See commentary by Viguera



# Pregnancy Outcomes With Exposure to Second-Generation Antipsychotics During the First Trimester

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## ABSTRACT

***Objective:*** To investigate the risk of major congenital malformations associated with exposure to second-generation antipsychotics (SGAs) in the first trimester.

***Methods:*** Pregnant women who received consultation on drug exposure from the Japan Drug Information Institute in Pregnancy from October 2005 to December 2016 were asked to complete a questionnaire at 1 month after the expected delivery date. The questionnaire included items on pregnancy outcome, date of delivery, gestational age at delivery, malformations in the infant that were confirmed by the pediatrician's report, and the following parameters at birth: height, weight, head circumference, and chest circumference. Odds ratios (ORs) for major congenital malformations among live-born children of pregnant women with SGA exposure during the first trimester (SGA group) relative to children of women not exposed to SGAs and medications known to be teratogenic (comparison group) were estimated using an inverse probability of treatment weighting approach.

***Results:*** Of 404 women with SGA exposure during the first trimester, there were 351 live births, 3 stillbirths, 34 spontaneous abortions, and 16 elective abortions. The rate of major congenital malformations among live-born children was 0.9% (3/351) in the SGA group and 1.8% (70/3,899) in the comparison group. No statistically significant differences were observed in the adjusted OR for major congenital malformations (adjusted OR = 0.44; 95% CI, 0.12–1.48; $P = .179$).

***Conclusions:*** SGA exposure during the first trimester is not associated with an increased risk of major congenital malformations. These findings might be reassuring for pregnant women who require SGAs.

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Among pregnant women with psychotic disorders, disease control is essential and urgently desired. Left untreated, perinatal psychotic disorders can have serious adverse effects on women and their children, ranging from decreased adherence to medical care; worsening medical condition; loss of interpersonal and economic resources; and increased risk of smoking, substance use, suicide, and infanticide.[1,2] Perinatal suicide is considered a relatively rare event. However, in some psychiatric disorders such as postpartum depression, bipolar disorder, and postpartum psychosis, a higher risk of suicidal ideation, suicide attempt, and suicide has been reported.[3] In Japan, suicide is currently a major perinatal problem. The suicide rate among perinatal women is 8.7 per 100,000 women in Tokyo, which is much higher than in Sweden and the United Kingdom.[4] Untreated or poorly controlled maternal psychosis is considered a major contributor to maternal suicide because suicides appear to be more prevalent among women who are less likely to be receiving any active treatment.[3]

Recently, increased use of second-generation antipsychotics (SGAs) during pregnancy has been reported in several countries.[5,6] In the United States, the prevalence of SGA use at any time during pregnancy increased from 0.4% in 2001% to 1.3% in 2010.[7] The association between maternal SGA exposure and risk of congenital malformations is controversial. The National Pregnancy Registry for Atypical Antipsychotics (NPRAA)[8–11] reported no statistically significant differences in the rate of congenital malformations, which is consistent with findings from other studies in the United States and[12] Finland[13] and from a Canadian study that included data from the Israeli teratogen information service (TIS).[14] In contrast, a significant increase in the incidence of congenital malformations was observed in Germany[15] and Australia.[16] Women and their health care providers are often faced with clinical decisions, but the risks and benefits are difficult to assess without high-quality studies in humans that address the reproductive safety of SGAs and other neuropsychiatric drugs. Thus, pertinent information for both pregnant women and health care providers is urgently needed.[17]

However, in Japan, the extent of perinatal exposure to SGAs or other psychotropic medications and subsequent major fetal congenital malformations

**Clinical Points**

- Although an increasing number of women are in need of antipsychotics, there is limited information in Japan on the effects of antipsychotics on the fetus during pregnancy.
- This study found no association between the use of antipsychotics during pregnancy and the occurrence of major malformations.
- These findings may be encouraging for women who require treatment with second-generation antipsychotics during pregnancy.

remains unknown. The Japan Drug Information Institute in Pregnancy (JDIIP)[18,19] was established by the Ministry of Health, Labor and Welfare in October 2005 within the National Center for Child Health and Development (NCCHD). We provide information about the effects of medication use during pregnancy on fetuses, pregnant women, and women intending to become pregnant. JDIIP has established base hospitals in all 47 prefectures in Japan and provides counseling at 53 facilities including NCCHD. We also collect information on the child at 1 month after the expected date of delivery from pregnant women who have accessed JDIIP and agreed to participate in a pregnancy outcome survey.

