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Antipsychotic continuation during pregnancy and risk of postpartum relapse in women with schizophrenia: nationwide register-based study

Sunghyuk Kang, Ji Su Yang, Bo Hyon Yun, Bizu Gelaye, Suk Kyoon An and Sun Jae Jung

Background

Women with schizophrenia frequently discontinue antipsychotic medications during pregnancy. However, evidence on the risk of postpartum relapse associated with antipsychotic use during pregnancy is lacking.

Aims

To investigate the within-individual association between antipsychotic continuation during pregnancy and postpartum relapse in women with schizophrenia.

Method

This retrospective cohort study used data of women with schizophrenia who gave live birth between 2007 and 2018 identified from the National Health Information Database of South Korea. Women were classified according to antipsychotic use patterns during the 12 months before delivery as non-users, discontinuers and continuers. Relapse was defined as admission for psychosis (ICD-10, F20–29). The incidence rate ratio (IRR) for admission for psychosis in the 6-month postpartum period was estimated using conditional Poisson regression, with the reference period set between 2 and 1 years before delivery. Additionally, we calculated the relative risk ratios (RRRs) for the IRRs of different antipsychotic use patterns.

Results

Among the 3026 women included in the analysis (median age 34 years, interquartile range 31–37), the within-individual risk of admission for psychosis in the 6-month postpartum period was 0.56 times (RRR, 95% CI 0.36–0.87) lower in continuers (IRR = 1.31, 95% CI 0.89–1.72) than in discontinuers (IRR = 2.34, 95% CI 1.87–2.91). Among discontinuers, the IRRs of admission for psychosis in the 6-month postpartum period did not change significantly with the timing of discontinuation (trend $P = 0.946$).

Conclusions

Antipsychotic continuation during pregnancy was associated with a reduced risk of postpartum relapse in women with schizophrenia. Continuing antipsychotics during pregnancy would be recommended after a risk–benefit assessment.

Keywords

Schizophrenia; pregnancy; antipsychotic agents.

Pregnancy and childbirth pose significant challenges for women with schizophrenia. Women with schizophrenia have a fertility rate less than half that of the general population and experience a higher rate of obstetric complications.[1–3] Particularly in the postpartum period, where individuals without a pre-existing illness often develop psychotic symptoms, it has been suggested that the risk of psychiatric admission is increased in those with schizophrenia.[4] The recurrence of psychotic symptoms after delivery may lead to difficulties in mother–infant bonding, disruptions to the family environment and even infanticide.[5,6] Accordingly, a number of pharmacological treatment guidelines for schizophrenia recommend that antipsychotic medications not be stopped during pregnancy.[7–9] Nevertheless, the majority of pregnant women discontinue their antipsychotics during pregnancy, possibly owing to concerns regarding the teratogenic effects of *in utero* exposure to antipsychotics.[10] However, recent large-scale epidemiological studies conducted across five Nordic countries and the USA found no significant association between *in utero* antipsychotic exposure and an increased risk of congenital malformations.[11,12] Therefore, considering the perspective of a risk–benefit decision, antipsychotic continuation during pregnancy would be more strongly recommended for women with schizophrenia. Evidence of the 'benefits' of antipsychotic continuation, including its effectiveness in preventing postpartum relapse in women with schizophrenia, is limited. However, in a UK study analysing mental healthcare data on 234 women with non-affective psychosis, the association between taking psychotropic medication (medication exposure) during the third trimester and relapse in the 3-month postpartum period was inconclusive (exposed versus unexposed, odds ratio OR = 1.25, 95% CI 0.63–2.45).[13] Since ethical considerations preclude controlled trials involving pregnant women, a retrospective study utilising health insurance claims data may help investigate the association between antipsychotic use during pregnancy and the risk of postpartum relapse of psychosis. Therefore, we aimed to investigate the association between antipsychotic continuation and postpartum relapse risk in women with schizophrenia using nationwide Korean register-based data. Additionally, we investigated the risk of postpartum relapse stratified by the timing of antipsychotic discontinuation.

Method

Data source

We collected data from the National Health Information Database (NHID) of South Korea (application number NHIS-2024-1-067). The NHID is a nationwide health information database of the National Health Insurance Service, the single provider of mandatory health insurance for the entire South Korean population.[14] The NHID contains sociodemographic details about insurance qualifications, ICD-10 codes for in-patient and out-patient care, information on prescribed medications and mortality information.

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human patients were approved by the Institutional Review Board of Yonsei University (YUIRB-Y-2020-0043). Informed consent was waived because of the retrospective observational nature of the study using registered and de-identified data.

Study population

We identified 160 178 women aged ≥18 years with schizophrenia from the NHID between 2007 and 2018. Schizophrenia was defined based on the following criteria: ≥1 hospital admissions with the main discharge ICD-10 code of F20 or F25; or ≥2 out-patient visits with the main ICD-10 codes of F20 or F25. We identified women who delivered live births after their first diagnosis of schizophrenia ($n = 3890$), defined based on ICD-10 codes (O80–84, Z370, Z372, Z373, Z375 and Z376) and considered the delivery to have occurred on the start date of the claims records where the delivery was recorded. Of these, we identified women who had a live birth delivery that gave a 2-year study period between first diagnosis of schizophrenia and delivery ($n = 3029$). We performed this selection process to establish the reference period (1–2 years before delivery) required to estimate the risks of the outcome in within-individual analyses. A '2-year study period prior to delivery' implies that the first main diagnosis record for schizophrenia preceded the time point of 2 years before delivery, and no other live birth deliveries occurred during this 2-year study period. If a woman had multiple live births that met the criteria, only the first live birth delivery was included. We excluded women aged >50 years at the time of delivery ($n = 3$), which left 3026 live births of 3026 women with schizophrenia for analysis (Supplementary Fig. 1 available at https://doi.org/10.1192/bjp.2024.247).

