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Research paper

Association between prenatal exposure to antidepressants and neonatal morbidity: An analysis of real-world data from a nationwide claims database in Japan

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ABSTRACT

Background: Depression during pregnancy is relatively undertreated; however, the relationship between prenatal exposure to antidepressants and neonatal outcomes remains controversial.
Methods: This retrospective cohort study used a Japanese nationwide claims database. Data of 114,359 singletons born between January 2005 and November 2019 were used to evaluate the relationship between prenatal exposure to antidepressants and neonatal morbidity.
Results: Of 2892 mothers with a history of depression before delivery, 352 (12.1%) received prescriptions within three months before delivery (MP3), and 2540 did not (non-MP3). The participants were propensity score matched (PSM) in a ratio of 1:3 using logistic regression (MP3_PSM [$n = 351$] vs non-MP3_PSM [$n = 1052$]), and maternal prescriptions of antidepressants within three months before delivery were associated with neonatal morbidity indicators, including admission to the neonatal intensive care unit (NICU) (15.7 vs. 9.1%, odds ratio (OR) 1.9 [95% confidence interval (CI): 1.3–2.6]), poor neonatal adaptation syndrome (6.0 vs 1.0%, OR 6.6 [95% CI: 3.1–14.2]), transient tachycardia (15.7 vs. 6.7%, OR 2.6 [95% CI: 1.8–3.8]), and meconium aspiration syndrome (3.1 vs 0.7%, OR 4.8 [95% CI, 1.9–12.5]). There were no significant differences in the long-term duration of stay at the NICU (>15 days).
Limitations: Confounding factors may remain even after the propensity matching.
Conclusion: Maternal prescription of antidepressants within three months before delivery was associated with increased admission to the NICU. However, the absolute risk of severe neonatal morbidity was low. Therefore, collaborative care for prenatal depression and the neonatal intensive care is warranted.

Abbreviations: ATC, Anatomical therapeutic chemical classification; CI, confidence interval; CS, cesarean delivery; GDM, gestational diabetes mellitus; HDP, hypertensive disorders in pregnancy; HR, Hazard ratio; ICD-10, International classification of diseases tenth revision; IQR, Interquartile range; JMDC, Japan Medical Data Center; MAS, meconium aspiration syndrome; MP3, Maternal Prescription within 3 months before delivery; non-MP3, No Maternal Prescription within 3 months before delivery; NICU, Neonatal Intensive Care Unit; OR, Odds ratio; PNAS, Poor neonatal adaptation syndrome; PPHN, persistent pulmonary hypertension of the newborn; PS, Propensity score; PSM, Propensity score matched; RWD, real-world data; RDE, real world evidence; SSRI, Selective serotonin reuptake inhibitor; TTN, transient tachycardia/other respiratory distress; VENT, Ventilator treatment.

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1. Introduction

Perinatal depression is not a rare disorder that affects more than 12% of pregnant women (Stewart, 2011). Untreated depression during pregnancy is associated with preterm birth, small for gestational age, stillbirth, low birth weight, and maternal morbidity; including perinatal complications, increased cesarean deliveries, and postpartum depression (Bonari et al., 2004; Jahan et al., 2021). Thus, perinatal depression needs to be assessed and well-managed.

The need for antidepressants during pregnancy is increasing (Molenaar et al., 2020a). It has been reported that 15.4% of women of reproductive age (Dawson et al., 2016) and 5–13% of pregnant women (Andrade et al., 2008; Mitchell et al., 2011) are prescribed at least one antidepressant. Selective serotonin reuptake inhibitors (SSRIs) are the most common treatment for perinatal depression (Huybrechts et al., 2013; Nishigori et al., 2017). However, pregnant women are likely to discontinue antidepressants in pregnancy (Ishikawa et al., 2020; Noh et al., 2022) because of concerns about possible safety of antidepressants for fetuses (McDonagh et al., 2014), including congenital malformations during early pregnancy (Alwan et al., 2007; Huybrechts et al., 2014; Louik et al., 2007; Källén and Otterblad Olausson, 2007; Furu et al., 2015) and neonatal morbidity during late pregnancy (Hayes et al., 2012; Singal et al., 2016; Källén, 2004).

