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Original Research

Pregnancy outcomes vary with disease progression in pregnant women with schizophrenia

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Summary

Purpose of investigation: It has been reported that pregnant women with schizophrenia have increased risk of adverse pregnancy outcomes. In this study, the authors aimed to investigate whether being admitted to the psychiatric ward during pregnancy affected pregnancy and neonatal outcomes in pregnant women with schizophrenia. *Materials and Methods:* One hundred and forty-eight women with schizophrenia who delivered after 22 gestational weeks at the present tertiary care center were classified into the inpatient group who needed to be admitted to the psychiatric ward because of aggravation of schizophrenia symptoms during pregnancy, and the outpatient group who did not require hospitalization. Patient characteristics, maternal outcomes, neonatal outcomes, and postpartum childcare environment were compared and analyzed. *Results:* There were no significant differences in the maternal outcomes between the inpatient and outpatient groups. The inpatient group had significantly higher rates of neonatal abstinence syndrome (13.8% *vs.* 0.8%, $p = 0.001$), placement in a child welfare facility (34.5% *vs.* 3.4%, $p < 0.001$), and intervention by hospital social workers (100% *vs.* 46.2%, $p < 0.001$) than the outpatient group. *Conclusions:* Maternal outcomes did not vary in pregnant women with schizophrenia regardless of disease conditions. Meanwhile, in mothers with poorly controlled disease condition, their neonates were at high risk of developing neonatal abstinence syndrome, and moreover, were more likely to need intervention by public authority such as social workers and child welfare facilities.

Key words: Antipsychotics; Inpatient; Neonatal abstinence syndrome; Pregnancy; Schizophrenia.

Introduction

The prevalence of schizophrenia is close to 1% worldwide. In case of women with this mental illness, its onset is commonly early in life. Because of the recent advances in mental healthcare and improvement in social support systems, more women with mental illness have the choice of becoming pregnant [1]. It has been reported that pregnant women with schizophrenia have increased risk for preterm birth, pre-eclampsia, small for gestational age (SGA), cesarean delivery, and thrombosis [2]. Moreover, they are at a risk of developing neonatal complications, such as neonatal abstinence syndrome, which is like somnolence tendency after exposure to psychotropic drugs in utero [3]. Although it is considered that their mental state is more likely to deteriorate during pregnancy because of endocrinological and psychological factors [4], the present authors' literature search on PubMed yielded no study mentioning the impact of disease progression of schizophrenia on pregnancy outcomes and on childcare environment. This study aimed to investigate whether being admitted to the psychiatric ward during pregnancy affected pregnancy and neonatal outcomes in pregnant women with schizophrenia.

Materials and Methods

In this study, the authors retrospectively analyzed data from medical records of 166 pregnant women with schizophrenia who delivered a live singleton infant on or after 22 weeks of gestation between January 2000 and July 2015 at the Perinatal Center for Maternity and Neonate, Yokohama City University Medical Center. This study was conducted with the approval of the ethics committee of the center. Eligible women were those who had been diagnosed as having schizophrenia before pregnancy according to the International Statistical Classification of Diseases and Related Health problems, 10th Revision (ICD-10, F20) and followed up by a psychiatrist. This study excluded six women who were newly diagnosed with schizophrenia during pregnancy and 12 women who were diagnosed with schizophrenia at another hospital but whose diagnosis was denied by the psychiatrists. The remaining 148 women were classified into the inpatient group including 29 women who needed to be admitted to the psychiatric ward because of aggravation of schizophrenia symptoms during pregnancy, and the outpatient group including 119 women who did not require hospitalization. Patient characteristics, pregnancy outcomes, neonatal outcomes, and postpartum childcare environment were compared and analyzed. Psychiatrists determined whether the women needed to be admitted to the psychiatric ward.