Self-controlled case series

To deal with the limitations of the claims data, wherein several potential confounders, such as the severity of schizophrenia, are difficult to measure, we adopted the self-controlled case series (SCCS) method.[15] The SCCS is a case-only epidemiological study design that utilises individuals as their own controls, making it a suitable approach to investigate associations between transient exposures and acute outcomes. The incidence of the outcome within the period of interest is compared with the incidence of the outcome in the reference period. It offers the advantage of automatically adjusting for all fixed confounders, as this method compares different periods for the same person.

We used the SCCS with transient exposure for delivery and the acute outcome of admission for psychosis. We set the reference period from 2 years before delivery to 1 year before delivery. To estimate postpartum relapse risk, we calculated the incidence rate ratio (IRR) by comparing the incidence rate of admission for psychosis in the 6-month postpartum period (+1 day to +6 months from the date of delivery)[16] with the incidence rate of admission in the reference period (Fig. 1(a)). Additionally, we compared the incidence rates around delivery with those in the reference period.[17]

Exposure

We constructed the antipsychotic use episodes of the included women from the NHID (for the list of included antipsychotics, see Supplementary Table 1). The NHID contains information on prescribed medications from both in-patient and out-patient care, including the prescription date and duration. We assumed that the individuals began using their prescribed medications on the prescription date and continued taking them daily for the specified duration. When there was an overlap between discrete prescriptions of antipsychotics, we merged them to create a single episode of antipsychotic use.

We categorised the included women into three distinct groups based on their antipsychotic use patterns in the 12 months preceding delivery: non-users, discontinuers and continuers (Fig. 1(b)). We defined 'non-users' as women who did not use antipsychotics in the period from 1 year before delivery to 39 weeks before delivery. Given that 39 weeks before delivery is the optimal estimate for the beginning of pregnancy in a register-based study,[18] 'non-users' can be considered as those who abstained from antipsychotic use before becoming pregnant. We further categorised women who used antipsychotics during this period as either 'discontinuers' or 'continuers' based on whether they discontinued antipsychotic use before the date of delivery. If a woman began antipsychotic use within 30 days of the end of a prior antipsychotic episode, it was regarded as a continuation of the same antipsychotic episode (30-day grace period).

Outcome

The outcome of this study was admission for psychosis, defined as an admission of more than 2 days with a main discharge code of F20–29. This definition has been commonly used to capture schizophrenia relapses in epidemiological studies utilising claims data.[19,20] To account for the continuity of episodes, admissions for psychosis within 30 days of discharge from a previous admission for psychosis were disregarded and considered an extension of the previous admission.

Other variables

Household income was assessed based on medical insurance premium payments in the year of delivery and categorised as follows: medical aid (for socioeconomically disadvantaged individuals who do not pay insurance premiums): first quartile Q1 (lowest), Q2, Q3 and Q4 (highest). Residential regions were classified into metropolitan, urban and rural. The mode of delivery – vaginal delivery or Caesarean section – was determined by the procedure code in the claims record. Prenatal care was defined as an out-patient visit with ICD-10 codes Z321 and Z33–36 within 1 year prior to delivery.

Women with comorbid mood disorders were defined as those diagnosed with schizoaffective disorder (ICD-10, F25), depressive disorder or bipolar disorder, defined from the first diagnosis of schizophrenia to 2 years before delivery (prior to the reference period). Comorbid depressive disorders were identified using ICD-10 codes F32–33 or consecutive antidepressant use for ≥90 days. Comorbid bipolar disorder was identified using ICD-10 codes F30–31 or consecutive mood stabiliser use for ≥90 days. The construction of medication episodes for antidepressants and mood stabilisers followed the same method used for antipsychotics (for the lists of antidepressants and mood stabilisers, see Supplementary Table 1).

Statistical analyses

The general characteristics of the included women were presented as frequency and percentage for categorical variables and median and interquartile range (IQR) for continuous variables. These variables were compared by antipsychotic use patterns using the chi-squared test for categorical variables and the Kruskal–Wallis test for continuous variables. The incidence rates of admission for psychosis in the periods around delivery were calculated as the number of admissions per 1000 person-years in the respective