Poor neonatal adaptation syndrome (PNAS) has been linked to SSRI exposure during the third trimester of pregnancy (Levinson-Castiel et al., 2006), with a reported frequency of approximately 30%. Historically, the US Food and Drug Administration initially instructed manufacturers to issue warnings about their products (Koren et al., 2005). Subsequently, studies have accumulated risk-benefit assessment data on neonatal outcomes (Ornoy and Koren, 2017), including NICU admissions (Norby et al., 2016), preterm births (Eke et al., 2016), and low birth weight (Nezvalova-Henriksen et al., 2016; Roca et al., 2011), to show that they are rare and less serious. Furthermore, some studies have suggested the dosage of SSRIs during pregnancy may affect birth weight (Molenaar et al., 2020b). However, because of ethical considerations, no randomized controlled trial studies have been conducted to evaluate the efficacy or safety of antidepressants during pregnancy (Coverdale et al., 2008; Stewart, 2011). Therefore, new methodology is warranted to provide evidence for unmet medical needs on drugs during pregnancy (Koren et al., 1998; Murashima et al., 2021).

Real-world evidence (RWE) is a new methodology recently proposed by the U.S. Food and Drug Administration (Sherman et al., 2016). By definition, real-world data (RWD) is the routinely collected data from various sources, while RWE is the clinical evidence derived from RWD analysis. Each data source, including claims databases, patient registries, and electronic medical records, has advantages and disadvantages (Nabhan et al., 2019; Ohtsu et al., 2022). Therefore, evaluation of the quality and relevance is necessary.

This is a retrospective cohort study aimed to evaluate a new RWD, a nationwide claims database of linked mothers and children in Japan, to analyze the association between prenatal exposure to antidepressants and neonatal morbidity.

2. Methods

2.1. Data source

This study involved the retrospective observational cohort analysis of the Japan Medical Data Center (JMDC) database, an anonymized patient-level claims database (Kimura et al., 2010). The JMDC maintains one of the largest claims databases from the National Universal Health Insurance System, with approximately 8.4 million insured subscribers registered as of 2020 (Nagai et al., 2021). JMDC anonymously links billing information collected from hospitals, clinics, and pharmacies and supplies it as a patient-centric relational database with tables including information on healthcare providers, insurance individuals, monthly receipts, diagnoses, drugs, surgeries, and diagnostic tests (Hashimoto et al., 2021; Ishikawa et al., 2020; Yamamoto-Sasaki et al., 2020). The coding system provided by JMDC is based on the International Classification of Disease, 10th edition (ICD-10), for diagnoses and the World Health Organization Anatomical Therapeutic Chemical Classification (ATC) for drug prescriptions. The codes have been indicated within square brackets in the manuscript (Supplementary Tables 1 and 2).

The Institutional Review Board of Juntendo University approved the protocol of this study (JM#20-322) according to the ethical guidelines for medical research involving human subjects (Ministry of Health, Labor, and Welfare of Japan). The need for informed consent was waived for this observational study because of the anonymity of the data.

2.2. Study population

The pregnancy cohort included women aged 15–50 years who gave birth to a singleton based on a family code between January 2005 and November 2019. As the Japanese insurance system does not include the last menstrual period or weeks of pregnancy (Ishikawa et al., 2020), we used the month of birth as the index (Hashimoto et al., 2021; Yamamoto-Sasaki et al., 2020). To minimize the impact on neonatal outcomes, we excluded multiple pregnancies [O30] and chromosomal abnormalities in babies [Q90–Q99]. In addition, to assess maternal risk factors, we excluded second or subsequent babies and mothers without at least six months of JMDC subscriptions before delivery.

2.3. Diagnosis of depression and antidepressant prescription

We identified the maternal diagnosis of depression as ICD-10 based JMDC code [F32]. The ATC-based JMDC code [N06A] and its subdivisions (SSRIs [N06A4], serotonin-noradrenaline reuptake inhibitors [N06A5], and other antidepressants (Others) [N06A9]) were designated as antidepressants. Newborns whose mothers had received at least one prescription for antidepressants within three months before birth were allocated to the exposed group.