The patient characteristics data collected were age, gravidity, parity, body mass index (BMI) before pregnancy, smoking, history of infertility treatment, presence or absence of partners, and use of oral psychotropic drugs at delivery. The maternal outcomes were

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incidence rates of gestational hypertension and gestational diabetes mellitus (GDM), cesarean delivery, intrapartum abnormal hemorrhage, SGA, and preterm birth. The neonatal outcomes were umbilical artery pH (UApH), incidence rates of neonatal congenital anomalies and abstinence syndrome, admission to the neonatal intensive care unit (NICU), placement in a child welfare facility, and presence or absence of intervention by social workers. These outcomes were compared and analyzed between the two groups. Moreover, to assess the risk of developing neonatal abstinence syndrome, the neonates were divided into those with and without the syndrome, and the dosages of psychotropic drugs orally administered to the mothers were compared and analyzed. The types of orally administered psychotropic drugs analyzed were antipsychotics and benzodiazepines. The antipsychotics were defined as typical and atypical antipsychotics. To compare and analyze the amount of drugs orally administered to the mothers immediately before delivery, chlorpromazine equivalent doses [3] were used for antipsychotics, and diazepam equivalent doses [5] were used for benzodiazepines.

Infertility treatment was defined as those involving assisted reproductive technology, such as ovulatory drugs and artificial insemination, while the definition of partners also included those not legally married to the women. The amount of orally administered drugs was determined based on the dosage at the time of delivery. Gestational hypertension was defined as the new onset of hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) at or after 20 weeks of gestation in the absence of proteinuria.[6] While apparent cases of diabetes mellitus found during pregnancy were excluded, GDM was defined as a condition satisfying at least one of the following values on a 75-gram oral glucose tolerance test: pretest value ≥ 92 mg/dL, one-hour value ≥ 180 mg/dL, and two-hour value ≥ 153 mg/dL [7]. Preterm birth was defined as delivery at or after 22 weeks and before 37 weeks of gestation. Intrapartum abnormal hemorrhage was defined as blood loss of 500 mL or more in women undergoing vaginal delivery, and 1,000 mL or more in those undergoing cesarean delivery. In addition, SGA was defined as having a birth weight at or below 10th percentile for that gestational age.

Neonatal abstinence syndrome was defined as a condition diagnosed by neonatologists based on Lipsitz scores [8]. Admission to the NICU was determined by neonatologists, and the neonates admitted to the NICU received systemic management and treatment. Neonates placed in a child welfare facility were defined as those reared at out-of-home care facilities in the local communities. Intervention by social workers was defined as social-service supervision performed by medical social workers or lifestyle support counselors at local public health centers after delivery.

Data are expressed as median (range) or incidence (%). Statistical analyses were performed using SPSS Statistics version 23. For determination of coefficient of variation, Mann-Whitney U-test was used, and for comparison of categorical data between the groups, Fisher's exact test was used. A *p*-value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Of the 148 pregnant women with schizophrenia, 19.6% (29/148) were admitted to the psychiatric ward. The duration of stay in the ward ranged from four to 88 (median, 37) days.

The patient characteristics of the inpatient and outpatient groups are shown in Table 1. In the inpatient group, the smoking rate was 27.6% *vs.* 10.9% ($p = 0.021$), and the proportion of women taking oral psychotropic drugs was 100% *vs.* 84% ($p = 0.021$). These values were significantly higher than those in the outpatient group. However, no significant difference was observed in age, gravidity, parity, BMI before pregnancy, history of infertility treatment, and presence or absence of partners between the groups. Moreover, the proportion of women taking oral psychotropic drugs was significantly higher for both antipsychotics (100% *vs.* 82.4%, $p = 0.015$) and benzodiazepines (72.4% *vs.* 40.3%, $p = 0.02$) in the inpatient group than in the outpatient group.

Table 1. — Comparison of patient characteristics between the inpatient and outpatient groups.

