OBSTETRICS

Perinatal outcomes among women with bipolar disorder: a population-based cohort study

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OBJECTIVE: To evaluate the risk of adverse perinatal outcomes among pregnant women previously hospitalized for bipolar disorder.

STUDY DESIGN: We completed a population-based cohort study of women with a singleton delivery in Ontario, Canada (2003 to 2011). Women previously hospitalized for bipolar disorder (n = 1859) or major depressive disorder (n = 3724) were each compared to women without a documented mental illness (n = 432,358). Main study outcomes were preterm birth, severe small for gestational age <3rd percentile birthweight, and severe large for gestational age >97th percentile birthweight. Secondary outcomes included stillbirth, congenital malformations, neonatal morbidity and readmission to hospital <28 days. Odds ratios (ORs) were adjusted for maternal age, parity, prepregnancy obesity, substance use, and diabetes mellitus or hypertension before or during pregnancy.

RESULTS: Bipolar disorder (adjusted OR [AOR], 1.95; 95% confidence interval [CI], 1.68—2.26) and major depressive disorder (AOR, 1.91; 95% CI, 1.72—2.13) were each associated with preterm birth. Bipolar

disorder was associated with severe large for gestational age (AOR, 1.31; 95% CI, 1.03—1.67). Major depressive disorder was associated with severe small for gestational age (AOR, 1.22; 95% CI, 1.05—1.42). Both mood disorder groups had significantly higher risk of congenital malformations, neonatal morbidity, and neonatal hospital readmission. Although study covariates explained some of the increased risk, we could not address all potential explanatory factors.

CONCLUSION: Women previously hospitalized for bipolar disorder are at increased risk of adverse perinatal outcomes compared with the general population. Their level of risk is comparable to women previously hospitalized for major depressive disorder. These risks must be considered in the management of pregnant women with a history of major mood disorders. Attention to potentially modifiable risk factors such as obesity, diabetes, and hypertension before and during pregnancy could reduce the risk for adverse perinatal outcomes.

Key words: bipolar disorder, gestational age birthweight, major depressive disorder, pregnancy, preterm birth

Bipolar disorder, with a lifetime prevalence of 1-2%, is considered the sixth leading cause of disability among women of reproductive age.[1] Many women with bipolar disorder become mothers but little is known about pregnancy outcomes in this group.[2] Some studies suggest that

affected women are at higher risk of adverse neonatal outcomes, including preterm birth (PTB) and low birthweight, which may be independent of psychotropic medication use in pregnancy.[3-5] However, minimal epidemiological research has been conducted in this area. Limitations to existing

population-based studies include small sample sizes that lack power to detect disparities in relatively rare outcomes, and inability to account for key prognostic factors that could confound analyses such as maternal medical morbidity. Also, bipolar disorder falls into the diagnostic category of a mood

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disorder. Several biologic and psycho-social risk factors for adverse perinatal outcomes such as underlying genetic susceptibility, increased maternal body weight, rates of comorbid substance use, and/or psychotropic medication may be shared among women with mood disorders in general.[6,7] Major depression during pregnancy has been repeatedly associated with increased risk for adverse perinatal outcomes, including miscarriage, low birthweight, and PTB.[8] As such, it remains unclear whether risk for adverse pregnancy outcomes among women with bipolar disorder is specific to that illness, or characteristic of severe mood disorders in general. Additional information on pregnancy outcomes among women with bipolar disorder will guide reproductive decision-making as well as maternal and child health management for this population.

We conducted a large, population-based cohort study of the risk of adverse perinatal outcomes among women previously hospitalized for bipolar disorder. We compared women with bipolar disorder and women previously hospitalized for major depressive disorder (as an active comparison group) with general population controls.