2.4. Maternal and neonatal characteristics

We assessed the following covariates as clinical predictors (Supplementary Table 1): maternal age, anemia, dyslipidemia, hypertension/hypertensive disorders of pregnancy (HDP), diabetes mellitus/gestational diabetes mellitus (GDM), autoimmune diseases, and ischemic heart disease (Hashimoto et al., 2021), sex of the newborn, cesarean section (CS), preterm birth, and low birth weight (Norby et al., 2016; Källén, 2004). The Japanese health insurance system includes a "tentative diagnosis" for billing purposes (Fujihara et al., 2021), which is known to reduce the specificity of the diagnosis alone. Therefore, the combination of diagnosis and treatment was used to assess the covariates as above.

2.5. Outcomes

We extracted the neonatal outcomes using JMDC diagnostic codes (Supplementary Table 2): admission to neonatal intensive care unit (NICU) (all), admission to NICU (>15 days), respiratory distress syndrome, transient tachycardia/other respiratory distress (TTN), persistent pulmonary hypertension of the newborn (PPHN), meconium aspiration syndrome (MAS), ventilator treatment (VENT) (all), VENT (>5 h), continuous positive airway pressure (CPAP), seizures, congenital hyper/hypotonia, intracranial hemorrhage, feeding difficulties, and PNAS. These covariates were selected according to previous studies (Norby et al., 2016; Hashimoto et al., 2021; Källén, 2004).

2.6. Statistical analysis

Baseline characteristics were summarized using mean values (standard deviation [SD]) for continuous data and counts (percentage, %) for categorical data. The groups were compared using crude analysis and propensity score (PS) matching (Rubin, 1997). PS was generated using logistic regression, with the maternal prescription of antidepressants within three months before delivery as the dependent variant. Independent variables were selected as potential confounding factors based on previous studies (Cantarutti et al., 2017; Hayes et al., 2012; Norby et al., 2016); they included maternal (age at delivery, birth year, anemia, hypertension, diabetes mellitus, autoimmune disease, and cesarean delivery) and neonatal (sex and low birth weight) factors. PS matching was performed using the greedy pair algorithm (Austin, 2009) with a 1:3 ratio without replacements and a caliper width of 0.2 (Austin, 2011). Standardized differences were used to assess residual differences in the subsets of matched participants. In addition, neonatal outcomes with or without maternal exposure to antidepressants were compared. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Data source and study population

Fig. 1 shows a flowchart of the study. From 7,447,761 JMDC subscribers and their families during the study period, we identified 114,359 eligible pregnancies. Only the first singleton babies linked with their mothers were been included. Of these, 6593 (5.8%) had a lifetime history of depression diagnosis, and 2892 (2.5%) had a diagnosis before delivery. These pregnancies were categorized into those prescribed within three months before delivery (MP3: $n = 352$) and those without antidepressant prescriptions (non-MP3: $n = 2540$). After 1:3 PS matching, two groups were extracted as MP3_PSM ($n = 351$) and non-MP3_PSM ($n = 1052$), respectively.

3.2. Maternal history of depression and antidepressant prescription

Fig. 2 shows the percentage of women with a diagnosis of depression before delivery who have at least one antidepressant prescription, trend by three months. The percentage of prescriptions for women with a history of depression before delivery was 30.1% (737/2446) 12 months before delivery, 12.2% (352/2892) within three months before delivery, and 18.6% (406/2180) 1.5 years after delivery (Fig. 2) (Supplementary Table 3).

3.3. Maternal and neonatal characteristics

The maternal and neonatal characteristics are shown in Table 1. In the MP3 group, the maternal mean age at delivery was 33.6 years [SD ± 4.37]. The rate of diagnosis and treatment of gestational diabetes was 3.7%, and the maternal cesarean delivery rate was 27.3%. After 1:3 propensity score matching, the maternal age and comorbidities mentioned above were corrected for the differences between the two groups. Regarding the frequency of preterm birth and low birth weight, MP3 had an increased frequency of 13.6% versus 6.5% (odds ratio (OR) 2.26 [95% confidence interval (CI) 1.60–3.18], $P < 0.001$) before PS matching, which was corrected to 13.4% versus 13.0% after PS matching.

There were few adolescents under the age of 20 (Supplementary Fig. 1).