In this study, we used information from pregnant women throughout Japan who have received counseling to analyze the association between SGA exposure in the first trimester, for which information is limited in Japan, and the risk of major congenital malformations.

## METHODS

### Study Population

The study population consisted of pregnant women who accessed JDIIP between October 2005 and December 2016 and consented to a pregnancy outcome survey. We included only women with singleton pregnancies. Women with multifetal pregnancies were excluded.

### Information on the Characteristics of Pregnant Women

Background data were collected from entries on the JDIIP consultation application form. The following data were obtained: age at contact; preconception weight and height to calculate body mass index (BMI); date of last menstruation; expected date of delivery; current folate intake and start date; planned pregnancy; type, amount, and timing of prescription medication, over-the-counter medication, and supplement use; smoking history; alcohol use; narcotic, stimulant, and other illegal drug use; occupational exposure to radiation and organic solvents; medical history; and obstetric history. Women self-reported medical diagnoses they received from their physicians.

### Exposure

The timing of exposure was determined based on the date of the last menstruation period, which was estimated from the reported date of the pregnancy outcome and gestational age at delivery. The first trimester was defined as gestational weeks 4 to 13. The SGA group consisted of women with exposure to at least 1 SGA (risperidone, paliperidone, perospirone, blonanserin, olanzapine, quetiapine, and aripiprazole) during the first trimester. The comparison group consisted of women who were not exposed to medications known to be teratogenic (eg, etretinate, carbamazepine, cyclophosphamide, methotrexate, misoprostol, mycophenolate mofetil, phenytoin, phenobarbital, warfarin potassium, and valproic acid) during pregnancy. To select only pregnant women with SGA exposure during the first trimester, we excluded women who had used SGAs before pregnancy or only during the second or third trimesters.

### Outcomes

Primary study outcomes were (1) the live birth rate and (2) the rate of major congenital malformation among live births. The secondary outcome was the rate of elective abortions. To collect data on pregnancy outcomes, a questionnaire on a prepaid postcard was mailed to participants 1 month after their expected date of delivery. It included the following items: pregnancy outcome (live birth, stillbirth, elective abortion, or spontaneous abortion); date of delivery; gestational age at delivery; method of delivery; issues identified by the pediatrician regarding the infant's health between birth and the 1-month medical examination; and infant height, weight, head circumference, and chest circumference at birth. JDIIP physicians reviewed the questionnaire responses and contacted women by phone if their responses were missing or incomplete. If we contacted the woman and the problem persisted, we contacted the child's doctor with the consent of the woman. If women did not return the postal questionnaire by 3 months after her expected date of delivery, another questionnaire was mailed.

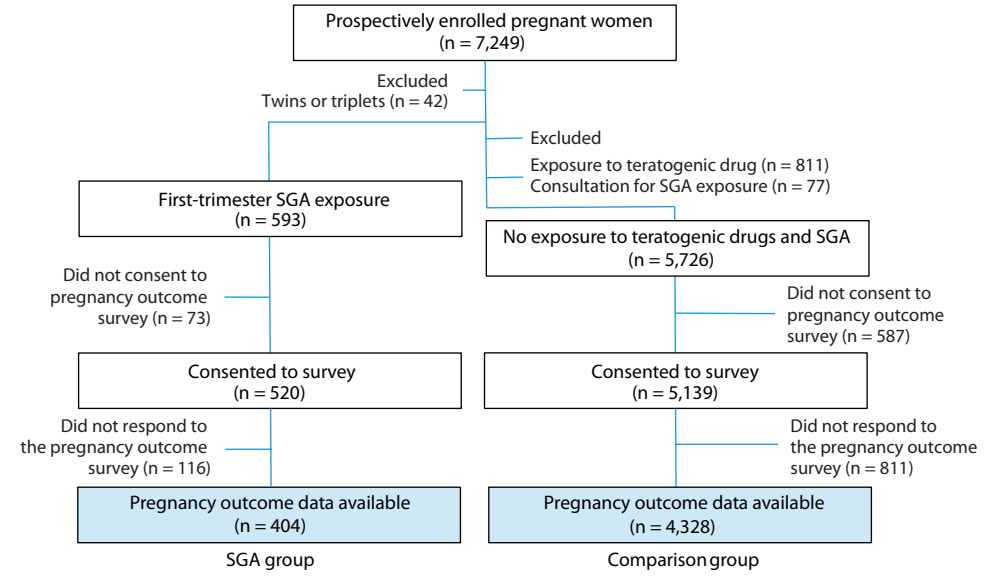
Malformations were diagnosed and confirmed by local pediatricians during the 1-month medical examination and recorded in maternal and child health handbooks. The examination included evaluation for physical and mental developmental disorders, including congenital morphological abnormalities. In Japan, all pregnant women receive such a handbook. Home-based records were found to be effective and useful for improving newborn and child health outcomes.[20] The handbook is publicly distributed and serves as a medical record to share information about the infant.

