Antipsychotic Use During Pregnancy and Risk for Gestational Diabetes: A National Register-Based Cohort Study in Sweden

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Abstract
Objective We aimed to study whether antipsychotic use during pregnancy is associated with gestational diabetes.
Methods This was a Swedish national register-based cohort study on the Medical Birth Register and the Prescribed Drug Register including all 1,307,487 singleton births between July 2006 and December 2017. Antipsychotics were divided into first-generation antipsychotics (n = 728), high-risk metabolic second-generation antipsychotics including olanzapine, clozapine and quetiapine (n = 1710), and other second-generation antipsychotics (n = 541). The risks for gestational diabetes, foetal growth disturbances, pre-eclampsia, caesarean section and preterm labour were assessed. Women treated during pregnancy were compared to women not treated during pregnancy and to women who used antipsychotics before/after but not during pregnancy.
Results The crude risk ratio for gestational diabetes for women treated with high-risk metabolic second-generation antipsychotics during pregnancy was 2.2 (95% confidence interval [CI] 1.6–2.9) compared to untreated pregnant women (n = 1,296,539) and 1.8 (95% CI 1.4–2.5) compared to women treated before/after pregnancy (n = 34,492). After adjustment for maternal factors including body mass index, the risk ratios were 1.8 (95% CI 1.3–2.4) and 1.6 (95% CI 1.2–2.1). Exposed infants had an increased risk of being large for gestational age: adjusted risk ratios 1.6 (95% CI 1.3–1.9) and 1.3 (95% CI 1.1–1.6) compared to no maternal antipsychotic use during pregnancy and maternal use before/after the pregnancy. Other antipsychotics were not associated with metabolic risks.
Conclusions Olanzapine, clozapine and quetiapine used during pregnancy were associated with increased risks for gestational diabetes and the infant being large for gestational age. Enhanced metabolic monitoring should be considered for pregnant women using these drugs.

Plain Language Summary
The use of second-generation antipsychotics amongst pregnant women is increasing. The side effects of these drugs, for example weight gain and increased blood sugar, are well described for the general population. In particular, olanzapine, quetiapine and clozapine are known to cause these effects. Studies on their effects on blood sugar control in pregnant women have however been conflicting. Pregnancy itself also imposes a risk for increased blood sugar levels and gestational diabetes. The purpose of this study was to evaluate the risk of gestational diabetes connected to the use of antipsychotics during pregnancy. The study was nationwide and register based including 1.3 million births in Sweden between July 2006 and December 2017. The rates of gestational diabetes and the infants being small for gestational age or large for gestational age amongst women treated with antipsychotics were compared to the rates in pregnant women who did not receive antipsychotics and to rates in a control group of women treated with antipsychotics before/after but not during pregnancy. Antipsychotics were divided...
into three groups: (i) first-generation antipsychotics, (ii) high-risk second-generation antipsychotics including olanzapine, quetiapine and clozapine, and (iii) other second-generation antipsychotics. Women treated with high-risk second-generation antipsychotics were found to have an increased risk of gestational diabetes and giving birth to an infant being large for gestational age, both when compared with untreated pregnant women and with the control group. Other antipsychotics were not connected to increased risks of these outcomes. Hence, pregnant women treated with olanzapine, quetiapine or clozapine should be monitored regarding blood sugar levels.

**Key Points**

Use of olanzapine, clozapine and quetiapine during pregnancy is associated with an increased risk for the metabolic complications of gestational diabetes and infant being large for gestational age.

These risks are not a reason for discontinuing an ongoing treatment but enhanced metabolic monitoring should be considered during pregnancy.

If treatment with antipsychotics is started during pregnancy or in a woman planning a pregnancy, prescription of other antipsychotics may be preferable from a metabolic point of view.

1 Introduction

The use of second-generation antipsychotic drugs (S-GAs) has more than doubled in the last decade, mainly explained by a wider spectrum of indications than for the first-generation antipsychotics (F-GAs), for example bipolar disorder [1–7]. The S-GAs have less extrapyramidal and prolactin-related side effects than F-GAs, but there are concerns regarding their metabolic side effects [8–13]. Clozapine, olanzapine and quetiapine have the most prominent metabolic side effects, including significant weight gain, whereas aripiprazole has weight loss as a common side effect [8, 14].