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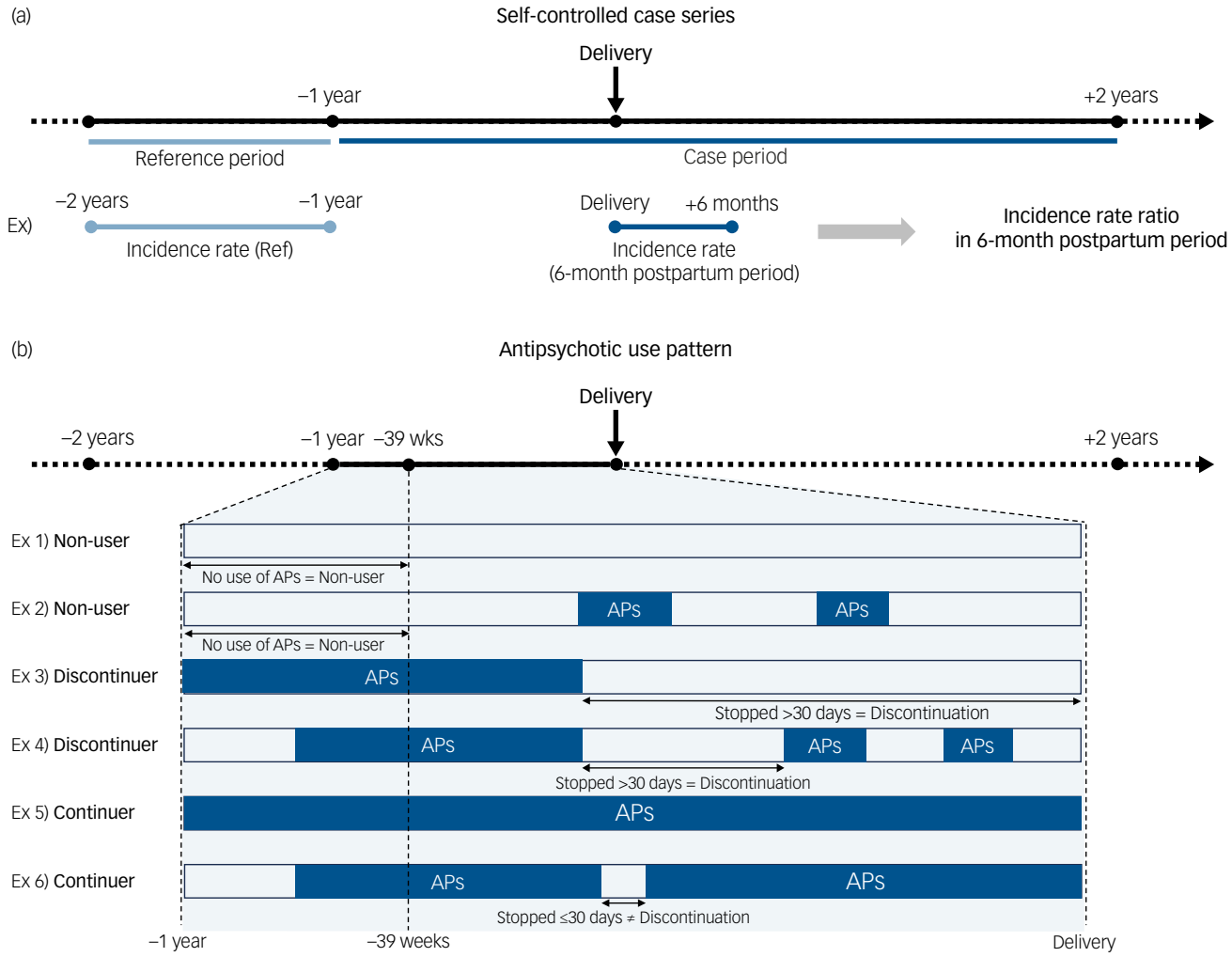

Fig. 1 Study design.

(a) Self-controlled case series. We estimated the incidence rate ratios of admission for psychosis during periods surrounding delivery compared with the incidence rate of admission for psychosis in the reference period (–2 years to –1 year from delivery). (b) Antipsychotic use pattern. Non-user, no antipsychotic use from 1 year to 39 weeks before delivery; discontinuer, antipsychotic use from 1 year to 39 weeks before delivery but discontinued antipsychotics before delivery; continuer, antipsychotic use from 1 year to 39 weeks before delivery and no discontinuation of antipsychotics before delivery; APs, antipsychotics; Ex, example.

period. After delivery, women were followed up for 2 years or until death, a subsequent live birth or 31 December 2018, whichever came first. Beyond the end of follow-up, women no longer contributed to the incidence of outcome. By comparing the incidence rate in the case period surrounding delivery with the incidence rate in the reference period, the IRRs and 95% CIs were estimated using the conditional Poisson regression model.[21] As the women in the analyses served as their own controls, we did not adjust for other variables in the model. We calculated the relative risk ratios (RRRs) for the IRRs of non-users and continuers relative to the IRR of discontinuers. The 95% CIs for the RRRs were estimated using the interaction term of the period variable (coded as case period, 1; reference period, 0) and the variable for the antipsychotic use pattern (coded as non-users or continuers, 1; discontinuers, 0) in the conditional Poisson regression model. Additionally, we conducted subgroup analyses stratified by the age at delivery, insurance premiums, mode of delivery, number of prenatal care visits, and diagnosis of schizoaffective disorder, comorbid depressive disorders and comorbid mood disorders. Variables for the subgroup analyses were selected based on their association with the risk of postpartum relapse in schizophrenia from previous studies.[22,23]

We performed six sensitivity analyses to robustly confirm the associations between antipsychotic use patterns and postpartum relapse. First, we excluded admissions with antidepressant use exceeding 2 days or mood stabiliser use exceeding 2 days from the outcomes. This analysis aimed to emphasise the postpartum recurrence of psychotic symptoms in schizophrenia rather than postpartum mood episodes. Second, we repeated the analyses with the reference period set as the period from 3 to 2 years before delivery. Third, we excluded women who had been admitted for psychosis within 1 year before delivery. In-patient treatment during this period would not only maintain the antipsychotic treatment during and after admission but also reduce the risk of relapse through non-pharmacological interventions (e.g. family therapy and cognitive–behavioural therapy).[24] Fourth, we restricted the analysis to women who used antipsychotics for ≥28 days within the 13 weeks before delivery. In this analysis, the difference in the risk of postpartum relapse between the discontinuers and continuers could not be interpreted solely as a difference in antipsychotic use just before delivery. Fifth, we repeated the analyses by changing the length of the grace period for antipsychotic discontinuation to 14 or 60 days. Last, to reduce uncertainty regarding the date of

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delivery, we excluded women who were admitted for more than 7 days for a live birth delivery.

