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Selective serotonin re-uptake inhibitor use during pregnancy: association with offspring birth size and gestational age

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SUMMARY

Background: Depression around the time of pregnancy affects at least 1 in 8 women and treatment with selective serotonin re-uptake inhibitors (SSRIs) in pregnant women has been increasing, but research on adverse effects on the fetus have so far commonly used designs unable to account for confounding. We aimed to examine the effects of prenatal SSRI exposure on offspring size outcomes and gestational age, and disentangle whether associations observed were due to the medication or other factors.

Methods: We used a Swedish population-based cohort of 392,029 children and national registers to estimate the associations between prenatal exposure to SSRIs and depression on the outcomes birth weight, birth length, birth head circumference, gestational age at birth, and preterm birth. A sub-sample of 1007 children was analyzed in a within-family design that accounts for unmeasured parental genetic and environmental confounds.

Results: Crude analyses revealed associations between prenatal SSRI exposure and offspring birth size, and gestational age. However, in the within-family analyses, only the association between SSRI exposure and reduced gestational age (-2.3 days; 95% CI -3.8 to -0.8) was observed.

Conclusions: This study indicates that prenatal SSRI exposure may not be causally related to offspring birth size. Rather, our analyses suggest that the association could be caused by other underlying differences instead of the medication per se. A small reduction of gestational age was associated with SSRI exposure in the within-family analysis and could be due to either the exposure, or other factors changing between pregnancies.

Keywords: Depression, medication, pregnancy, antidepressants, pharmacoepidemiology

INTRODUCTION

Major depressive disorder, a common psychiatric disorder characterized by persistent depressed mood with both cognitive and physiological symptoms, is expected to be the second leading cause of disability worldwide by 2020.[1-4] Estimates show that at least 1 in 8 women suffers from perinatal depression, making the time around pregnancy a high-risk period for substantial morbidity, mortality, and personal and societal costs.[5-10] Treating depressed pregnant women is imperative because depression can also confer risk of suicidal or infanticidal ideation.[11] Selective serotonin re-uptake inhibitors (SSRIs) are frequently used to treat depression, and the prescriptions of these drugs have increased both in general,[12] and among pregnant women.[13, 14] Treatment with SSRIs is considered both efficacious and well tolerated by patients,[15] but less is known about possible adverse effects on the unborn fetus.

Studies have reported smaller head size in mice prenatally exposed to SSRIs,[16] and in serotonin transporter knockout mice; the corresponding high levels of serotonin is thought to cause abnormal wiring of the somatosensory cortex and the lateral geniculate nucleus in the brain.[17] In humans, studies have shown that antidepressants pass the placenta, and ratios between 0.29 and 0.89 of the maternal serum levels of antidepressants and their metabolites can be detected in umbilical cord blood, with the highest ratio reported for the SSRI citalopram.[18] Further, studies in humans have reported associations between prenatal SSRI exposure and preterm birth,[19-21] persistent pulmonary hypertension,[22, 23] septal heart defects,[24] lower birth weight,[21, 25] lower gestational age,[19, 25] malformations at birth,[26] fetal death,[21] and reduced fetal head growth.[27]

Research has shown that women suffering from depression during pregnancy are frequently missed by the healthcare.[28] With better understanding, screening, and treatment of depression around the time of pregnancy, the use of SSRIs among pregnant women can be expected to increase even further. It is, therefore, of high importance to further study the possible adverse

effects on children exposed to SSRIs during pregnancy. However, due to safety reasons, the effects of medication exposure on unborn children are not studied in randomized settings[29] leading studies on adverse effects of medication in pregnant women to rely on observational data. One major obstacle in observational studies is confounding, and in pharmacoepidemiological studies specifically confounding by indication or confounding by broader underlying factors affecting both the indication and subsequent medication. Medicated and non-medicated individuals will have different underlying risks for the factors that caused the treatment, and these underlying differences may, wholly or partially, explain an observed difference in the outcome studied. In this case, it could be the case that women with depression (or liability for depression) have an increased risk for adverse pregnancy outcomes, which may account for the previously found associations between SSRI and adverse pregnancy outcomes. One way of addressing this issue would be to use within-family designs that can account for familial liability.[30]

In this study, we estimated the effects of prenatal exposure to SSRIs on birth weight, birth length, birth head circumference, gestational age at delivery, and preterm birth. We first used a population-based cohort of almost 400,000 Swedish children in an ordinary epidemiological analysis controlling for a number of confounding factors. We then used a sub-sample of the cohort in a within-family design that controlled for all environmental factors affecting the parents prior to the pregnancy of the first child, the mother's and father's genetic makeup, maternal factors consistent between the births, the children’s genetic makeup, and all other covariates that did not change between the births of the children.