	Inpatient group n=29	Outpatient group n=119	*p*-value
Hospitalization duration (days)	37 (4-88)	-	
Maternal age (years)	33 (24-41)	34 (16-46)	0.371
Gravidity	0 (0-7)	1 (0-8)	0.741
Multipara	10 (34.5%)	40 (33.6%)	0.929
Body mass index[a]	24.0 (17.0-34.5)	22.3 (17.1-44.4)	0.182
Smoking	8 (27.6%)	13 (10.1%)	**0.021**
Infertility treatment	0 (0%)	10 (8.4%)	0.106
Loss of partner	2 (6.9%)	6 (5.0%)	0.692
Medication	29 (100%)	100 (84%)	**0.021**
Antipsychotics[b]	29 (100%)	98 (82.4%)	**0.015**
	800 mg (75-3280)	200 mg (0-1703)	**<0.001**
Benzodiazepines	21 (72.4%)	48 (40.3%)	**0.002**
	10mg (0-65)	0mg (0-68)	**0.001**

[a]BMI before pregnancy was analyzed in 138 women, excluding ten women without data on height or weight. [b]Antipsychotics include typical and atypical antipsychotics.

In the inpatient group, no woman discontinued taking oral psychotropic medications on her own judgment after becoming pregnant. All women in this group were taking one type or more of oral psychotropic medications at the time of delivery. On the other hand, in the outpatient group, 16% (19/119) of the women were not receiving oral drug treatment at the time of delivery. Among them, oral medications were discontinued at the discretion of psychiatrists in 2.5% (3/119), based on the judgment of the women themselves in 1.7% (2/119), and not required in the remaining 11.7% (14/119) during pregnancy. In the inpatient group, 86.2% (25/29) of the women were admitted to the psychiatric ward immediately before delivery, and 72% (18/25) of them needed to continue inpatient care immediately after delivery. For the remaining seven women, psychiatrists determined that the continuation of hospitalization was unnecessary after delivery. In 2.5% (3/119) of the women in the outpatient group, their mental states deteriorated immediately after delivery, and they needed to be admitted to the psychiatric ward. Of the three women who needed hospitalization, two had discontinued oral medications during pregnancy on their own judgment.

The pregnancy outcomes of the inpatient and outpatient

Table 2. — *Comparison of pregnancy outcomes between the inpatient and outpatient groups*[a].

	Inpatient group	*Outpatient group*	*Odds ratio 95%CI*
Gestational week	39.9 (33.7-41.6)	39.4 (35.1-41.7)	
Gestational hypertension[b]	0 (0%)	2 (1.7%)	-
Gestational diabetes mellitus	5 (17.9%)	23 (19.3%)	0.870 0.300-2.524
Cesarean delivery	8 (27.6%)	26 (21.8%)	1.367 0.541-3.430
Preterm birth	2 (6.9%)	6 (5%)	1.395 0.267-7.297
Intrapartum abnormal hemorrhage	11 (37.9%)	33 (27.7%)	1.593 0.680-3.729
SGA	2 (6.9%)	11 (9.2%)	1.375 0.288-6.573
UApH	7.28 (7.14-7.37)	7.29 (7.07-7.45)	
Congenital anomaly[c]	3 (10.3%)	7 (5.9%)	1.846 0.447-7.624
Neonatal abstinence syndrome	4 (13.8%)	1 (0.8%)	18.880 2.023-176.178
Admission to NICU	5 (17.2%)	8 (6.7%)	2.891 0.870-9.610
Out-of-home care	10 (34.5%)	4 (3.4%)	15.132 4.305-53.186
Social service use	29 (100%)	55 (46.2%)	1.527 1.308-1.784

[a]*Adjusted for smoking.* [b]*There was no woman with proteinuria.*
[c]*Congenital anomalies of the neonates included cleft lip and palate, brachydactyly, cardiac malformation, esophageal hiatal hernia, Down syndrome, abdominal dropsy, hydronephrosis, accessory auricles, angioma, and nevus.*
95% CI: 95% confidence interval

groups are shown in Table 2. Between the two groups, no significant difference was observed in the incidence of gestational hypertension, GDM, cesarean delivery, preterm birth, intrapartum abnormal hemorrhage, and SGA.