To investigate whether the risk of postpartum relapse differs according to the timing of antipsychotic discontinuation, we stratified the analyses into four groups among discontinuers, according to the time point of antipsychotic discontinuation: −1 year to −39 weeks, −39 to −26 weeks, −26 to −13 weeks, and −13 weeks to −1 day (with the date of delivery as the fiducial time point). We examined the linear tendency of IRRs across these groups using a variable coded from 1 to 4, representing each group's time point of antipsychotic discontinuation. All analyses were performed using SAS 9.4 and R version 4.0.3 for Windows.

Results

In total, 3026 women with schizophrenia who delivered a live birth were included, with a median age of 34 years (IQR: 31–37 years) at delivery, classified into 1303 (43.1%) non-users of antipsychotics, 1260 (41.6%) discontinuers and 463 (15.3%) continuers. Among discontinuers, the proportion who used antipsychotics within 1 year before delivery mainly decreased during the period from 39 to 26 weeks before delivery (Supplementary Fig. 2). The mean follow-up period after delivery was 1.74 years (1.71, 1.77 and 1.74 years for non-users, discontinuers and continuers respectively) during the 2-year follow-up period. Among the 3026 included women, 9.3% (280/3026) were admitted for psychosis in the 6-month postpartum period. Stratified by antipsychotic use pattern, 5.9% of non-users (77/1303), 12.9% of discontinuers (162/1260) and 8.9% of continuers (41/463) were admitted for psychosis in this period. The general characteristics of the women by antipsychotic use patterns are shown in Supplementary Table 2.

Risk of postpartum relapse in the entire study population

Among the 3026 women, 255 admissions for psychosis occurred during the reference period and 290 occurred during the 6-month postpartum period. The incidence rates of admission for psychosis were 84.3 per 1000 person-years in the reference period and 200.5 per 1000 person-years in the 6-month postpartum period. Hence, the estimated IRR of admission for psychosis in the 6-month postpartum period was 2.35 (95% CI 1.99–2.78). The IRR of admission for psychosis was highest immediately after delivery (1–10 days after delivery; IRR = 5.44, 95% CI 3.87–7.65) and gradually decreased to a level similar to the risk in the reference period (1–2 years after delivery: IRR = 0.97, 95% CI 0.80–1.18) (Supplementary Fig. 3).

Risk of postpartum relapse by antipsychotic use patterns

The numbers of admissions for psychosis during the reference period among non-users, discontinuers and continuers were 39, 149, and 67 respectively (incidence rates: 29.9, 118.3 and 144.7 per 1000 person-years respectively). The numbers of admissions for psychosis during the 6-month postpartum period among non-users, discontinuers and continuers were 80, 168, and 42 respectively (incidence rates: 128.5, 277.9 and 191.3 per 1000 person-years respectively).

In all three groups, the IRR of admission for psychosis peaked immediately after delivery and gradually fell (Supplementary Table 3). Non-users showed an IRR of 9.36 (95% CI 4.67–18.8) in the first 10 days after delivery, and they had a high risk until the end of the 6-month postpartum period (90–180 days after delivery, IRR = 3.06, 95% CI 1.89–4.95). Discontinuers showed a generally similar pattern to non-users but had an overall lower risk (1–10 days after delivery, IRR = 5.14, 95% CI 3.26–8.12; 90–180 days after delivery, IRR = 1.74, 95% CI 1.29–2.34). Continuers had a high risk in the first 10 days (1–10 days after delivery, IRR = 3.81, 95% CI 1.75–8.31), but their risk then rapidly decreased to a level similar to that in the reference period.

The IRR in the 6-month postpartum period among non-users was significantly higher than the IRR in that period among discontinuers (non-users *v.* discontinuers, IRR = 4.18, 95% CI 2.85–6.12 *v.* IRR = 2.34, 95% 1.87–2.91; RRR = 1.79, 95% 1.15–2.78). Moreover, the IRR in the 6-month postpartum period among continuers was significantly lower than the IRR in that period among discontinuers (continuers *v.* discontinuers, IRR = 1.31, 95% CI 0.89–1.92 *v.* IRR = 2.34, 95% CI 1.87–2.91; RRR = 0.56, 95% CI 0.36–0.87) (Fig. 2).

In the subgroup analyses, continuers generally showed a lower risk of postpartum relapse than discontinuers (Supplementary Fig. 4). The associations between antipsychotic continuation and postpartum relapse in the sensitivity analyses remained generally significant, as in the main analysis (Fig. 3). First, when excluding admissions with antidepressant or mood stabiliser use from the outcomes, the RRR of continuers to discontinuers was similar to that in the main analysis (RRR = 0.56, 95% CI 0.33–0.97). Second, the RRR of continuers to discontinuers was 0.55 (95% CI 0.34–0.90) when the reference period was the period from 3 to 2 years before delivery. Third, excluding 221 women admitted for psychosis in the period of antipsychotic use pattern ascertainment (within 1 year before delivery), the RRR of continuers to discontinuers was 0.56 (95% CI 0.33–0.95). Fourth, analysing 893 women who used antipsychotics ≥30 days within 13 weeks before delivery, the RRR of continuers to discontinuers was 0.56 (95% CI 0.31–0.98). Fifth, in sensitivity analyses with other lengths of the grace period for antipsychotic discontinuation, the RRRs of continuers to discontinuers were generally consistent with the main analysis, although these associations were not significant (14 days, RRR = 0.60, 95% CI 0.34–1.05; 60 days, RRR = 0.66, 95% CI 0.44–1.00). Lastly, when excluding 376 women admitted for live birth delivery for ≥7 days, the RRR of continuers to discontinuers was 0.57 (95% CI 0.35–0.93).