METHODS

Study population

We used the Swedish personal identification number to link national Swedish registers with high accuracy.[31] The Swedish Medical Birth Register (MBR) covers 99% of all births since 1973,[32] and was used to create a population-based cohort (N=392,029) consisting of all children born between April 1st 2006 and December 31st 2009. Stillborn births and twin births were excluded. Using the birthdate and information on gestational age at birth, provided in the MBR, we could calculate date of conception.

The cohort was further linked to the Multi-Generation Register (MGR) that contains information on first-degree relatives for persons born 1932 and later.[33] The MGR was used to identify both parents and consequently the relatedness of the children. In total, a within-family sub-sample of 1007 full siblings where the siblings had different prenatal SSRI exposure was identified.

Exposures

SSRIs during pregnancy

Medication with SSRIs was determined by linking the mothers to the Swedish Prescribed Drug Register. The register contains information on all prescribed and dispensed prescription drugs since July 1st 2005,[34] including the name of the drug, prescription- and dispensation dates, and a code in accordance with the Anatomical Therapeutic Chemical Classification System (ATC). We identified dispensations of SSRI medication around the time of pregnancy using ATC codes under the category N06AB (SSRIs), and defined a binary exposure variable (1: no dispensations from three weeks before pregnancy until the childbirth (no SSRI exposure). 2: more than one dispensation between conception and childbirth, or one dispensation within the pregnancy period and at least one more dispensation within 6 months before or after the dispensation during pregnancy (SSRI exposure).

Depression diagnosis

The National Patient Register, providing information on Swedish psychiatric inpatient and outpatient care,[35] was used to identify treatment contacts for depression. The register contains dates along with the main discharge diagnosis code, and up to eight secondary diagnosis codes in accordance with the International Classification of Disease (ICD). Depression was defined as at least one treatment contact for depression (ICD-10 F32.0/.1/.2/.3/.8/.9, F33.0/.1/.2/.3/.4/.8/.9, F34.1, F41.2) between conception and delivery. It should be noted that this diagnosis might not reflect an on-going depression, but could be part of a planned follow-up visit from a previous depressive episode.

Exposure categories

A categorical exposure variable was created based on SSRI medication and hospital care for depression (0: No SSRI exposure, and no hospital care for depression during pregnancy. 1: SSRI exposure. 2: At least one treatment contact for depression during pregnancy, and no SSRI medication).

Outcomes

In Sweden, a newborn child is routinely measured and weighted at birth and the information is recorded in the MBR. Gestational age at birth, also in the MBR, is calculated through standardized ultrasound measurements at pregnancy week 16-18. We used birth weight (grams), birth length (cm), birth head circumference (cm), gestational age at delivery (days), and preterm birth (gestational age at birth <259 days) as outcomes.

The birth size measurements of the child will depend on the gestational age at birth, and therefore the growth outcomes were standardized by gestational age at birth. Birth weight, birth length, and birth head circumference were standardized by gestational age at birth using the

mean and standard deviation of children in the cohort born within the same gestational week. The standardized values of birth weight displayed a correlation of 0.98 with a previous method based on ultrasound measurements at different gestational ages during pregnancy in healthy children.[36]

Covariates

We adjusted for several factors that might confound the associations. The BMI of the mother was calculated (weight in kilograms divided by height in meters squared) based on weight and length measured at the first antenatal care visit (from the MBR), and divided into four categories (<18.5, 18.5-25, 25-30, >30). The height of the mother was also used as a separate covariate. The birth order was also included from the MBR as there might be systematical differences for using SSRI depending on the mother's parity at the specific pregnancy. Previous psychiatric history was ascertained using any hospital contact with a psychiatric diagnosis from the NPR prior the specific childbirth using ICD 7th-10th revisions. The mother's age at delivery (years), and smoking status (1: does not smoke. 2: 1-9 cigarettes per day. 3: >9 cigarettes per day) at first antenatal care visit, was obtained from the MBR. The highest completed education (1: compulsory school. 2: upper secondary school. 3: post secondary education less than three years. 4: university three years or more) the year of delivery was obtained by linking the subjects to the Swedish longitudinal integration database for health insurance and labour market studies.