The prevalence of gestational diabetes (GDM) is increasing, with a huge geographic variation between 2 and 23% within Europe, likely mainly owing to differing diagnostic criteria between countries [15, 16]. Predisposing factors for GDM are obesity, family history of diabetes, increasing parity, unhealthy diet, sedentary lifestyle and lower socioeconomic status, many of which are overrepresented in women treated with antipsychotics [17–21]. Hyperglycemia in expectant mothers caused by untreated or unnoticed diabetes mellitus leads to increased transplacental glucose transfer, which causes foetal hyperinsulinism. As insulin is a major growth factor, this causes increased foetal growth and the infant being large for gestational age (LGA). Women with LGA infants are at risk for delivery complications such as shoulder dystocia and emergency caesarean section, and the infants are at risk for neonatal hypoglycaemia and treatment at a neonatal intensive care unit. Gestational diabetes is also a risk factor for pre-eclampsia in the mother and type 2 diabetes mellitus later in life for both the mother and child [22–27]. In Sweden, practices regarding screening for GDM vary between regions and women are usually not screened with an oral glucose tolerance test, unless they have risk factors or a pathological random blood glucose test [28, 29].

Studies on the association between antipsychotic use during pregnancy and GDM are conflicting. Some have shown an increased risk for GDM [7, 10, 19, 21, 30, 31], not confirmed by others [16, 32–35]. Increased risks for prematurity and the infant being small for gestational age (SGA) and LGA have also been shown [10, 21, 32, 36–38]. The metabolic effects of antipsychotics seem difficult to separate from the risks of the underlying disease and lifestyle [16, 33, 34]. Changing an effective antipsychotic during pregnancy is not recommended, as treatment discontinuation increases the risk of relapse, which is harmful for both mother and child [39–41]. The primary objective of this study was to investigate whether the different groups of antipsychotics were associated differently with metabolic complications and whether the women treated during pregnancy had an increased risk for pregnancy complications when compared to the control group of women who used antipsychotics before or after but not during the actual pregnancy.

2 Methods

The study was a register-based study using prospectively collected data, combining data from the Swedish Medical Birth Register (MBR) [42] and the Prescribed Drug Register [43]. Swedish personal identification numbers were used for linkage between the registers. The MBR was used to collect information about maternal and foetal background characteristics as well as the main outcome GDM. The MBR contains data from the delivery, the paediatric examination of the newborn and antenatal care including body mass index (BMI), medications and smoking habits registered in the first trimester for > 97% of all births.

The study population consisted of all singleton births in Sweden, a total of 1,307,487 infants, registered in the MBR between 1 July, 2006 and 31 December, 2017. After
exclusion of pregnancies with pre-pregnancy diabetes, defined as *International Classification of Diseases* codes O24.0, O24.1, O24.3 and O24.8 and women using valproic acid during pregnancy, a total of 1,299,216 pregnancies were included in the search. Users of valproic acid were excluded because of its known teratogenicity and metabolic side effects [44]. An outline of the study design is presented in Fig. 1.

### 2.1 Drug Exposure

Exposure data for prescription drugs were acquired from both the MBR and the Prescribed Drug Register. The Prescribed Drug Register stores data on drugs prescribed in ambulatory care and dispensed at Swedish pharmacies but does not include medications used in hospitals for in-patient care. The MBR includes drug use reported at the first visit at the maternal care centre, usually in the first trimester. The drugs are classified according to the Anatomical Therapeutic Chemical classification system. Drugs belonging to Anatomical Therapeutic Chemical class N05A were included. Exposures to dixyrazine (N05AB01), prochlorperazine (N05AB04), melperone (N05AD03) and lithium (N05A N01) were excluded because their indications for use and pharmacological properties differed from the other antipsychotics. The included antipsychotics were divided into F-GAs mainly consisting of levomepromazine, haloperidol and flupentixol, \( n = 728 \), high metabolic risk S-GAs (HR S-GAs) including quetiapine (\( n = 1026 \)), olanzapine (\( n = 771 \)) and clozapine (\( n = 29 \)), and other S-GAs including aripiprazole (\( n = 334 \)), risperidone (\( n = 191 \)), ziprasidone (\( n = 34 \)), paliperidone (\( n = 9 \)) and sertrindole (\( n = 2 \)). The different antipsychotics were not compared to each other because of the small numbers of exposures to individual antipsychotics.

