Cather C, Schoenfeld DA, Goff DC. Glucose metabolism in patients with schizophrenia treated with olanzapine or quetiapine: a frequently sampled intravenous glucose tolerance test and minimal model analysis. *J Clin Psychiatry*. 2006;67(5):789-797.
30. Thonnard-Neumann E. Phenothiazines and diabetes in hospitalized women. *Am J Psychiatry*. 1968;124(7):978-982.