Major congenital malformations were determined by congenital anomaly experts with reference to the European Congenital Anomaly Monitoring classification system.[21] The experts were blinded to exposure group, and they did not participate in contacting the women by phone.

### Statistical Analysis

Variables were summarized by group and compared using the Fisher exact test or the Wilcoxon rank sum test. Crude odds ratios (ORs) were estimated using logistic regression with adjustment for alcohol consumption and smoking status. Adjusted ORs were estimated using the inverse probability

**Figure 1. Study Flowchart**




Abbreviation: SGA = second-generation antipsychotic.

weighting (IPW) approach standardized to the SGA group. Since it is difficult to adjust for many confounding factors in the case of rare events such as major congenital malformations with logistic regression and propensity score matching, the IPW approach was used to adjust for confounders.[22,23] The propensity score was based on a logistic regression model with all maternal characteristics. We also estimated crude and adjusted ORs for elective abortion. All statistical analyses were performed using R software, version 4.1.1 (R Foundation for Statistical Computing; Vienna, Austria).

### Ethics

This study was approved by the ethics committee of the NCCHD (accession No. 2186).

## RESULTS

From October 2005 to December 2016, JDIIP received applications for medication counseling from 7,249 pregnant women. In our study, 593 women were exposed to at least 1 SGA during pregnancy. Of these, 520 (87.7%) provided informed consent for participation in the pregnancy outcome survey. Valid responses were received from 404 pregnant women (77.7%). Moreover, among 5,726 pregnant women who were not exposed to any known teratogens, 5,139 (89.7%) provided consent. We received valid responses from 4,328 pregnant women (84.2%). The SGA group had a lower survey response rate (77.7%) than the comparison group (84.2%), although the percentages of patients who initially agreed to participate were similar (87.7% and 89.7%, respectively) (Figure 1). The SGA group included women exposed to risperidone (n = 71), paliperidone (n = 2), perospirone (n = 32), blonanserin (n = 24), olanzapine (n = 83), quetiapine (n = 91), aripiprazole (n = 147), and more than 1 SGA (n = 45).

### Maternal Characteristics

We presented demographic and other background characteristics in Table 1. The percentage of primiparas was significantly higher in the SGA group. Preconception BMI was higher in the SGA group ($P < .001$). The percentage of women who reported drinking alcohol after knowing that they were pregnant was 2.2% in the SGA group and 1.6% in the comparison group. The percentage of nonsmokers was 73.8% in the SGA group and 86.1% in the comparison group ($P < .001$). After becoming aware of their pregnancy, 10.4% of women in the SGA group continued to smoke, compared with 3.7% in the comparison group.

Among 404 women in the SGA group, none used narcotics or methamphetamine and 1 woman used other illicit drugs. Among 4,324 women in the comparison group, 3 used narcotics, 3 used methamphetamines, and 1 used other illicit drugs; data were missing for 4 women. Regarding occupational exposures, 1 of 404 women in the SGA group was exposed to radiation and 3 of 404 women were exposed to organic solvents, with data missing for 1 woman. In the comparison group, 36 of 4,319 women were occupationally exposed to radiation and 52 of 4,319 were exposed to organic solvents, with data missing for 9 women.

A history of diabetes mellitus was observed in 3.0% of women in the SGA group and 1.1% of women in the comparison group ($P = .005$). In the SGA group, 98.0% of women had history of a psychiatric disorder (depression, 32.4%; schizophrenia, 31.2%; and bipolar disorder, 9.4%), compared with 27.1% of women in the comparison group ($P < .001$).