Risk of postpartum relapse by timing of antipsychotic discontinuation among discontinuers

We further stratified the analysis of discontinuers by the time point of antipsychotic discontinuation: −1 year to −39 weeks ($n = 468$), −39 to −26 weeks ($n = 625$), −26 to −13 weeks ($n = 124$) and −13 weeks to date of delivery ($n = 43$). The IRRs of admission for psychosis in the 6-month postpartum period did not differ by the timing of antipsychotic discontinuation (IRR = 2.28, 95% CI 1.58–3.31, IRR = 2.41, 95% CI 1.76–3.30, IRR = 2.34, 95% CI 1.15–4.76 and IRR = 2.03, 95% CI 0.76–5.40 respectively) (Fig. 4, Supplementary Table 4). Additionally, we did not find a linear trend in the postpartum relapse risks according to the timing of antipsychotic discontinuation (trend $P = 0.946$).

Discussion

In this nationwide study analysing data on 3026 women with schizophrenia who had a live birth delivery, an increase in relapse risk was observed in the postpartum period, exhibiting a peak-and-decline pattern. To disentangle the strands of this increased risk of postpartum relapse based on antipsychotic use during pregnancy, the risk was 0.56 times lower in 'continuers' (women who continued their antipsychotics during the 1 year before delivery) compared with 'discontinuers' (women who discontinued their antipsychotics in that period). The difference in the risk of postpartum relapse between these groups was generally consistent across several subgroup and sensitivity analyses. Additionally,

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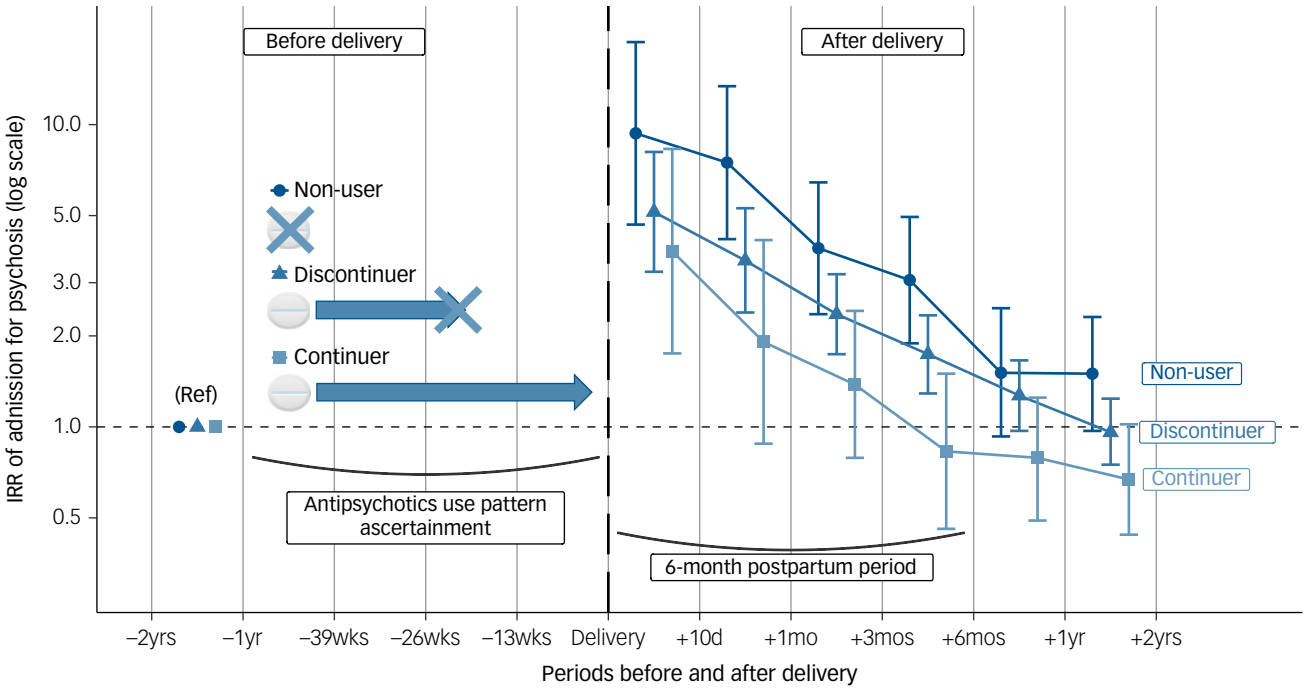

Antipsychotic use pattern before delivery	No.	Incidence rates of admission for psychosis (/1000 per year)		IRR of admission for psychosis in 6-month postpartum period (95% CI)	Relative risk ratios for IRR in 6-month postpartum period (95% CI)
		Reference period	Six-month postpartum period		
Non-user	1303	29.9	128.5	4.18 (2.85–6.12)	1.79 (1.15–2.78)
Discontinuer	1260	118.3	277.9	2.34 (1.87–2.91)	1.00 (Ref.)
Continuer	463	144.7	191.3	1.31 (0.89–1.92)	0.56 (0.36–0.87)

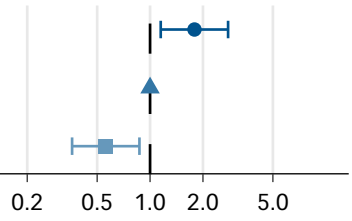

Fig. 2 Risk of admission for psychosis surrounding delivery by antipsychotic use pattern.