MATERIALS AND METHODS
Data sources
We used population-level health administrative data housed at the Institute for Clinical and Evaluative Sciences (ICES) in the Province of Ontario, Canada. ICES is an independent non-profit research organization that has the capacity to link multiple provincial administrative health databases using unique identifiers for every Ontario resident with a provincial health card number. At ICES, patient-level records are linked anonymously via the Registered Persons Database (RPDB) that contains the sex, age, postal code, and date of birth and death for all Ontario residents. Obstetric deliveries were identified using the MOMBABY dataset, which is derived from the Canadian Institute of Health Information Discharge Abstract Database (CIHI-DAD). MOMBABY captures deliveries and provides linked maternal and

newborn health records for all births occurring in an Ontario hospital (>99% of deliveries). It also provides information on gestational age at birth, allowing for accurate estimation of conception date. Psychiatric admissions were captured either in the CIHI-DAD or through Ontario Mental Health Reporting System Database where admissions to designated psychiatric beds have been recorded since 2005. Diagnoses of bipolar disorder and major depressive disorder were captured within 5 years preceding the index pregnancy using the *International Classification of Diseases, Ninth Revision* (ICD-9) and ICD-10CA diagnoses (CIHI-DAD) and the text revision of *the Diagnostic and Statistical Manual of Mental Disorders-IV* diagnostic system (Ontario Mental Health Reporting System Database). Perinatal outcomes were captured during the index delivery hospitalization or on subsequent hospitalizations within 42 days after delivery, based on ICD-10CA diagnoses or Canadian Classification of Health Interventions procedure codes recorded in the CIHI-DAD.[9,10] Mortality outcomes were identified through the RPDB, which identifies death arising in or outside of a hospital setting. Additional datasets used to measure study covariates included the National Ambulatory Care Reporting System Database for emergency department data, and the Ontario Health Insurance Plan Database for outpatient physician service use data. The databases used in this study have been found to be complete, reliable and accurate with respect to demographic information and primary diagnoses for inpatient services.[11]

Participants
We identified 1,032,831 obstetric deliveries among Ontario women ages 15 to 50 years whose estimated date of conception was between April 1, 2002, and March 31, 2010. Deliveries to non-Ontario residents, those with an invalid health card number and those where mother-infant matching was unsuccessful were excluded (n = 2216), as were those with a diagnosis of schizophrenia, schizoaffective disorder, or another psychotic disorder in the 5 years preceding

conception (n = 1628), the focus of a previous study.[12] We identified the 3 groups within the remaining cohort of 1,028,987 deliveries. The bipolar disorder group comprised 1859 unique women with 2124 deliveries, and who had been hospitalized for bipolar disorder within 5 years before conception in the index pregnancy (kappa = .93; 95% confidence interval [CI], 0.88−0.97).[13] From the remaining women, we identified the major depressive disorder group which comprised 3724 unique women with 4487 deliveries, who had been hospitalized for major depressive disorder within 5 years before conception (kappa = .80; 95% CI, 0.74−0.87).[13] Hospital-based diagnoses were required for this classification because the ability to discriminate between these 2 disorders using only outpatient service claims is likely to be poor.[14] The reference group comprised 432,358 unique women with 553,840 deliveries, and who had no documented mental illness, that is, the absence of a hospitalization or physician service claim from a psychiatrist or family physician associated with any mental health or addictions diagnosis within the 5-year period before the index pregnancy.[15]

Within each of the 3 exposure groups, we randomly selected 1 delivery per woman using a computer-generated randomization list.

Outcomes
The main study outcomes were: (1) PTB <37 weeks' gestation; (2) severe small for gestational age (SGA), defined as a same-sex, same-gestational age birthweight <3rd percentile; and (3) severe large for gestational age (LGA), defined as a same-sex, same-gestational age birthweight >97th percentile.[16] These outcomes were chosen because they are prevalent, reliably measured, and are major determinants of perinatal morbidity and mortality.[17-19] As secondary outcomes, we evaluated other key perinatal health indicators: PTB <32 weeks and PTB <28 weeks' gestation; SGA <10th percentile; LGA >90th percentile; congenital malformations; serious neonatal morbidity, comprising respiratory distress syndrome (RDS),