3.4. Neonatal outcomes

Table 2 shows the neonatal outcomes. The NICU admission rates were significantly higher before propensity score matching (55/352 (15.6%) vs 165/2540 (6.5%), $P < 0.0001$, OR 2.67, [95% CI 1.92–3.70]); after PS matching, there was a significant increase in NICU admissions (55/352 (15.7%) vs. 96/1052 (9.1%), $p < 0.0001$, OR 1.85, [95% CI 1.30–2.64]). However, there was no difference in long-term hospitalization at the NICU (>15 days) between the two groups, (9/

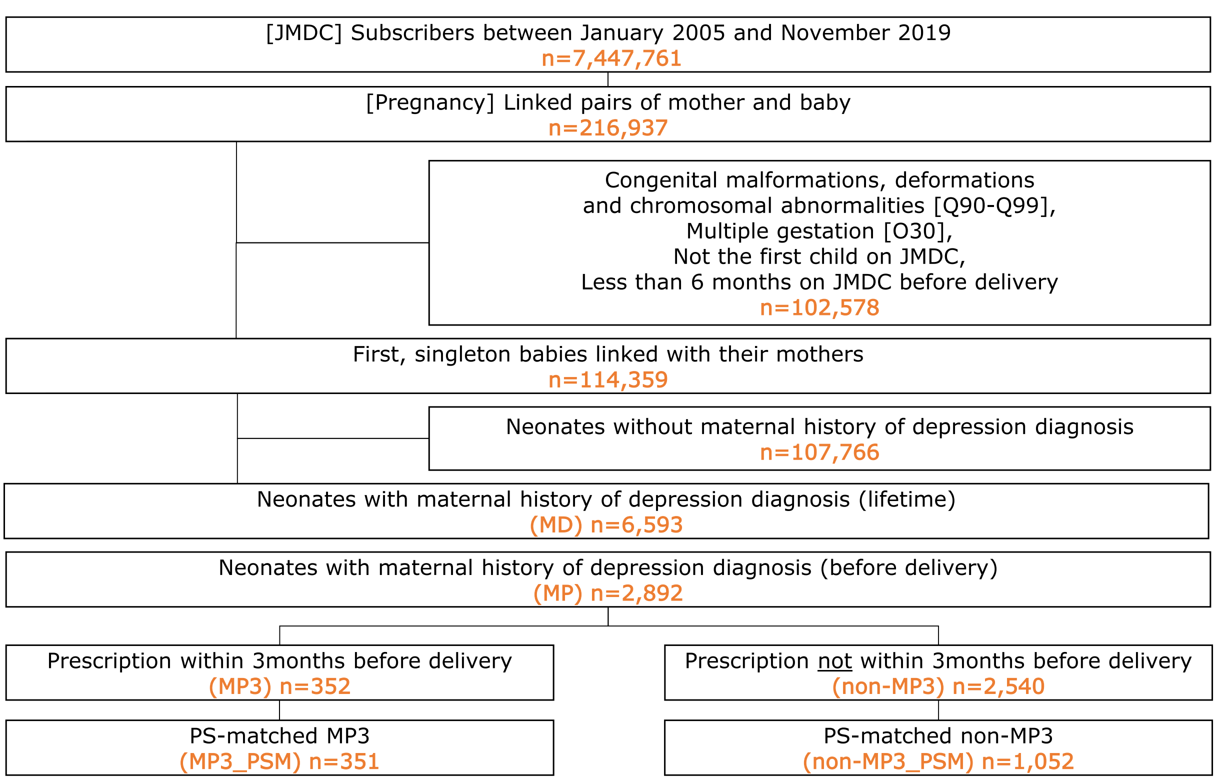

Fig. 1. Flow chart of the study.

Fig. 2. Percentage of women with a diagnosis of depression who have at least one antidepressant prescription, trend by three months.

Table 1
Maternal and neonatal characteristics.