### Pregnancy Outcomes

We summarized pregnancy outcomes in Table 1. The live birth rate in the SGA group was 86.9%, which was slightly lower than the rate in the comparison group (90.1%). No

**Table 1. Maternal Characteristics and Pregnancy Outcomes With and Without SGA Exposure During the First Trimester[a]**

| Variable | Pregnant Women | | | Pregnant Women With Live Births | | |
|---|---|---|---|---|---|---|
| | SGA Group (n = 404) | Comparison Group (n = 4,328) | *P* Value | SGA Group (n = 351) | Comparison Group (n = 3,899) | *P* Value |
| Age at contact, median (interquartile range), y | 33 (29–36) | 32 (29–35) | .055 | 33 (29–36) | 32 (29–35) | .060 |
| Gestational age at contact, median (interquartile range), wk | 9.1 (6.7–14.7) | 8.6 (6.7–12.0) | .017 | 9.9 (7.0–16.2) | 8.9 (8.9–12.6) | .002 |
| BMI, median (interquartile range), kg/m$^2$ | 21.4 (19.3–24.5) | 20.0 (18.7–22.0) | < .001 | 21.5 (19.3–24.2) | 20.0 (18.7–22.0) | < .001 |
| Missing, n | 2 | 2 | | 1 | 2 | |
| Pregnancy history | | | | | | |
| ≥ 1 prior pregnancy | 163 (40.3) | 2,488 (57.5) | < .001 | 140 (39.9) | 2,226 (57.1) | < .001 |
| Missing, n | 0 | 4 | | 0 | 3 | |
| ≥ 1 prior spontaneous abortion | 62 (15.3) | 695 (16.1) | .776 | 53 (15.1) | 616 (15.8) | .818 |
| Missing, n | 1 | 4 | | 1 | 3 | |
| ≥ 1 elective abortion | 69 (17.1) | 613 (14.2) | .119 | 58 (16.5) | 553 (14.2) | .233 |
| Missing, n | 1 | 3 | | 1 | 2 | |
| Folic acid use | | | | | | |
| No | 217 (53.7) | 2,468 (57.0) | .140 | 182 (51.9) | 2,198 (56.4) | .072 |
| Yes | | | | | | |
| Before conception | 66 (16.3) | 574 (13.3) | | 56 (16.0) | 515 (13.2) | |
| After pregnancy was known | 120 (29.7) | 1,232 (28.5) | | 112 (31.9) | 1,138 (29.2) | |
| Missing, n | 1 | 49 | | 1 | 44 | |
| Alcohol use | | | | | | |
| No | 235 (58.2) | 2,429 (56.1) | .463 | 204 (58.1) | 2,193 (56.2) | .537 |
| Yes | | | | | | |
| Until pregnancy was known | 160 (39.6) | 1,828 (42.2) | | 140 (39.9) | 1,644 (42.2) | |
| Even after becoming pregnant | 9 (2.2) | 68 (1.6) | | 7 (2.0) | 60 (1.5) | |
| Missing, n | 0 | 2 | | 0 | 2 | |
| Smoking | | | | | | |
| No | 298 (73.8) | 3,727 (86.1) | < .001 | 262 (74.6) | 3,378 (86.6) | < .001 |
| Yes | | | | | | |
| Until pregnancy was known | 64 (15.8) | 439 (10.1) | | 58 (16.5) | 385 (9.9) | |
| Even after becoming pregnant | 42 (10.4) | 161 (3.7) | | 31 (8.8) | 135 (3.5) | |
| Missing, n | 0 | 1 | | 0 | 1 | |
| Unplanned pregnancy | 209 (51.7) | 2,743 (63.4) | < .001 | 179 (51.0) | 2,445 (62.7) | < .001 |
| Missing, n | 2 | 17 | | 0 | 7 | |
| Diabetes* | | | | | | |
| Yes | 12 (3.0) | 49 (1.1) | .005 | 12 (3.4) | 43 (1.1) | .001 |
| No | 392 (97.0) | 4,271 (98.7) | | 339 (96.6) | 3,849 (98.7) | |
| Missing, n | 0 | 8 | | 0 | 7 | |
| Hypertension* | | | | | | |
| Yes | 5 (1.2) | 50 (1.2) | .808 | 5 (1.4) | 44 (1.1) | .598 |
| No | 399 (98.8) | 4,268 (98.6) | | 346 (98.6) | 3,846 (98.6) | |
| Missing, n | 0 | 10 | | 0 | 9 | |
| Epilepsy* | | | | | | |
| Yes | 5 (1.2) | 54 (1.2) | 1.000 | 4 (1.1) | 52 (1.3) | 1.000 |
| No | 399 (98.8) | 4,265 (98.5) | | 347 (98.9) | 3,839 (98.5) | |
| Missing, n | 0 | 9 | | 0 | 9 | |
| Psychiatric disorder* | | | | | | |
| Yes | 396 (98.0) | 1,176 (27.2) | < .001 | 345 (98.3) | 1,049 (26.9) | < .001 |
| Depression | 131 (32.4) | 454 (10.5) | | 114 (32.5) | 394 (10.1) | |
| Schizophrenia | 126 (31.2) | 9 (0.2) | | 110 (31.3) | 6 (0.2) | |
| Bipolar disorder | 38 (9.4) | 26 (0.6) | | 32 (9.1) | 23 (0.6) | |
| No | 8 (2.0) | 3,147 (72.7) | | 6 (1.7) | 2,846 (73.0) | |
| Missing, n | 0 | 5 | | 0 | 4 | |
| Pregnancy outcome | | | | | | |
| Live birth | 351 (86.9) | 3,899 (90.1) | .073 | … | … | … |
| Stillbirth | 3 (0.7) | 18 (0.4) | | … | … | |
| Spontaneous abortion | 34 (8.4) | 313 (7.2) | | … | … | |
| Elective abortion | 16 (4.0) | 98 (2.3) | | … | … | |
| Major malformation | … | … | … | 3 (0.9) | 70 (1.8) | .280 |