With the period from 2 years to 1 year before delivery as the reference, the incidence rate ratio (IRR) of admission for psychosis in each period was estimated using conditional Poisson regression analyses. Non-user, no antipsychotic use from 1 year to 39 weeks before delivery; discontinuer, antipsychotic use from 1 year to 39 weeks before delivery but discontinued antipsychotics before delivery; continuer, antipsychotic use from 1 year to 39 weeks before delivery and no discontinuation of antipsychotics before delivery.

among the discontinuers, the risk of postpartum relapse did not differ according to the timing of antipsychotic discontinuation.

Within-individual risk of postpartum relapse

We adopted a within-individual design that compared incidence of relapse during the postpartum period with the incidence of relapse before pregnancy, essentially the baseline frequency of schizophrenia episodes. This design is necessary because physicians are more likely to prescribe antipsychotics continuously during pregnancy for patients with more severe illness who are expected to relapse. The incidence rate of relapse was higher among continuers than among discontinuers in the reference period, but lower among continuers than among discontinuers in the 6-month postpartum period (reference period, continuers versus discontinuers: 144.7 per 1000 person-years *v.* 118.3; 6-month postpartum period, continuers versus discontinuers: 191.3 *v.* 277.9). If continuers and discontinuers had the same levels of incidence rates in the reference period, the difference in incidence rates in the postpartum period would be larger. Consequently, the RRR of 0.56 can be interpreted as the effect size of antipsychotic continuation, obtained after controlling for the pre-pregnancy severity of schizophrenia.

Antipsychotic continuation throughout pregnancy

The risk of postpartum relapse did not decrease as the time of antipsychotic discontinuation approached delivery. In our sensitivity analysis that included women who used antipsychotics within the 13 weeks before delivery, the risk of postpartum relapse among discontinuers was not lower than in the main analysis. This sensitivity analysis implies that for women who once discontinued antipsychotics during pregnancy, the risk of postpartum relapse may not change whether or not they restarted antipsychotics. Overall, these results suggest that continuing antipsychotics throughout pregnancy, rather than administering them close to delivery, is more important in preventing postpartum relapse in women with schizophrenia. This interpretation is in line with a previous study that investigated the association between exposure to psychotropic medication in the third trimester and 3-month postpartum relapse, which also yielded inconclusive results.[13]

Postpartum relapse and bipolar disorder

Acute psychotic symptoms after delivery can occur in women with schizophrenia and in those without schizophrenia (postpartum psychosis). Women with postpartum psychosis frequently present

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Sensitivity analyses	Antipsychotics use pattern	No.	IRR of admission for psychosis in 6-month postpartum period (95% CI)	Relative risk ratios for IRR in 6-month postpartum period (95% CI)
1. Excluding admission with antidepressant use or mood stabiliser use from the outcome	Non-user	1303	4.68 (2.95 – 7.41)	2.05 (1.21–3.50)
	Discontinuer	1260	2.28 (1.74 – 2.98)	1.00 (Ref.)
	Continuer	463	1.29 (0.81 – 2.04)	0.56 (0.33–0.97)
2. Reference period as the period from 3 years before delivery to 2 years before delivery	Non-user	1025	3.60 (2.33 – 5.56)	1.77 (1.08–2.90)
	Discontinuer	996	2.04 (1.60 – 2.59)	1.00 (Ref.)
	Continuer	401	1.12 (0.73 – 1.71)	0.55 (0.34–0.90)
3. Excluding women having outcomes in the period from 1 year before delivery to the date of delivery	Non-user	1271	4.50 (2.98 – 6.78)	1.70 (1.04–2.77)
	Discontinuer	1111	2.65 (2.04 – 3.44)	1.00 (Ref.)
	Continuer	423	1.49 (0.94 – 2.34)	0.56 (0.33–0.95)
4. Women who used antipsychotics ≥30 days in the period from 13 weeks before delivery to the date of delivery	Non-user	56	2.05 (0.77 – 5.48)	0.87 (0.30–2.54)
	Discontinuer	374	2.35 (1.55 – 3.57)	1.00 (Ref.)
	Continuer	463	1.31 (0.89 – 1.92)	0.56 (0.31–0.98)
5. Sensitivity analyses by grace period of antipsychotics use				
14 days	Non-user	1303	4.18 (2.85 – 6.12)	1.93 (1.25–2.98)
	Discontinuer	1410	2.17 (1.76 – 2.66)	1.00 (Ref.)
	Continuer	313	1.30 (0.77 – 2.19)	0.60 (0.34–1.05)
60 days	Non-user	1303	4.18 (2.85 – 6.12)	1.81 (1.16–2.83)
	Discontinuer	1106	2.31 (1.83 – 2.91)	1.00 (Ref.)
	Continuer	617	1.53 (1.09 – 2.14)	0.66 (0.44–1.00)
6. Excluding women who were admitted >7 days for live-birth delivery	Non-user	1174	4.25 (2.84 – 6.36)	1.79 (1.12–2.87)
	Discontinuer	1076	2.37 (1.85 – 3.04)	1.00 (Ref.)
	Continuer	400	1.36 (0.89 – 2.07)	0.57 (0.35–0.93)