The drug exposure was allocated into any use (drugs dispensed at any time during pregnancy including 1 month before the pregnancy), late use (drugs dispensed during the last 90 days of the pregnancy with or without earlier dispenses) and early use only (dispensed 1 month before and during pregnancy but not during the last 90 days of the pregnancy) to explore whether the timing of the drug use was connected to the risk of GDM. Timing was used as a proxy for the duration of antipsychotic treatment. We also created a comparison group with

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Fig. 1 Flowchart over the study design. 1Women with pre-pregnancy diabetes mellitus (type 1 or 2). 2Use of valproic acid during pregnancy. *GDM* gestational diabetes
women treated with antipsychotics at any time during the study period but not during the interval of 1 month before the actual pregnancy to delivery, attempting to control for the effect of the underlying psychiatric illness and its associated psychosocial background factors. The women treated during pregnancy were compared to both this control group and to all women not treated during pregnancy, including the control group. Exposure data were also collected for other psychotropic drugs: antidepressants (N06A), antiepileptics (N03A), opioids (N02A), lithium (N05A N01), centrally acting sympathomimetics (N06B), sedatives and anxiolytics (N05B and N05C), and milder sedatives and antiemetics including promethazine (R06AD02, R06AD52), alimemazine (R06AD01), dixyrazine (N05A B01), prochlorperazine (N05A B04) and melperone (N05A D03). These drugs are presented in Table 1 and were adjusted for in a separate analysis.

2.2 Maternal and Pregnancy Outcomes

The maternal and pregnancy outcomes were extracted from the MBR, where diagnoses are registered according to the International Classification of Diseases, 10th Edition. The main outcome GDM was defined as a recorded International Classification of Diseases, 10th Edition code of O24.4 during pregnancy. The secondary outcomes were the infant being LGA (Z-score > 2 standard deviations) or SGA (Z-score < −2 standard deviations) measured with Z-scores based on infant weight for gestational age and sex [45], pre-eclampsia (yes/no), caesarean section (acute or planned, vs vaginal birth), gestational age (classified as < 32 weeks, 32–36 weeks, 37–41 weeks, ≥ 42 weeks, with the reference being normal gestational age of 37–41 weeks) and perinatal death (vs survival).

2.3 Statistical Analyses

Risk ratios (RRs) were obtained for all dichotomous outcomes: GDM vs no GDM, LGA vs appropriate for gestational age, SGA vs appropriate for gestational age, pre-eclampsia vs no pre-eclampsia, caesarean section (acute/planned) vs vaginal birth, premature labour/prolonged pregnancy vs normal gestational age (37–41 weeks) and perinatal death (vs survival) by using modified Poisson regression in multivariate regression models. Crude and adjusted RRs were calculated. Robust standard error estimation was used to correct for time-invariant confounding. The exposures were any antipsychotic use vs no use, use of the different antipsychotic groups vs no use, late use vs early use only, and use during vs use before or after pregnancy. In the final analyses, adjustments were made for maternal factors: maternal age (continuous), primiparity (vs multiparity), maternal smoking (ordinal: 1 = no smoking, 2 = smoking <10 cigarettes/day, 3 = smoking ≥ 10 cigarettes/day, entered as a continuous variable), BMI (continuous). Maternal use of other neurotropic drugs was added to the list of adjusted factors in a sensitivity analysis on GDM, LGA and SGA.

3 Results

Maternal background characteristics for women treated with antipsychotics during pregnancy, before and/or after but not during pregnancy and women not treated with antipsychotics during pregnancy are described in Table 1. There were 2677 individual pregnancies during which the women were treated with an antipsychotic. In 302 pregnancies, the women were treated with more than one category of antipsychotics.

3.1 Time Trends in Antipsychotic Prescriptions

A total of 803 prescriptions of F-GAs and 2396 of S-GAs were filed during pregnancy in Sweden 2006–17. In this period, the yearly number of pregnant women prescribed F-GAs decreased with 30%, whereas the prescriptions of S-GAs increased by 300%, from 91 to 367 yearly prescriptions during pregnancy. The three most prescribed antipsychotics were quetiapine, olanzapine and aripiprazole. The prescriptions rates over time are presented in Fig. 2 on a group level and individually for the S-GAs in Fig. 3.