	Crude			PS-matched		
	MP3	Non-MP3	OR [95% CI]	MP3_PSM	Non-MP3_PSM	OR [95% CI]
	n = 352	*n* = 2540	*p*-value	n = 351	*n* = 1052	*p*-value
Age at delivery (mean) (±SD) (Min–max)	33.6 (±4.37) (22–47)	33.3 (±4.87) (20–47)	$p = 0.28$	33.6 (±4.39) (22–47)	33.5 (±4.60) (20–47)	$p = 0.81$
Anemia	140 (39.77%)	986 (38.82%)	OR 1.04 [0.82–1.30] $p = 0.73$	140 (39.89%)	397 (37.74%)	OR 1.09 [0.85–1.40] $p = 0.47$
DL	4 (1.14%)	14 (0.55%)	OR 2.07 [0.67–6.34] $p = 0.26$*	4 (1.14%)	7 (0.67%)	OR 1.72 [0.50–5.91] $p = 0.48$*
HT/HDP	23 (6.53%)	140 (5.51%)	OR 1.20 [0.76–1.89] $p = 0.44$	23 (6.55%)	62 (5.89%)	OR 1.31 [0.81–2.13] $p = 0.27$
DM/GDM	13 (3.69%)	44 (1.73%)	OR 2.18 [1.16–4.08] $p = 0.01$	12 (3.42%)	38 (3.61%)	OR 0.94 [0.49–1.83] $p = 0.87$
Autoimmune disease	3 (0.85%)	12 (0.47%)	OR 1.81 [0.51–6.45] $p = 0.23$*	3 (0.85%)	10 (0.95%)	OR 0.90 [0.25–3.28] $p = 1$*
IHD	1 (0.28%)	1 (0.04%)	OR 7.23 [0.45–115.9] $p = 0.23$*	1 (0.10%)	1 (0.34%)	OR 3.00 [0.19–48.1] $p = 0.44$*
CS	96 (27.27%)	593 (23.35%)	OR 1.23 [0.96–1.58] $p = 0.11$	96 (27.35%)	277 (26.33%)	OR 1.05 [0.80–1.38] $p = 0.71$
Babis' gender (girl)	162 (46.02%)	1244 (48.98%)	OR 0.89 [0.71–1.11] $p = 0.30$	161 (45.87%)	472 (44.87%)	OR 1.41 [0.81–1.33] $p = 0.79$
PB/LBW	48 (13.64%)	166 (6.53%)	OR 2.26 [1.60–3.18] $p < 0.01$	47 (13.39%)	137 (13.02%)	OR 1.03 [0.72–1.47] $p = 0.86$

OR, odds ratio.
SD, standard deviation.
PS, propensity score.
DL, dyslipidemia.
HT, hypertension.
HDP, hypertensive disorders in pregnancy.
DM, diabetes mellitus.
GDM, gestational diabetes mellitus.
IHD, ischemic heart disease.
CS, cesarean section.
PB, preterm birth.
LBW, low birth weight.
MP3, maternal prescription, within 3 months before delivery.
non-MP, no maternal prescription, within 3 months before delivery.
MP3_PS, MP3, PS matched.
non-MP3_PSM, non-MP3, PS matched.
* Fisher's exact test.

Table 2
Neonatal outcomes.