When the neonatal outcomes were compared between the inpatient and outpatient groups, significant differences were observed in the incidence of neonatal abstinence syndrome (13.8% vs. 0.8%, $P = .001$), placement in a child welfare facility (34.5% vs. 3.4%, $P < .001$), and intervention by hospital social workers (100% vs. 46.2%, $P < .001$). No significant difference was observed in the incidence of congenital anomalies in the neonates and rate of admission to the NICU. There were 13 neonates who needed to be admitted to the NICU in both groups combined, including 5 neonates with neonatal abstinence syndrome, 4 with a congenital disorder (i.e., pulmonary atresia, esophageal hiatal hernia, trisomy 21, and causeless abdominal dropsy), 3 with respiratory disturbance (i.e., 1 with pneumothorax and 2 with transient tachypnea of the newborn), and 1 with severe fetal growth restriction (FGR). This neonate with severe FGR was admitted to the NICU for detailed examination because the neonate was delivered at37 weeks and 3 days of gestation with a birth weight of 1720 g. The dosages of antipsychotics orally administered to the five mothers of the neonates with neonatal abstinence syndrome were significantly higher than the dosages for the 143 mothers of the neonates without the syndrome (800 mg vs. 277 mg, $P = .005$). Similarly, the dosages of benzodiazepines orally administered to the five mothers of the neonates with neonatal abstinence syndrome were significantly higher than the dosages for the mothers of the neonates without the syndrome (44 mg vs. 0 mg, $P < .001$). In the five neonates with neonatal abstinence syndrome, the median duration of hospital stay was 13 days (12–62 days). Although three neonates required respiratory support (mask ventilation and intratracheal intubation) because of unstable respiratory status, respiratory support was withdrawn for all of them by the age of 2 days. The other two neonates were drowsy and irritable, but their conditions were ameliorated during follow-up.

Discussion

Among the pregnant women with schizophrenia, the inpatient group requiring admission to the psychiatric ward because of poor control of disease progression showed maternal pregnancy outcomes that were comparable to those shown by the outpatient group, in which the disease progression had been controlled favorably. However, in the inpatient group, the proportion of neonates who developed neonatal abstinence syndrome was significantly higher, and they were significantly more likely to need social support provided by social workers, child welfare facilities, and the like.

First, the pregnant women with schizophrenia showed no difference in maternal pregnancy outcomes regardless of disease progression. Views on whether pregnancy outcomes in pregnant women with schizophrenia are poorer than those in the general population vary among researchers, many of whom report that pregnancy outcomes tend to be comparable or slightly poorer in pregnant women with schizophrenia.[1,2, 4, 9-12] Vigod *et al.* [2] reported that the risks of preterm birth, hypertensive disorders of pregnancy, SGA, cesarean delivery, and thrombosis are higher in pregnant women with schizophrenia than in pregnant women without schizophrenia. In our study, in which the women were classified according to the disease progression of schizophrenia based on whether they had been admitted to the psychiatric ward, the smoking rates and the dosages of orally administered psychotropic drugs as patient background factors differed between the two groups. However, no intergroup difference in maternal pregnancy outcomes was observed after adjustment was made for smoking rates as a confounding factor. This result suggests that the disease progression of schizophrenia does not affect maternal outcomes.

Second, the neonatal outcomes were poorer in the inpa-

tient group because of a significantly higher incidence of neonatal abstinence syndrome and a higher proportion of the neonates requiring admission to the NICU. This was assumed to be because the dosages of psychotropic drugs orally administered to the mothers were significantly higher in the inpatient group than in the outpatient group. The reasons for the high risk of neonatal abstinence syndrome are reported to be associated with the dosage, timing, and duration of oral administration of benzodiazepine [13]. The higher incidence of neonatal abstinence syndrome in the inpatient group taking higher dosages of oral medications immediately before delivery in the present study supported the previously reported observation. Moreover, many reports indicate that, when mothers are taking oral antipsychotics or benzodiazepines, the incidence of neonatal complications, such as congenital anomalies and respiratory disturbance, is high [14, 15]. Consistent with this finding, the present study also showed that the neonates in the inpatient group who had been exposed to higher dosages of orally administered psychotropic drugs were more likely to be admitted to the NICU. Although some of the neonates with neonatal abstinence syndrome required respiratory care, the effect of the syndrome was temporary, and no neonate required any medical intervention at the time of discharge.

