OBSTETRICS

Sertraline use during pregnancy and the risk of major malformations

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OBJECTIVE: Given the current debate and growing public concerns on selective serotonin reuptake inhibitors (SSRIs) and birth defects generated by Food and Drug Administration warnings, we aim to quantify the association between first-trimester exposure to sertraline, a first-line treatment, and the risk of congenital malformations in a cohort of depressed women.

STUDY DESIGN: This was a population-based cohort study in Quebec, Canada, 1998 through 2010. From a cohort of 18,493 depressed/anxious pregnancies, sertraline-exposed, nonsertraline SSRI-exposed, non-SSRI exposed, and unexposed (reference category) women were studied. Major malformations overall and organ-specific malformations in the first year of life were identified. Generalized estimating equation models were used to obtain risk estimates and 95% confidence intervals (CIs). Analyses were adjusted for potential confounders.

RESULTS: Among the 18,493 eligible pregnancies, 366 were exposed to sertraline, 1963 to other SSRIs, and 1296 to non-SSRI antidepressants during the first trimester of pregnancy. Sertraline use was not statistically significantly associated with the risk of overall major malformations when compared to nonuse of antidepressants. However, sertraline exposure was associated with an increased risk of atrial/ventricular defects specifically (risk ratio [RR], 1.34; 95% CI, 1.02—1.76; 9 exposed cases), and craniosynostosis (RR, 2.03; 95% CI, 1.09—3.75; 3 exposed cases). Exposure to SSRIs other than sertraline during the first trimester of pregnancy was associated with craniosynostosis (RR, 2.43; 95% CI, 1.44—4.11; 19 exposed cases), and musculoskeletal defects (RR, 1.28; 95% CI, 1.03—1.58; 104 exposed cases).

CONCLUSION: Sertraline use during the first trimester of pregnancy was associated with an increased risk of atrial/ventricular defects and craniosynostosis above and beyond the effect of maternal depression. Nonsertraline SSRIs were associated with an increased risk of craniosynostosis and musculoskeletal defects.

Key words: cardiac defect, craniosynostosis, major congenital malformations, pregnancy, selective serotonin reuptake inhibitor, sertraline

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Depression is common during pregnancy, and selective serotonin reuptake inhibitors (SSRIs) are the most frequently used antidepressants to treat pregnant women.[1-3] Studies concerning the adverse effects of SSRI exposure during gestation on the developing fetus have indicated an increased risk of various congenital malformations,[4-9] but inconsistencies between study results remain.[10-14] These could potentially be explained by indication bias where the effect of the drug and the indication are correlated and not fully accounted.

Sertraline is one of the most frequently used SSRIs during pregnancy globally[3,13-16] and is one of the first-line treatments for depression at present. Sertraline has been suggested to increase the prevalence of heart defects[6-8,17] and craniosynostosis.[7] It remains, however, that the majority of studies have low statistical power due to small sample size, or are potentially biased by unaccounted maternal depression effect. Given the current debate, and the public health impact and clinical implication of prescribing and using SSRI in general, and sertraline specifically, during pregnancy on the fetus, we aim to study the association between first-trimester exposure to sertraline and the risk of major congenital malformations in a cohort of depressed pregnant women.

Materials and Methods

Setting

We conducted a register-based cohort study using data from the Quebec Pregnancy Cohort (QPC). The QPC is an ongoing population-based cohort with prospective data collection on all pregnancies that occurred from January 1998 through December 2010 in the province of Quebec. Data on the mothers and children after the end of pregnancy are

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also collected. Individual-level information is obtained from province-wide databases and linked using unique personal identifiers. The QPC was first constructed by identifying all pregnancies in the Régie de l'assurance maladie du Québec (RAMQ) and the Quebec hospitalization archives (MedEcho) databases; subsequently, first day of the last menstrual period (1DLMP) was defined using data on gestational age, which was validated against patients' charts.[18] Prospective follow-up was available from 1 year before the 1DLMP, during pregnancy, and until December 2010. Analyses of major malformations overall and specific malformations were performed. The data sources for this study included the medical service database (RAMQ: diagnoses, medical procedures, socioeconomic status of women and prescribers), Quebec's public prescription drug insurance database (drug name, start date, dosage, duration), the hospitalization archive database (MedEcho: diagnoses and procedures), and the Quebec statistics database (Institut de la statistique du Quebec: patient sociodemographic, birthweight). The data sources used and the QPC are described in Bérard and Sheehy.[19]