Statistical methods

In the population analyses, the association between prenatal exposure of SSRI medication, or depression without SSRI medication, and the continuous variables birth weight, birth length, birth head circumference, and gestational age at birth were estimated by linear regression analyses, while the binary preterm birth outcome was analyzed by logistic regression. The children not exposed to depression or SSRI was used as the reference group and the analyses

adjusted for all the covariates. Robust standard errors were used, as several children from the same mother were included in the analysis.

The within-family analyses were done by estimating models with a fixed effects regression estimator (xtreg statement, within mother) for continuous variables and conditional logistic regression for preterm birth. This design will automatically control for all covariates that did not change between the births. In these analyses we included all families with at least two siblings discordant for SSRI exposure, but if more than two siblings were identified they were also included. The children not exposed to depression or SSRI was used as the reference group.

All analyses were performed in STATA/IC 13.1.

RESULTS

Population analyses

See Table 1 for descriptive statistics of the cohort. We identified 392,029 children born between April 1st 2006 and December 31st 2009. During pregnancy, 6572 (1.7%) were exposed to SSRI, and 1625 (0.4%) children were exposed to a depressive mother not treated with an SSRI.

Children born to mothers using SSRIs during pregnancy displayed lower birth length and smaller birth head circumference, shorter gestational age at birth, and a higher probability of preterm birth (Table 2).

Within-family analyses

By applying a within-family design one automatically control for a wide range of unmeasured confounding factors that are shared within the family but not possible to control for with population analyses.

Table 3 provides descriptive characteristics of the within-family sub-sample. From the initial cohort, we identified 496 women giving birth to more than one child with the same father and with children discordant for SSRI exposure.

The associations between SSRI exposure and birth length, birth head circumference, and birth weight observed in the full cohort was all attenuated in the within-family analyses and no differences were observed (Table 2).

Gestational age at delivery was lower (-2.27 days; 95% CI -3.79 to -0.75; *P*=0.004) in the group of children exposed to SSRI, and the odds ratio for preterm birth was similar as in the population cohort, although with confidence intervals overlapping zero (Table 2).

One possibility is that this remaining difference is due to the depression underlying the medication and that women with a depression have a greater likelihood of shorter gestational age. We therefore compared children exposed to depression (without SSRI exposure during fetal life) with children of mothers without a diagnosis of depression or SSRI medication. As seen in Table 2 also these children had lower gestational age (-1.69; 95% CI -2.51 to -0.86; *P*<0.001) and higher probability of preterm birth (OR 1.31; 95% CI 1.07 to 1.60; *P*=0.009).

DISCUSSION

There is concern that SSRI-exposure influences fetal development.[19-27] Similar to previous studies,[21, 25, 27] we observed lower birth length and birth head circumference in children where the mother was medicated with an SSRI during the pregnancy when analyzing the total-population cohort. However, when applying a within-family design where full siblings with different prenatal exposures of SSRIs were compared, consequently adjusting the analyses for unmeasured genetic and environmental factors shared by siblings, we observed no differences in

the estimates. While the group of children prenatally exposed to SSRIs in the population analyses indeed had lower birth size, findings from this study suggest that the offspring birth outcomes were likely not caused by the SSRI medication. Rather, the associations between the outcomes and SSRI exposure could be due to underlying factors causing both the SSRI medication of the mother and the lower birth size of the children.

Lower gestational age and preterm birth have also been associated with prenatal SSRI exposure in previous studies.[19-21, 25] We also observed an association between prenatal SSRI exposure and lower gestational age in our population analysis (-3.1 days). In contrast to the other pregnancy outcomes studied, an association was also observed in the within-family analysis (-2.3 days). An association between prenatal SSRI exposure and preterm birth was observed in the population sample, but in the within-family sample the confidence intervals overlapped zero. However, the estimates for preterm birth were similar using both methods. It is likely that the broader confidence intervals are due to power, as using a binary outcome variable reduces the number of informative sibling pairs. A within-family association between SSRI exposure during fetal life and gestational age and preterm birth could have several potential explanations. The association could be due to a causal effect of the SSRI. An alternative explanation would be that a depression underlying the medication is causing the association. A third possibility would be that the association is due to liability for depression. We tried to address these alternatives by comparing women having at least one treatment contact with a discharge diagnosis code for depression but no SSRI medication during pregnancy to women not having a treatment contact for depression or SSRI medication during pregnancy. First, note that a treatment contact with a discharge diagnosis code for depression might not reflect a current ongoing depressive episode but could rather be part of a planned follow up visit and that lack of SSRI medication could indicate that these women were either not depressed during pregnancy, or had a less severe depression. Yet, the analyses showed that women with a depression diagnosis during pregnancy