3.2 Gestational Diabetes and Foetal Growth

When compared with women without antipsychotic treatment during pregnancy, the crude risk for GDM was significantly increased in the group of women treated with HR S-GAs and in women treated with F-GAs but not in women treated with other S-GAs. After adjustment for age, parity, smoking and BMI, only the women treated with HR S-GAs had an increased risk of GDM (Table 2). Increased BMI was strongly
Table 1  Background characteristics of the study population

|                                | Antipsychotic use during pregnancy, \( n = 2677 \) | Antipsychotics before or after but not during pregnancy, \( n = 34,492 \) | No antipsychotic use during pregnancy, \( n = 1,296,539 \) | \( P \)-value for heterogeneity between groups<sup>b</sup> |
|--------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Year of childbirth             |                                                  |                                                  |                                                  | <0.001                                           |
| 2006–10                       | 1013 37.8                                       | 19,279 55.9                                      | 630,942 48.7                                     |
| 2011–17                       | 1664 62.2                                       | 15,213 44.1                                      | 665,597 51.3                                     |
| Maternal age, years           | <0.001                                          |                                                  |                                                  |                                                  |
| < 20                          | 70 2.6                                          | 1059 3.1                                        | 26,613 2.1                                       |
| 20–35                         | 1883 70.3                                       | 26,638 77.2                                      | 991,018 76.4                                     |
| 35+                           | 724 27.0                                        | 6795 19.7                                       | 278,908 21.5                                     |
| Parity                        | <0.001                                          |                                                  |                                                  |                                                  |
| Primipara                     | 1891 70.6                                       | 20,727 60.1                                      | 818,330 63.1                                     |
| Multipara                     | 786 29.4                                        | 13,764 39.9                                      | 470,320 36.3                                     |
| Maternal BMI in early pregnancy<0.001 |                                                  |                                                  |                                                  |                                                  |
| < 18.5                        | 51 1.9                                          | 928 2.7                                         | 29,242 2.3                                       |
| 18.5–24.9                     | 1015 37.9                                       | 16,356 47.4                                      | 705,995 54.5                                     |
| 25–29.9                       | 772 28.8                                        | 8516 24.7                                       | 306,678 23.7                                     |
| ≥ 30                          | 618 23.1                                        | 5723 16.6                                       | 153,350 11.8                                     |
| Unknown                       | 221 8.3                                         | 2969 8.6                                        | 101,271 7.8                                      |
| Maternal smoking in early pregnancy<0.001 |                                                  |                                                  |                                                  |                                                  |
| No                             | 1818 67.9                                       | 26,774 77.6                                      | 1,154,817 89.1                                   |
| Yes                            | 733 27.4                                        | 5939 17.2                                       | 73,287 5.7                                       |
| Missing information           | 126 4.7                                         | 1779 5.2                                        | 68,435 5.3                                       |
| Maternal country of birth     | <0.001                                          |                                                  |                                                  |                                                  |
| Sweden                        | 2018 75.4                                       | 27,655 80.2                                      | 956,473 73.8                                     |
| Other Nordic                  | 123 4.6                                         | 946 2.7                                         | 52,169 4.0                                       |
| Non-Nordic                    | 525 19.6                                        | 5844 16.9                                       | 263,103 20.3                                     |
| Maternal cohabitation         | <0.001                                          |                                                  |                                                  |                                                  |
| Not living with the father of the child<0.001 |                                                  |                                                  |                                                  |                                                  |
| Maternal disease              |                                                  |                                                  |                                                  |                                                  |
| Hypothyroidism                | 122 4.6                                         | 973 2.8                                         | 27,672 2.1                                       |
| Essential hypertension        | 15 0.6                                          | 182 0.5                                         | 5130 0.4                                        |
| Use of other neurotropic drugs<0.001 |                                                  |                                                  |                                                  |                                                  |
| Lithium (N05A N01)            | 124 4.6                                         | 292 0.8                                         | 294 0.0                                         |
| Opioids (N02A)                | 44 1.6                                          | 604 1.8                                         | 5352 0.4                                        |
| Antiepileptics (N03A)         | 215 8.0                                         | 725 2.1                                         | 3714 0.3                                        |
| Antidepressants (N06A)        | 755 28.2                                        | 4409 12.8                                       | 28,335 2.2                                       |
| Psychostimulants (N06B)       | 88 3.3                                          | 328 1.0                                         | 1118 0.1                                        |
| Anxiolytics, sedatives (N05B, N05C)<0.001 | 436 16.3 | 1429 4.1 | 6049 0.5 | <0.001 |
| Mild anxiolytics, sedatives and antiemetics<sup>c</sup> | 366 13.7 | 2516 7.3 | 26,938 2.1 | <0.001 |

<sup>a</sup> Includes all pregnant women during the study period who have not used antipsychotics during pregnancy, including those from the control group “antipsychotics before or after but not during pregnancy”. However, these women were extracted from the group in the statistical analysis of the heterogeneity between the groups.