Patients

We included pregnancies with continuous prescription drug insurance coverage of at least 12 months before the 1DLMP and during pregnancy; pregnancies with a diagnosis of depression and/or anxiety (Appendix, Supplementary Table 1) or exposed to antidepressants in the 12 months before pregnancy (Supplementary Table 2); and pregnancies ending with a liveborn singleton. Given that we wanted to have a sample of depressed/anxious women diagnosed before pregnancy, we only considered those who had a diagnosis or were treated with antidepressants in the year before their pregnancy, increasing the specificity of the diagnosis. Within this predefined cohort of depressed/anxious pregnancies, we further considered pregnancies that were exposed to only one type of antidepressant or nonexposed to antidepressants during the first trimester of pregnancy. This excluded pregnancies with multiple different antidepressant exposures during organogenesis, which are likely at increased risk of adverse pregnancy outcomes. We excluded pregnancies exposed to known teratogens during the first trimester of pregnancy according to Chaabane and Bérard,[20] Briggs et al,[21] and Kulaga et al,[22] and pregnancies with newborn diagnosed with chromosomal abnormalities. We further excluded pregnancies resulting in minor malformations alone in newborns. All pregnancies meeting eligibility criteria were analyzed. The study was approved by the Quebec Data Access Agency and the Sainte-Justine Hospital Institutional Review Board.

Sertraline and other antidepressants

We identified prescription fillings for sertraline dispensed to women in the cohort from the Quebec public prescription drug insurance database, with the timing of exposure determined by the dispensed date and duration of prescription. The relevant exposure time window was the first trimester confirmed by ultrasound.

Three comparator groups were defined to take into account the underlying maternal depression. First, 2 active comparator groups included pregnancies with exposure to: (1) nonsertraline SSRI and (2) non-SSRI antidepressant during the relevant time window. Codes of all antidepressants considered are presented in Supplementary Table 2. Second, a nonexposure category was defined as pregnancies with no exposure to antidepressants (sertraline or others) during the time window of interest; the reference category was therefore depressed/anxious pregnant women who were not using any antidepressants, enabling us to better control for the underlying indication.

Duration of exposure during the first trimester of gestation in the 3 exposure study groups was calculated by adding all antidepressant filling durations over the 14 weeks of the first trimester. Average daily dose (mg/d) of sertraline use during the first trimester was calculated by dividing the cumulative daily dose of sertraline exposure (mg) by the total duration of sertraline use during the first trimester of pregnancy (day). Data on prescription fillings have been validated and compared to real-time maternal reports.[23]

Outcomes

Major congenital malformations diagnosed in the first year of life were identified in the RAMQ and MedEcho databases and defined according to *International Classification of Diseases, Ninth Revision* codes and *International Statistical Classification of Diseases, 10th Revision* codes (Supplementary Table 3). Minor malformations were excluded because they are likely diagnosed selectively (leading to outcome misclassification); chromosomal abnormalities were also excluded given that they are likely not related to the drug of interest. *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases, 10th Revision* codes of major congenital malformations in the QPC have been validated against patient charts.[24] All organ systems were considered but more specifically: overall cardiac defects; atrial septal defect (ASD)/ventricular septal defect (VSD); and craniosynostosis defined according to the European Registration of Congenital Anomalies and Twins registry.[25]

Statistical analyses

Within the study cohort, we conducted separate analyses for overall major congenital malformations, and for each organ system malformation.

Potential confounders were considered for all analyses: (1) sociodemographic variables including maternal age on the 1DLMP, maternal marital status (living alone or cohabiting), receipt of social assistance during pregnancy or 1 year before, education level in years ($\leq$12 or $>$12), and area of residence on the 1DLMP (urban/rural); and (2) maternal chronic comorbidities during the 12 months prior and during pregnancy including hypertension (chronic and pregnancy induced), diabetes (mellitus and gestational), and asthma. The previous conditions were identified from either diagnoses or disease-specific medications. History of depression, anxiety, and other mental conditions were taken into account per design given