[a]Data shown as n (%) unless otherwise noted.
*Information on diagnosis was up to the point of contact.
Abbreviations: BMI = body mass index, SGA = second-generation antipsychotic.

**Table 2. Odds Ratios (ORs) for Live Births (n = 4,618) and Major Malformations (n = 4,250) by SGA Exposure Status**

| | | | Univariate | | | | Multivariate (Excludes Participants With Missing Data) | | | | | | IPW Using the Estimated Propensity Score (Excludes Participants With Missing Data) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Variable | n | Live Birth | OR | 95% CI | *P* Value | | Variable | n | Live Birth | aOR | 95% CI | *P* Value | Variable | n | Live Birth | aOR | 95% CI | *P* Value |
| Comparison group | 4230 | 3,899 | 1.00 | | | | Comparison group | 4,227 | 3,896 | 1.00 | Reference | | Comparison group | 4,146 | 3823 | 1.00 | | |
| SGA group | 388 | 351 | 0.81 | 0.56–1.15 | .235 | | SGA group | 388 | 351 | 0.88 | 0.58–1.19 | .307 | SGA group | 382 | 346 | 0.78 | 0.50–1.21 | .273 |
| | | | | | | | | | Alcohol use | | | | | | | | | |
| | | | | | | | No | 2,603 | 2,396 | 1.00 | Reference | | | | | | | |
| | | | | | | | Yes | 2,012 | 1,851 | 1.01 | 0.81–1.26 | .918 | | | | | | |
| | | | | | | | | | Smoking | | | | | | | | | |
| | | | | | | | No | 3,942 | 3,638 | 1.00 | Reference | | | | | | | |
| | | | | | | | Yes | 673 | 609 | 0.81 | 0.60–1.07 | .141 | | | | | | |
| Variable | n | MM | OR | 95% CI | *P* value | | Variable | n | MM | aOR | 95% CI | *P* value | Variable | n | MM | aOR | 95% CI | *P* value |
| Comparison group | 3899 | 70 | 1 | Reference | | | Comparison group | 3,896 | 70 | 1.00 | Reference | | Comparison group | 3,823 | 69 | 1.00 | Reference | |
| SGA group | 351 | 3 | 0.47 | 0.15–1.50 | .204 | | SGA group | 351 | 3 | 0.47 | 0.15–1.50 | .201 | SGA group | 346 | 3 | 0.44 | 0.12–1.48 | .179 |
| | | | | | | | | | Alcohol use | | | | | | | | | |
| | | | | | | | No | 2,396 | 47 | 1.00 | Referent | | | | | | | |
| | | | | | | | Yes | 1,851 | 26 | 0.71 | 0.44–1.16 | .175 | | | | | | |
| | | | | | | | | | Smoking | | | | | | | | | |
| | | | | | | | No | 3,638 | 64 | 1.00 | Referent | | | | | | | |
| | | | | | | | Yes | 609 | 9 | 0.92 | 0.45–1.88 | .829 | | | | | | |

Abbreviations: aOR = adjusted odds ratio, IPW = inverse probability weighting, MM = major malformation, OR = odds ratio, SGA = second-generation antipsychotic.

statistically significant difference was observed in the crude OR for live births ($P = .235$), OR adjusted for alcohol use and smoking ($P = .307$), and OR adjusted for all maternal characteristics with the IPW approach ($P = .273$) (Table 2).