<sup>b</sup> Chi²: A comparison between women using antipsychotics during pregnancy, women who used antipsychotics before or after but not during the actual pregnancy and women who have never used antipsychotics.

<sup>c</sup> Including promethazine (R06AD02, R06AD52), alimemazine (R06AD01), dixyrazine (N05A B01), prochlorperazine (N05A B04) and melperone (N05A D03)
associated with GDM, and smoking was negatively associated with GDM. Women treated with HR S-GAs had a significantly increased risk for GDM also when compared with women treated with antipsychotics before and/or after but not during the actual pregnancy. An analysis without adjustment for BMI gave an adjusted RR for GDM of 1.6 (95% CI 1.0–2.5) for women treated with F-GAs, 2.0 (95% CI 1.5–2.7) for women treated with HR S-GAs and 1.5 (95% CI 0.9–2.5) for women treated with other S-GAs when compared with the women not treated during pregnancy. The association between antipsychotic use and GDM was also studied separately in BMI strata. The adjusted RR for GDM for women treated with HR S-GAs compared to women not treated during pregnancy in normal weight women (BMI <25) was 1.3 (95% CI 0.5–3.6), in overweight women (BMI 25–30) was 2.4 (95% CI 1.4–3.9) and in obese women (BMI >30) was 1.4 (95% CI 0.9–2.2). Even though the BMI-strata-specific RRs for GDM differed, no significant heterogeneity was detected between the strata (p = 0.298). The risk for GDM was not increased after use of HR SGAs in late pregnancy compared to early pregnancy only, adjusted RR 1.3 (95% CI 0.7–2.3), p = 0.345.

The risk for the child being LGA was increased for women treated with HR S-GAs, both when compared with women not treated during pregnancy and when compared with women treated with antipsychotics before and/or after but not during pregnancy. The risk for the child being SGA was not increased after use of any group of antipsychotics after adjustment for age, parity, smoking and BMI (Tables 2, 3). Adjustment for concomitant medication with other psychotropic drugs listed in Table 1 altered the risk estimates for GDM, SGA and LGA only marginally.

### 3.3 Other Pregnancy Outcomes

The risk of moderate to late prematurity (gestational age 32 to 36+6 weeks) was increased for women treated with antipsychotics, when compared with both women not treated during pregnancy and with the comparison group of women treated with antipsychotics before or after but not during the actual pregnancy. The risk of caesarean section, both emergency and planned, was increased compared with women not treated during pregnancy but only marginally increased when compared with the comparison group. The risks for pre-eclampsia and perinatal death were not increased after antipsychotic use during pregnancy (Table 4).

### 4 Discussion

#### 4.1 Key Results

Treatment with the HR S-GAs clozapine, quetiapine and olanzapine during pregnancy was associated with increased risks of GDM and the child being LGA. The other S-GAs did not share this same metabolic risk increase, possibly explained by the high percentage of women treated with aripiprazole in that group. The crude risk for the child being SGA was also increased for the HR S-GA group, but the risk increase was not significant after adjustment for maternal factors. This might be explained by the high frequency of smokers in this group, as smoking is known to be strongly connected to intrauterine growth restriction [46].

The adjusted model where BMI was not adjusted for showed higher relative risks for GDM in women in all exposure groups compared with when BMI was adjusted for. Most S-GAs have weight gain as a common side effect and the risk for GDM is known to increase with increased BMI. Maternal BMI is therefore most likely mediating this correlation [33, 47]. However, as patients with severe psychiatric diagnoses tend to have increased BMI regardless of medication, BMI is
Use of Antipsychotics in Pregnancy and Risk for Gestational Diabetes

also a confounder for the studied correlation [48]. In this study, BMI is adjusted for, as not doing so would over-estimate the association between the drug treatment and the outcome. This study shows a significant risk increase for GDM even after adjustment for BMI, which other studies with smaller sample sizes have not been able to demonstrate [10, 33, 34].

The stratification by BMI in this study showed similar tendencies as were found previously [33], with a higher risk increase for GDM in overweight women treated with antipsychotics than in normal weight and obese women. However, the CIs for the risk estimates were wide and the difference between the strata was not statistically significant. It would have also been hard to explain why this would be the case from a biological standpoint.