Outcomes	Crude			PS-matched		
	MP3	Non-MP3	OR [95% CI]	MP3_PSM	Non-MP3_PSM	OR [95% CI]
	n = 352	n = 2540	*p*-value	n = 351	n = 1052	*p*-value
Admission to NICU	55 (15.63%)	165 (6.50%)	OR 2.67 [1.92–3.70] $p < 0.01$	55 (15.67%)	96 (9.12%)	OR 1.85 [1.30–2.64] $p < 0.01$
Admission to NICU (over 15 days)	9 (2.56%)	30 (1.18%)	OR 2.20 [1.03–4.66] $p = 0.04$	9 (2.56%)	18 (1.71%)	OR 1.51 [0.67–3.40] $p = 0.31$
PNAS	21 (6.00%)	16 (0.63%)	OR 10.01 [5.17–19.4] $p < 0.01$	21 (5.98%)	10 (0.95%)	OR 6.63 [3.09–14.2] $p < 0.01$
RDS	6 (1.70%)	23 (0.91%)	OR 1.90 [0.77–4.69] $p = 0.16$	6 (1.70%)	15 (1.43%)	OR 1.20 [0.46–3.12] $p = 0.70$
TTN	55 (15.63%)	144 (5.67%)	OR 3.08 [2.21–4.30] $p < 0.01$	55 (15.67%)	70 (6.67%)	OR 2.61 [1.79–3.80] $p < 0.01$
PPHN	1 (0.28%)	5 (0.20%)	OR 1.44 [0.17–12.4] $p = 0.54$**	1 (0.28%)	2 (0.19%)	OR 1.50 [0.27–8.23] $p = 1.00$*
MAS	11 (3.12%)	20 (0.79%)	OR 4.06 [1.93–8.56] $p = 0.03$	11 (3.12%)	7 (0.67%)	OR 4.83 [1.86–12.6] $p = 0.03$
Ventilator treatment	21 (6.00%)	60 (2.36%)	OR 2.62 [1.57–4.37] $p < 0.01$	21 (5.98%)	38 (3.61%)	OR 1.70 [0.98–2.94] $p = 0.055$
Ventilator treatment (over 5 h)	15 (4.26%)	49 (1.93%)	OR 2.26 [1.26–4.08] $p < 0.01$	15 (4.27%)	32 (3.04%)	OR 1.42 [0.76–2.66] P = 0.27
CPAP	1 (0.28%)	6 (0.24%)	OR 1.20 [0.14–10.0] $p = 0.60$*	1 (0.28%)	3 (0.29%)	OR 1.00 [0.10–9.64] $p = 1$*
Seizures	2 (0.57%)	8 (0.31%)	OR 1.81 [0.38–8.55] $p = 0.35$*	2 (0.57%)	4 (0.38%)	OR 1.50 [0.27–8.23] $p = 0.64$*
Congenital hyper/hypotonia	1 (0.28%)	2 (0.08%)	OR 3.62 [0.33–40.0] $p = 0.32$*	1 (0.28%)	0 (0%)	NA $p = 0.25$*
Intracranial hemorrhage	5 (1.42%)	23 (0.91%)	OR 1.58 [0.60–4.17] $p = 0.38$*	5 (1.42%)	13 (1.23%)	OR 1.15 [0.41–3.26] $p = 0.79$*
Feeding difficulties	20 (5.69%)	88 (3.46%)	OR 1.68 [1.01–2.76] $p = 0.04$	20 (5.70%)	42 (3.99%)	OR 1.45 [0.84–2.51] $p = 0.18$
Prescription of surfactant	3 (0.85%)	20 (0.79%)	OR 1.08 [0.32–3.66] $p = 0.75$*	3 (0.85%)	14 (1.33%)	OR 0.64 [0.18–2.24] $p = 0.59$

PNAS, poor neonatal adaptation syndrome.
RDS, respiratory distress syndrome.
TTN, transient tachycardia/other respiratory disease.
PPHN, persistent pulmonary hypertension of the newborn.
MAS, meconium aspiration syndrome.
CPAP, continuous positive airway pressure.
* Fisher's exact test.

352 (2.6%) vs. 18/1052 (1.7%), $P = 0.31$, OR 1.51, [95% CI 0.67–3.40]). The MP3 group showed increased rates of TTN (matched P < 0.0001, OR 2.61, [1.79–3.80]) and MAS (matched $P = 0.03$, OR 4.83, [1.86–12.6]), respectively. VENT (matched $P = 0.055$, OR 1.70, [95% CI 0.98–2.94]) were tend to increased risk in MP3 group. There was no longer a difference between the two groups related to respiratory treatment for more than 5 h (matched $P = 0.27$, OR 1.42, [95% CI 0.76–2.66]). Adding the prolonged NICU stay mentioned earlier, the risk of developing a serious condition did not seem to increase. There were no significant increases in other respiratory diagnoses such as PPHN, neurological symptoms such as neonatal seizures, or gastrointestinal symptoms.

Supplementary Table 4 shows the neonatal outcomes, tabulated by antidepressant class. SSRIs were the most commonly prescribed antidepressants in the mothers with a diagnosis before delivery.

4. Discussion

To the best of our belief, this is the first study in Japan to investigate the relationship between maternal exposure to antidepressants and neonatal outcomes using a nationwide claims database. Prenatal prescription of antidepressants was associated with increased neonatal morbidity and associated events, including a higher rate of admission to the NICU. However, the absolute risk of severe neonatal outcomes was low.