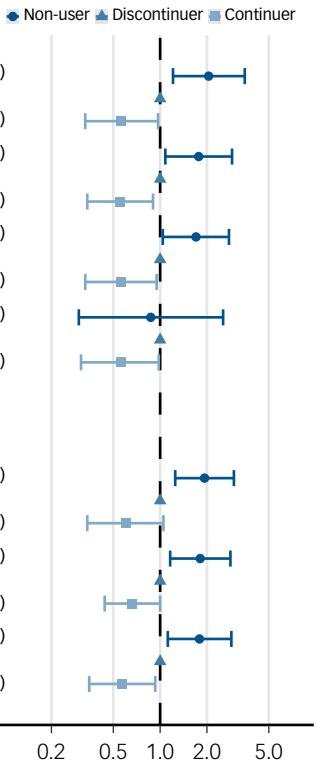

Fig. 3 Sensitivity analyses.

With the period from 2 years to 1 year before delivery as the reference, the incidence rate ratio (IRR) of admission for psychosis in each period was estimated using conditional Poisson regression analyses. Non-user, no antipsychotic use from 1 year to 39 weeks before delivery; discontinuer, antipsychotic use from 1 year to 39 weeks before delivery but discontinued antipsychotics before delivery; continuer, antipsychotic use from 1 year to 39 weeks before delivery and no discontinuation of antipsychotics before delivery.

with rapid mood fluctuation and irritability, and up to 80% of women with postpartum psychosis develop bipolar disorder.[25,26] Given that postpartum psychosis has been shown to be specifically associated with genetic liability to bipolar disorder, it can be regarded as the severe presentation of bipolar disorder.[27] Therefore, although evidence is limited, the risk of postpartum relapse in women with schizophrenia may be strongly influenced by a history of bipolar disorder. In our study, however, the association between antipsychotic continuation and the risk of postpartum relapse in the subgroup analysis stratified by comorbid bipolar disorder, as well as in the sensitivity analysis excluding outcomes with antidepressant or mood stabiliser use, was consistent with the main analysis. These findings suggest that antipsychotic continuation during pregnancy is effective in preventing the relapse of schizophrenia after delivery, regardless of bipolarity. Further studies are needed to examine the role of bipolar disorder in postpartum relapse of schizophrenia.

Postpartum relapse in non-users

Women who were not taking antipsychotics before pregnancy (non-users) showed a higher risk of postpartum relapse compared with discontinuers and continuers. Non-users included relatively mild cases of schizophrenia, as supported by the low incidence of admission for psychosis in the reference period (29.9 per 1000 person-years). Additionally, non-users consisted of women who terminated treatment before pregnancy and those who prepared for pregnancy. Given that non-users during pregnancy showed a similar risk of relapse compared with the reference period (Supplementary Table 3), they might face an unexpectedly high risk of relapse starting from the day of delivery and thereafter. Taken together, even individuals who had a mild course of disease and were mentally well without antipsychotics at conception should be monitored very carefully in the postpartum period. Further studies are needed to explore how to lower the risk of postpartum relapse in patients who were not taking antipsychotics before pregnancy.

Overall postpartum relapse risk

Returning to the overall increased risk of postpartum relapse in the entire population, our findings are highly consistent with those of a study using Danish claims-based data.[4] In that study, women with schizophrenia-like disorders showed an increased risk of psychiatric admission in the postpartum period, particularly in the early postpartum period. Furthermore, a study analysing health administrative data in Canada demonstrated that although women with schizophrenia had a decreased risk of psychiatric admission in the postpartum period overall, their risk was elevated in the very early postpartum period (first 9 days).[17] It seems obvious that women with schizophrenia are at an increased risk of relapse immediately after the delivery, similar to the presentation of postpartum psychosis in the general population.[25] However, the relapse risk later in the postpartum period should be further confirmed, particularly in relation to healthcare systems and social services.

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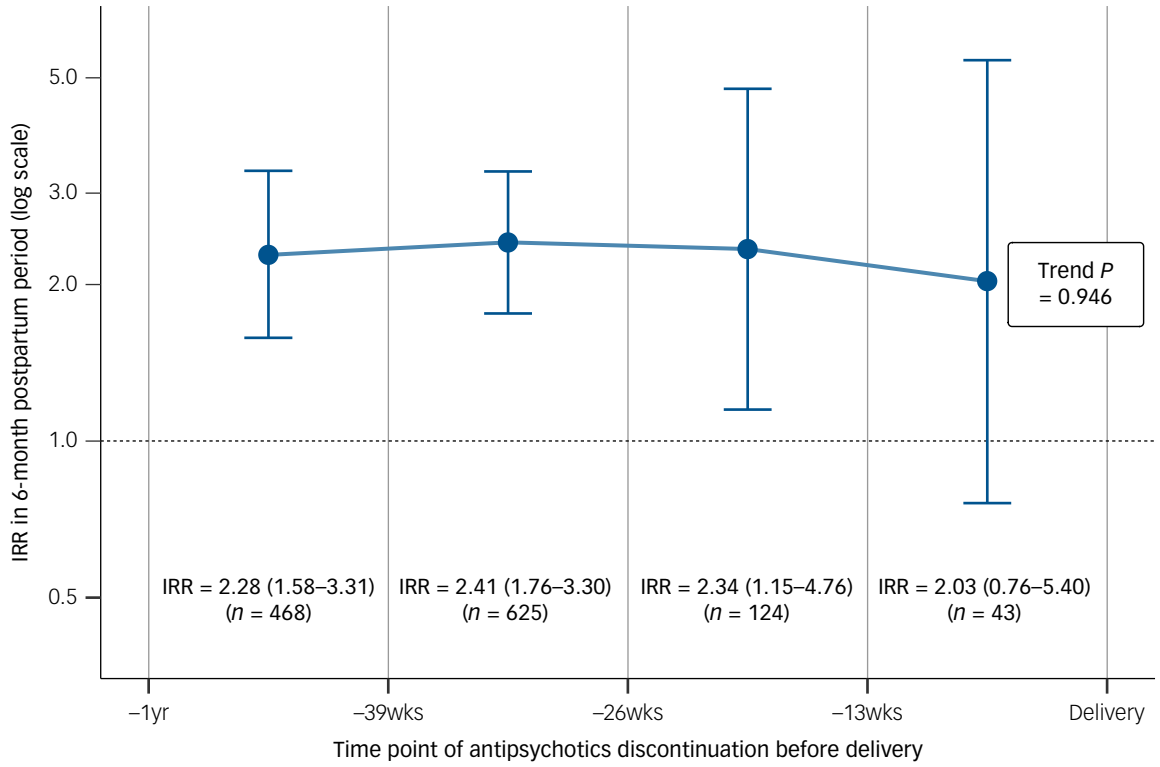