This study also confirmed the slightly increased risk for prematurity suggested by previous studies [37, 49–52]. There is probably an effect of the underlying disease and lifestyle factors behind the association seen between an increased risk for moderate to late prematurity. The frequency of moderate to late prematurity was also increased amongst the women treated with antipsychotics before or after but not during the actual pregnancy. This is in line with the results of a study on antipsychotic use during pregnancy with a sibling analysis [53]. The risk increase for caesarean sections was clearly decreased when the women treated with antipsychotics were compared with the control group of women treated with antipsychotics before or after but not during the pregnancy. This suggests

### Table 2

| Outcomes                  | Use vs no use during pregnancy | Use during pregnancy vs use before/after pregnancy |
|---------------------------|--------------------------------|---------------------------------------------------|
|                           | Crude RR 95% CI | Adjusted RR 95% CI | Crude RR 95% CI | Adjusted RR 95% CI |
| F-GAs Gestational diabetes| 1.86 1.17–2.93 1.34 | 0.86–2.08 1.65 | 1.05–2.58 1.24 | 0.80–1.93 |
| Small for gestational age | 1.58 1.09–2.28 1.25 | 0.86–1.80 1.42 | 0.98–2.04 1.20 | 0.83–1.73 |
| Large for gestational age | 0.82 0.53–1.25 0.79 | 0.52–1.21 0.72 | 0.47–1.10 0.70 | 0.46–1.06 |
| High metabolic risk S-GAs | 2.16 1.59–2.92 1.77 | 1.33–2.37 1.83 | 1.35–2.48 1.62 | 1.20–2.12 |
| Small for gestational age | 1.57 1.23–2.02 1.23 | 0.96–1.57 1.38 | 1.07–1.77 1.17 | 0.91–1.50 |
| Large for gestational age | 1.53 1.23–1.98 1.58 | 1.28–1.96 1.29 | 1.04–1.61 1.32 | 1.06–1.63 |

BMI body mass index, CI confidence interval, F-GAs first-generation antipsychotics, RR risk ratio, S-GAs second-generation antipsychotics

**a** All women not using antipsychotics during pregnancy. Sum of women who never used antipsychotics and women who used before/after but not during pregnancy

**b** Adjusted for maternal age, parity, BMI and smoking

### Table 3

| Outcomes                  | F-GAs (n = 728) | HR S-GAs (n = 1710) | Other S-GAs (n = 541) | Use of any antipsychotic before/after pregnancy (n = 34,492) | No antipsychotic use during pregnancy (n = 1,296,539) |
|---------------------------|-----------------|---------------------|-----------------------|-------------------------------------------------------------|--------------------------------------------------|
|                           | n %             | n %                 | n %                   | n %                                                         | n %                                              |
| Gestational diabetes      | 21 2.9          | 49 2.9              | 14 2.6                | 493 1.4                                                     | 15,464 1.2                                      |
| Small for gestational age | 30 4.1          | 66 3.9              | 17 3.1                | 929 2.7                                                     | 30,102 2.3                                     |
| Large for gestational age | 22 3.0          | 85 5.0              | 26 4.8                | 1410 4.1                                                    | 41,873 3.2                                     |

F-GAs first-generation antipsychotics, HR S-GAs high metabolic risk second-generation antipsychotics, S-GAs second-generation antipsychotics

**a** All women not using antipsychotics during pregnancy. Sum of women who never used antipsychotics and women who used before/after but not during pregnancy
### Table 4 Pregnancy outcomes after use of any antipsychotics during pregnancy

| Outcomes                          | Use vs no use during pregnancy | Use during pregnancy vs use before/after pregnancy |
|-----------------------------------|--------------------------------|---------------------------------------------------|
|                                   | n %                            | n %                                               |
|                                   | Crude RR 95% CI                | Adjusted RRb 95% CI                               |
|                                   | Crude RR 95% CI                | Adjusted RRb 95% CI                               |
| Pre-eclampsia                     | 25 0.9                         | 10,691 0.8                                       |
| No pre-eclampsia                 | 2652 99.1                      | 1,285,848 99.2                                   |
| Caesarean section                | 687 25.7                       | 213,764 16.4                                     |
| Planned                          | 310 11.6                       | 92,445 7.1                                       |
| Emergency                        | 377 14.1                       | 121,319 9.3                                      |
| Vaginal birth                    | 1990 74.3                      | 1,082,775 83.5                                   |
| Gestational age, weeks           |                                |                                                   |
| < 32                             | 31 1.3                         | 9970 0.8                                         |
| 32–36                            | 227 8.5                        | 51,884 4.0                                       |
| 37–41                            | 2268 84.7                      | 1,146,409 88.4                                   |
| ≥ 42                             | 151 5.6                        | 88,273 6.8                                       |
| Perinatal death                  | 16 0.6                         | 5219 0.4                                         |
| Perinatal survival               | 2661 99.4                      | 1,291,320 99.6                                   |