Untreated depression in pregnancy could have adverse effects on women, their fetuses, other children, and their partners (Bonari et al., 2004; Jahan et al., 2021). However, concerns about the increased risk of several maternal and fetal conditions, including malformations, low birth weight, preterm birth, PPHN, and PNAS (MHLW, 2021), have led pregnant women with depression to discontinue antidepressants (Ishikawa et al., 2020; Noh et al., 2022). In 114,359 eligible mothers, we extracted "antepartum history of depression diagnosis" (MP: $n = 2892$), and then "history of antidepressant prescriptions in the 3 months before delivery" (MP3: $n = 352$) (Fig. 1). These numbers are consistent with previous reports from Japan (Ishikawa et al., 2020; Nishigori et al., 2017). Fig. 2 showed a declining rate of antidepressant prescriptions among pregnant women with depression. The percentage of prescriptions for women with a history of depression before delivery was 30.1% (737/2446) 12 months before delivery, 12.2% (352/2892) within three months before delivery, and 18.6% (406/2180) 1.5 years after delivery (Supplementary Table 3). In particular, the lowest rate of prescription was during late pregnancy, and this suggests that the primary concern of pregnant women is the impact on neonatal outcomes.

Antidepressants during late pregnancy have been extensively studied (Simon et al., 2002; Källén, 2004; Davis et al., 2007; Colvin et al., 2012), and are associated with adverse neonatal outcomes, including preterm birth and low birth weight (Bandoli et al., 2020; Eke et al., 2016; Huang et al., 2014; Nezvalova-Henriksen et al., 2016; Roca et al., 2011). In contrast, depression during pregnancy is associated with increasing risk of preterm births (Malm et al., 2015). In other words, the causal relationship between antidepressant treatment and depression has not been elucidated yet. In this study, we have taken advantage of the nationwide claims database under universal health coverage in Japan and used PS matching to adjust for potential confounding factors. After PS matching, we found a significant increase in the incidence of adverse neonatal outcomes, such as admission to the NICU, TTN, MAS, and PNAS. However, there was no difference in severe neonatal outcomes, including long-term NICU hospitalization (>15 days), long-term ventilation treatment (>5 h), and seizures (Table 2).

PNAS has been reported in up to 30% of pregnancies after intrauterine exposure to various SSRIs and serotonin-noradrenaline reuptake inhibitors during the third trimester of pregnancy (Ornoy and Koren, 2017). The clinical features of neonatal maladaptive syndrome include irritability, abnormal crying, tremors, jitteriness, lethargy, dyspnea or tachypnea, muscle tone and color, and seizures (rarely). These symptoms are generally mild and transient, and are similar to those seen with the use of other psychotropic drugs in late pregnancy. In this study, the claims data did not provide detailed descriptions of clinical features. Although JMDC has diagnostic codes of PNAS, the specificity of the diagnostic codes alone could be low. Therefore, we evaluated with codes such as NICU admission, respiratory symptoms, neurological symptoms, and gastrointestinal symptoms, all of which have been evaluated in previous studies (Cantarutti et al., 2017, Norby et al., 2016, Malm et al., 2015, Colvin et al., 2012, Källén, 2004), which also represent symptoms of PNAS. Our evaluation using these codes showed that symptoms considered to be associated with PNAS were few but not severe. The rationale for this is that NICU admissions increased but were not prolonged, and respiratory management tended to increase but was not prolonged (Table 2), which was consistent with an earlier study (Norby et al., 2016; Colvin et al., 2012).

One of the main objectives of this study is to assess whether JMDC has "fit for purpose" quality and relevance as an RWD. In this study, we found advantages of the JMDC, one of the largest nationwide insurance claims data-base in Japan, including fee-for-service universal health coverage (Hashimoto et al., 2021), few missing values to allow cross-hospital analysis between the maternal antidepressant prescriptions in clinics and the neonatal care in NICUs, and anonymized data linkage (Kimura et al., 2010). For example, as mentioned above, prescriptions for women with a history of depression before delivery and neonatal outcomes, including severe adverse events. Therefore, we now believe that the JMDC claims database, a commercially available database of health insurance claims routinely collected from daily practice, can be used as one of the new source of data with reasonable quality and relevance to conduct future RWD studies for drugs in pregnancy, efficiently.