were more likely to have both shorter gestational age and preterm birth offspring compared to women without a treatment contact for depression or SSRI medication during pregnancy. If depression liability was the only factor influencing gestational age, no association should be observed in the within-family analyses. However, an association was observed, indicating influence from factors other than the liability, for example the SSRI medication, or the depression leading to the treatment. Regardless of which of the alternatives is most influential, we found no difference in any of the birth size outcomes in the within-family analyses. Therefore, the small reduction in gestational age observed in the prenatally SSRI exposed child, compared to a non-exposed full sibling, does not seem to be correlated with impaired growth.

Our study focused on a finite number of outcomes and therefore cannot reject or replicate any studies focusing on the association between prenatal SSRI exposure and other outcomes. However, our study shows that confounding factors play a major role in the complex relationship between pharmacological treatment of pregnant women and adverse pregnancy outcomes. Observational studies of prenatal drug exposure not using a genetically-informed design are at risk of drawing incorrect conclusions regarding the causality of associations observed in the population.

This study has several strengths, including the large population-based cohort of mothers and children linked to Swedish nation-wide registers and a healthcare system with equal access. The study used standardized growth outcomes that had been adjusted for gestational age at birth. Further, the additional within-family analyses allowed controlling for unmeasured confounding factors that full-cohort analyses cannot, and could thereby provide better understanding of the causality of the observed associations.

This study uses prescription and pharmacy dispensation data, but the adherence to the prescribed treatment is unknown and is a limitation. Furthermore, the Swedish National Patient Register

used to identify treatment contacts for depression does not include information from primary care. Consequently, identified depressed mothers without SSRI treatment will be on the more severe end of the depressive spectrum as they have received treatment in a specialist care setting. This might explain the low numbers of mothers with depression lacking SSRI medication. The absence of primary care data will also lead mothers without SSRI medication and primary care only to be classified as unexposed. However, potentially mis-classified mothers only make up a very small portion of the unexposed group. Further, the sub-sample of families used in the within-family analysis required at least two full siblings. The study only included children born between April 1st 2006 and December 31st 2009, and by giving birth to more than one child within this time frame, the mothers in the within-family sub-sample could differ from the general population. Additionally, a sibling design is not free from potential bias, and the design could oversample measurement errors. Further, while a family approach allows adjustment for the parent's genetics, environmental exposures prior the pregnancy of the first child, and factors consistent between pregnancies, the sibling design become very unbalanced when exposures and outcomes changes over time and parity or calendar time adjustments will not adjust for changes in exposures related to the outcome of previous births.[37] For example, a within family analysis does not adjust for changes in behavior as a consequence of perceived consequences of exposure. That might be the case if a first pregnancy is exposed and results in e.g. low gestational age, and that results in both changes in exposure and relevant behavior. If this type of bias is present, the small association between prenatal SSRI exposure and reduced gestational age might be an overestimate.

In conclusion, this study indicates that prenatal SSRI exposure may not be causally related to offspring birth size. Rather, our analyses suggests that associations between prenatal SSRI exposure and the studied offspring size outcomes may be due to other factors, including the

underlying depression or different characteristics of women taking SSRI during pregnancy compared to women with a lower liability for depression. This study did find an association between SSRI exposure and reduced gestational age in both the population analysis, and in the within-family analysis. However, this reduction of gestational age was small (-2.3 days) and could be due to the exposure of the antidepressant, or due to factors changing between the pregnancies compared. In addition to provide further information for the clinical decision whether to prescribe SSRIs or not during a pregnancy, our study highlights the strong presence of confounding factors in pharmacoepidemiological studies.

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KEY MESSAGES

- Maternal depression around the time of pregnancy is not uncommon and antidepressant medication prescriptions have increased both in the general population and among pregnant women.
- When comparing children prenatally exposed to SSRI or to a depressed mother without SSRI treatment, crude analyses revealed associations with lower birth size and gestational age, as well as increased odds ratios for preterm birth.
- Within-family analyses of full siblings with different exposure to SSRI did not reveal associations between prenatal SSRI exposure and birth size. However, the association with lower gestational age was still observed, but did not seem to have a strong effect on growth.
- This indicates that the associations with birth size, seen in the crude analyses, could be due to underlying confounding factors such as parental genetic or environmental factors rather than the medication per se.

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