Fig. 4 Risk of admission for psychosis in the 6-month postpartum period by timing of antipsychotic discontinuation among discontinuers.

With the period from 2 years to 1 year before delivery as the reference, incidence rate ratios (IRRs) of admission for psychosis for the period from the date of delivery to 6 months after delivery were estimated using conditional Poisson regression analyses. Discontinuer, antipsychotic use from 1 year to 39 weeks before delivery but discontinued antipsychotics before delivery.

Mechanisms in postpartum relapse

Several biological mechanisms, such as hormonal, immunological and genetic factors, have been suggested to explain the pathophysiology of postpartum psychosis. For instance, levels of oestrogen, which can modulate dopamine receptors in the brain, drop rapidly after delivery in pregnant women, potentially triggering increased dopamine sensitivity and psychotic symptoms.[28] This explanation aligns with the pattern of relapse risk over time observed in our study, which was highest immediately after delivery and gradually decreased. Additionally, stress from caregiving and changes in support systems may provoke psychotic symptoms, although evidence remains controversial.[29,30] Since the pathophysiology and aetiology of postpartum psychosis has not yet been fully elucidated,[31] further studies on biological and psychosocial mechanisms are needed.

Strengths and limitations

Our study has several strengths. To the best of our knowledge, this is the first study to investigate the association between antipsychotic continuation before delivery and the risk of postpartum relapse in women with schizophrenia. As we included most live birth deliveries of women with schizophrenia in South Korea using nationwide register-based data, we were able to conduct various subgroup and sensitivity analyses. Additionally, using a within-individual design, we could eliminate the confounding effect of fixed variables such as the pre-pregnancy severity of schizophrenia.

Despite these strengths, our study has several limitations. First, we were unable to include specific ingredients or antipsychotic doses in our analyses. Further studies on the impact on postpartum relapse of the type of antipsychotic or tapering of antipsychotics during pregnancy are required. Second, we could not obtain detailed information on pregnancy and delivery, such as the gestational age of the newborn and parity. Therefore, we did not make any assumptions regarding the beginning of pregnancy (i.e. date of conception) in the study design. To deal with the uncertainty of the date of delivery, we conducted a sensitivity analysis, excluding women who were admitted for delivery for ≥7 days. However, the influence of primiparity and multiple births needs to be controlled in future studies. Third, categorisation based on antipsychotic use patterns could be misclassified owing to poor adherence. However, this would primarily misclassify patients who were prescribed antipsychotics but did not take them (actual discontinuers) as continuers and would bias the association towards the null. Fourth, as we defined a relapse of schizophrenia based on hospital admissions, milder relapses treated in out-patient care were disregarded. Fifth, although we tried to control for confounding of the fixed variables using a within-individual design, unmeasured confounding of time-varying factors such as life stress and changes in support systems could not be ruled out. Finally, we could not perform a risk–benefit assessment of continuing antipsychotics during pregnancy because information on neonatal adverse events was unavailable in our data.

Conclusion

In women with schizophrenia, antipsychotic continuation during pregnancy was associated with a reduced risk of postpartum relapse. For physicians treating pregnant women with schizophrenia, continuing antipsychotics during pregnancy may not only prevent relapse during pregnancy but also improve long-term outcomes after delivery. Further controlled trials or large epidemiological studies are required to provide evidence-based recommendations for antipsychotic maintenance therapy during pregnancy.

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Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2024.247.

Data availability

Customised research data from the National Health Information Database can be assessed by submitting a request to the National Health Insurance Sharing Service (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do). Please note that we are not permitted to share the data we used in this study.

Author contributions

S.K.: study design and concept, drafting of the manuscript and statistical analysis. S.J.J.: obtained funding and supervised the study. S.K., J.S.Y. and S.J.J.: acquisition, analysis or interpretation of data. S.K. and J.S.Y.: verification of data. J.S.Y., B.H.Y., B.G., S.K.A. and S.J.J.: critical revision of the manuscript for important intellectual content. All authors had full access to the data and take final responsibility for the submission for publication.

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Declaration of interest

None.

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