Major congenital malformations occurred in 0.9% of live births (3/351) in the SGA group and 1.8% of live births (70/3,899) in the comparison group (Table 1). Three live children born to mothers in the SGA group had the following major congenital malformations: right hydronephrosis, complex malformation, and spina bifida and hydrocephalus (n = 1 for each). Right hydronephrosis as well as spina bifida and hydrocephalus were reported in children with prenatal exposure to quetiapine, whereas spina bifida and hydrocephalus were found with prenatal valproate exposure (Table 3). Six live children born to mothers in the SGA group had minor congenital malformations: hemangioma (risperidone), patent foramen ovale (quetiapine), inguinal hernia (quetiapine), right inguinal hernia (risperidone), hydrocele (aripiprazole), and hypertrophic pyloric stenosis (quetiapine). No statistical significance was observed for the crude OR for major congenital malformations among live births ($P = .204$), and we did not find differences after adjustment for alcohol and smoking ($P = .201$) or all maternal characteristics ($P = .179$) (Table 2).

The elective abortion rate in the SGA group was 4.0%, which was moderately higher than that of the comparison group (2.3%). The crude OR for elective abortion in the SGA group relative to the comparison group was 1.78 (95% CI, 1.04–3.05; $P = .036$). However, the OR adjusted for alcohol use and smoking was not statistically significant (adjusted OR = 1.61; 95% CI, 0.93–2.77; $P = .090$). The OR adjusted for all maternal characteristics derived from the IPW approach was not statistically significant (adjusted OR = 1.72; 95% CI, 0.95–3.09; $P = .073$).

## DISCUSSION

SGA exposure during the first trimester was not associated with an increased risk of major congenital malformations in Japan. This study is the first Japanese observational cohort study to evaluate the risk of major congenital anomalies associated with first-trimester SGA exposure. Our study identified major congenital malformations in 0.9% of children (3/351) with first-trimester SGA exposure and 1.8% of children (78/3,899) without exposure to known teratogens. First-trimester SGA exposure is not associated with a significant difference in the risk of major congenital malformations compared with no exposure to teratogenic drugs (adjusted OR = 0.44; 95% CI, 0.12–1.48). Spina bifida and hydrocephalus have been reported in children with prenatal exposure to valproic acid, which was associated with an increased risk of major congenital malformations, especially spina bifida.[24,25] Only one case series[26] has investigated SGA exposure from days 28 to 50 of gestation in a Japanese population. There were no major malformations among 25 live-born children. In general, the International Clearinghouse for Birth Defects Surveillance and Research

**Table 3. Summary of Major Malformations (n = 3)**

| Major Malformation | First-trimester SGA exposure | Maternal | | Gestational age | Other first-trimester exposures | Alcohol use and smoking |
|---|---|---|---|---|---|---|
| | | Age at delivery, y | Medical history | | | |
| Right hydronephrosis | Quetiapine | 40 | Bipolar disorder, hypertension | 34 w, 5 d | Etizolam, brotizolam, valproic acid, zopiclone, perphenazine | No |
| Abnormalities of the heart, kidney, head, and ear (details unknown) | Perospirone | 26 | Schizophrenia | 40 w, 6 d | Trazodone | No |
| Spina bifida, hydrocephalus | Quetiapine | 36 | Bipolar disorder | 38 w, 3 d | Sertraline, valproic acid | No |

Abbreviation: SGA = second-generation antipsychotic.

JAPAN includes approximately 10% of all Japanese infants, and the frequency of malformations was 2.90% in 2018.[27]

Several studies have reported results similar to ours.[8,9,12–14] In studies of the general population and the prospective study involving TIS in Canada and Israel and women in England,[14] major congenital malformations were reported in 1 of 110 live-born children with first-trimester SGA exposure. Pregnant women who were not exposed to teratogenic agents were used as a comparison group, which was similar to the comparison group in our study. In a study using the Medicaid Analytic Extract database,[12] the prevalence of major malformations was 4.5% (412/9,258); no elevation in overall risk was observed. Furthermore, a study based on data from NPRAA on patients with psychiatric disorders as controls reported major congenital malformations in 1.4% of live infants (3/214) exposed to SGAs during the first trimester.[8] According to an updated report from NPRAA,[9] no elevation of risk was observed in 2.5% of live infants (16/640).