In developed countries, suicide is the most common cause of perinatal death (Paschetta et al., 2014), and social support systems have been highlighted (Tachibana et al., 2020; Yonemoto et al., 2013). Women with a history of depression are at high risk for perinatal depression, and it has been suggested that symptoms may worsen when antidepressants are discontinued during pregnancy. Our claims-based analysis showed an association between maternal prescription of antidepressants before delivery and admission to the NICU. However, the absolute risk of severe neonatal morbidity was low, consistent with others (Norby et al., 2016). Therefore, we believe that women with depression should not discontinue treatment during late pregnancy only because of overconcern regarding neonatal outcomes, as long as they are warranted to have access to perinatal care providers, including NICU, for high-risk pregnancies.

4.1. Strength and limitations of this study

As with any observational study, the present study has some strengths and limitations.

One of the strengths of this study is that it was conducted using a nationwide administrative database in Japan with high coverage of data because this database shows the sizes of the medical institutions that treated the patients. Another strength is the statistical effort, including PS matching, to minimize biases.

This study has some limitations. First, we used PS matching to minimize potential bias; however, unmeasured confounding factors may remain because this was a retrospective observational study. Randomized controlled trials remain the gold standard for exploratory studies using real-world data to validate causal relationships. Second, the JMDC does not contain information, including imaging, laboratory data, and clinical symptoms, as a claims database. Therefore, the specificity of the PNAS, PPHN, and MAS codes must be carefully interpreted. Third, we mainly focused on prescriptions during late pregnancy, and not during early pregnancy, and JMDC codes for preterm birth may have some margin of error, as in other claims-based analyses. Fourth, there may be a survivor bias in this study because we only included pairs of mothers and their children. However, previous studies have suggested that prenatal exposure to antidepressants has few fatal adverse events. Fifth, while missing data on antidepressant prescriptions are rare in the fee-for-service Japanese health insurance system, it may not be a direct indicator of intrauterine exposure because there is no feedback from mothers on how many of them have been used and when. Sixth, although there were few women under the age of 20 years in our current study, it should be noted that there are ongoing debates on the efficacy and safety of antidepressant use in children and adolescents (Thapar et al., 2012). Finally, the JMDC Claims Database included an employed, working-age population. Accordingly, mainly young and middle-aged adults were included in the present study, and the average of socioeconomical status is relatively high (Hashimoto et al., 2021). Therefore, a "healthy worker" bias might be present in this population (Hashimoto et al., 2021). Further investigation is needed to determine whether our results can be generalizable to other populations of different ethnicities, races, educational levels, and incomes.

4.2. Conclusion

In conclusion, the claims-based analysis showed an association between maternal prescription of antidepressants within 3 months before delivery and admission to the NICU. However, the absolute risk of severe neonatal morbidity was low. Furthermore, the prescription rate decreased while there was still a need for antidepressants during pregnancy. Therefore, further studies on treatments for prenatal depression and neonatal access to intensive care are warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.04.103.

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Conflict of interest

Hiroshi Ohtsu received a consultant fee from EPS International outside of the submitted study. Naohiro Yonemoto is an employee and shareholder of Pfizer outside the submitted study. Kazuhiro Sase has received lecture fees from Daiichi Sankyo, Novartis, Pfizer, and Bristol-Myers Squibb, outside the submitted study. The other authors have no conflicts of interest to declare.

IRB information

The Institutional Review Board of Juntendo University approved the protocol of this study (JM#20-322) according to the ethical guidelines for medical research involving human subjects (Ministry of Health, Labor, and Welfare of Japan) and the World Medical Association (WMA) Declaration of Helsinki. Written consent was not required in this observational study because of the anonymity of the data.

CRediT authorship contribution statement

Izumi Fujioka: Writing – original draft, conceptualization, visualization, formal analysis, and data curation.

Hiroshi Ohtsu: Formal analysis, Data curation, and Writing—review & editing.

Naohiro Yonemoto: Formal analysis, Data curation, Writing—review & editing.

Kazuhiro Sase: formal analysis, data curation, Writing—review and editing, funding acquisition, and supervision.

Atsuko Murashima: conceptualization, visualization, formal analysis, data curation, writing – review and editing, funding acquisition, and supervision.

Submission declaration

No prior posting or presentation and no research sponsor is associated with this paper.

Data availability

Data may be obtained from a third party and are not publicly available. Data may be made available through the JMDC (www.jmdc.co.jp/en/jmdc-claims-database/).

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