**BMI** body mass index, **CI** confidence interval, **RR** risk ratio

*All women not using antipsychotics during pregnancy. Sum of women who never used antipsychotics and women who used before/after but not during pregnancy

*Adjusted for maternal age, parity, BMI, and smoking*
that the increased risk for caesarean section might not necessarily be associated with the medication itself, but the underlying disease and its associated risks, and lifestyle factors.

4.2 Strengths and Limitations

The nationwide health registers used in this study have a 98% coverage of pregnancies in Sweden. Therefore, studies like this have strengths such as completeness of data, almost no sampling bias and large sample sizes. However, a methodological limitation for pharmacoepidemiologic studies is basing the exposure variable only on filed drug prescriptions, therefore not reporting the actual drug intake and excluding drugs prescribed in hospitals. The latter one is most likely not a significant source of bias when it comes to antipsychotics, as they are rarely used solely in hospitals without a following prescription for continuous use after discharge. The current project did not have access to information on the duration of drug treatment and the drug dosage. Therefore, register-based studies, such as this, lack the ability to study whether the risks of developing the studied outcomes are dose dependent.

As the information on drug use inherits some uncertainty, some women might have been erroneously misclassified to the wrong exposure group in this study. Some women could have used previously purchased drugs during pregnancy and thus been erroneously classified as non-exposed, whereas some women who purchased the drugs may not have used them during pregnancy. As information on drug use was recorded before the pregnancy outcome was known, the misclassification is unbiased by pregnancy outcome, and therefore unlikely to seriously bias the results.

Another common limitation to register-based studies is how to control for the severity of the underlying disease and its associated lifestyle and psychosocial factors. One of the strengths of this study is addressing this issue by having a comparison group of women with prescriptions of antipsychotics before and/or after but not during the pregnancy. The risk for GDM varies widely internationally. The absolute risk of GDM in this study is low in all groups, 1.2% in the untreated women and 2.9% in women treated with HR S-GAs. Other studies from both Europe and the USA have presented a prevalence of GDM of 5–25% both in women with and without treatment with antipsychotics [15, 19, 30]. One explanation for this large variation is the different definitions and diagnostic thresholds used for the diagnosis of GDM [15]. In Sweden, there was a lack of consensus regarding screening for GDM until 2015 when the national guidelines were published, meaning that women with GDM might have gone undiagnosed [28, 29, 54, 55]. However, the low screening rates should not affect the generalizability of the results of this study as the potential misclassification by underdiagnosis of GDM should be similar across the different exposure groups. This hypothesis is reinforced by the similar studies from the USA and Finland leading to similar results to this study [19, 30].

5 Conclusions

Use of quetiapine, olanzapine and clozapine during pregnancy is associated with an increased risk of GDM and the child being LGA. Use of any antipsychotic during pregnancy was associated with slightly increased risks of moderate to late prematurity and caesarean section. These risk increases might be caused by underlying factors rather than the medication itself. We recommend screening for GDM in women treated with quetiapine, olanzapine or clozapine, but not discontinuation of treatment. In the case of starting a new antipsychotic treatment in pregnancy or, preferably, before a planned pregnancy, some other antipsychotic might be considered to avoid these metabolic risks.

Declarations

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**Conflict of interest** EH, LF, UN, KW and KK declare that they have no competing interests.

**Ethics approval** The study was approved by the Regional Ethical Review Board in Lund (dnr. 2013/342-31/5).

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Availability of data and material** Data from the Swedish registers are protected, but some aggregated data can be available on request from the authors.

**Code availability** Not applicable.

**Author contributions** KK conceptualized and designed the study, was responsible for the data collection, carried out the initial analyses, and reviewed and revised the manuscript. EH conceptualized and designed the study and drafted the initial manuscript. UN, LF and KW conceptualized and designed the study and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work outlined in the manuscript.

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