The choice of control group sometimes affects the results. In a prospective TIS-based study in Berlin,[15] malformations were reported in 5.1% of infants (22/430) with first-trimester SGA exposure. Among infants with first-trimester exposure to drugs without known teratogenic effects, an increased risk was observed (adjusted OR = 2.17; 95% CI, 1.20–3.91). However, the risk did not differ if infants who were exposed to first-generation antipsychotics were used as the control group. In this study, ascertainment of malformations was based on maternal self-report. Hospital discharge summaries were requested. However, no overall differences in risk were observed between those exposed to SGAs and either those exposed to first-generation antipsychotics or those unexposed to antipsychotics in a population-based birth cohort study in Finland.[13] Moreover, the general expected rate of malformations, instead of controls, was used in another large prospective study in Australia[16] with malformations in 6% (8/130) of live births, which was higher than the expected rate (3.1%).

The spontaneous abortion rate was 8.4% in the SGA group and 7.2% in the comparison group. Our results are consistent with those of a TIS-based study in Berlin,[15] which had spontaneous abortion rates of 8.2% and 9.6% in the SGA and comparison groups, respectively. Another study[14] showed a higher rate of abortion (14.5%) among pregnant women exposed to SGAs. Spontaneous abortions occur up to gestational week 12, whereas consultation occurred at weeks 8–9. The timing of the consultation might be a reason for the lower-than-average rate of spontaneous abortion observed in this study.

Maternal diabetes mellitus might be a potential confounder since uncontrolled diabetes is associated with fetal malformations in general. Weight gain and hyperglycemia are known adverse reactions to SGAs. The percentage of pregnant women with diabetes was 3.4% in women with SGA exposure and 1.8% in women without SGA exposure in a recent study.[12] In our study, the SGA group had a higher percentage of women with a history of diabetes than the comparison group (3.0% versus 1.1%), but there were no children of mothers with diabetes who had malformations. Another prospective study reported no significant between-group differences among women with diabetes by SGA exposure status.[14]

Several study limitations need to be acknowledged. First, we were unable to control for confounding factors such as maternal diagnosis or illness severity. Thus, we could not use women with illness as controls. This information was not available because data came from interactions with patients as part of a drug information service, not to diagnose or manage disease. In our study, 98.0% of women in the SGA group had a history of a psychiatric disorder. It was possible that the correct psychiatric diagnosis was intentionally not provided. To overcome the effects of other confounders, our IPW method was useful in adjusting for more confounders along with logistic regression. We adjusted for alcohol consumption and smoking using the IPW approach, which allowed us to obtain the effect of these exposures on the outcome.[22] Second, the percentage of women in the SGA group who agreed to complete the questionnaire was 87.7%, which was 2.0% lower than in the comparison group (89.7%). In contrast, the percentage of women who consented to the survey but did not return a completed questionnaire was 22.3% in the SGA group, which was higher than in the comparison group (15.8%). Reasons for not returning the postal questionnaire are unknown. If nonrespondents had a higher prevalence of malformations, we might have underestimated the risk. Third, underestimation of risk might have occurred with elective abortions. In the SGA group, 16 participants (4.0%) reported undergoing an elective abortion, which was higher than in the comparison group (2.3%).

Similar results were observed in another prospective study,[14] which reported an elective abortion rate of 9.9% in the SGA group and 1.3% in the control group. JDIIP counseling might have contributed to a lower elective abortion rate. Fourth, we interviewed women about over-the-counter supplements and concomitant medications, but we could not analyze these variables. Finally, there are potential differences between women who contact TIS and those who do not.[28,29] Thus, TIS data require attention to selection bias.

Despite these limitations, first-trimester SGA exposure might not be associated with an increased risk of major congenital malformations in Japan. It is important for women and health care providers to consider both the risk of medication exposure and the risk of untreated or undertreated psychiatric disorders when deciding whether to use SGAs during pregnancy. We previously demonstrated that accurate information on various medications from JDIIP could help concerned pregnant women with appropriate decision-making, and effective pregnancy counseling might increase the proportion of women wishing to continue their pregnancy.[30] Our findings might reassure pregnant women who require SGA therapy.

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