Third, the inpatient group was significantly more likely to require social support provided by social workers, child welfare facilities, and the like. Women with schizophrenia have reduced likelihood of having a partner or spouse. These contribute to the worsening of the relationship between a mother and a child in addition to the direct impact of schizophrenia [9, 16]. In the present study, although no difference in the presence or absence of partners was observed between the two groups, the need for appropriate intervention by public authority, including social workers and child welfare facilities, was significantly higher in the hospitalized patients who were mentally unstable. Because pregnant women with schizophrenia requiring hospitalization, due to mentally unstable condition during pregnancy, are also at high risk of experiencing difficulty in child rearing, it was suggested that social support is required for such mothers and their children.

The present is a retrospective study with a small sample size. Although the dosages of orally administered psychotropic drugs were assessed in the analysis regarding neonatal abstinence syndrome, there is no specific protocol for the dosages, which were determined at the discretion of psychiatrists. Furthermore, the authors did not examine pregnancies that resulted in spontaneous abortion or pregnancy termination. Because women with a more advanced disease are expected to more likely choose pregnancy termination, the impact of the disease progression of schizophrenia on pregnancy outcomes might have been underestimated. Despite these limitations, the present study showed that the impact of the disease progression of schizophrenia on maternal pregnancy outcomes was limited even in women with a more advanced disease who choose pregnancy. These results provide helpful information on pregnancy for affected women and their families.

Conclusion

In conclusion, maternal pregnancy outcomes did not vary in pregnant women with schizophrenia with disease progression. Meanwhile, in mothers with poorly controlled disease condition, their neonates were at high risk of developing neonatal abstinence syndrome. It was suggested that the high dosages of oral psychotropic drugs might be a reason for this. Moreover, women with schizophrenia that is more advanced and their neonates were more likely to need intervention by public authority including social workers and child welfare facilities.

References

[1] Vigod S.N., Seeman M.V., Ray J.G., Anderson G.M., Dennis C.L., Grigoriadis S., *et al.*: "Temporal trends in general and age-specific fertility rates among women with schizophrenia(1996-2009): A population-based study in Ontario, Canada". *Schizophrenia Res.,* 2012, *139*, 169.

[2] Vigod S.N., Kurdyak P.A., Dennis C.L., Newman A., Seeman M.V.: "Maternal and newborn outcomes among women with schizophrenia: a retrospective population-based cohort study". *BJOG*, 2014, *121*, 566.

[3] Kane JM.: "Schizophrenia". *NEJM*., 1996, *334*, 34.

[4] Jablensky A.V.: "Morgan V. Zubrick SR. Bower C. Yellachich LA.: "Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders". *Am. J. Psychiatry*, 2005, *162*, 79.

[5] Ashton H.: "The diagnosis and management of benzodiazepine dependence". *Current Opinion in Psychiatry*, 2005, *18*, 249.

[6] American College of Obstetricians and Gynecologists, Task Force on Hypertension in Pregnancy: "Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy". *Obstet. Gynecol*., 2013, *122*, 1122.

[7] Metzger B.E., Gabbe S.G., Persson B.: "International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy". *Diabetes Care*, 2010, *33*, 676.

[8] Lipsitz P.J.: "A Proposed Narcotic Withdrawal Score for Use with Newborn Infants. A pragmatic evaluation of its efficacy". *Clin. Pediatr*., 1975, *14*, 592.

[9] Robinson G.E.: "Treatment of Schizophrenia in pregnancy and postpartum". *J. Popul. Ther. Clin. Pharmacol*., 2012, *19*, e380.

[10] Matevosyan N.R.: "Pregnancy and postpartum specifics in women with schizophrenia: a meta-study". *Arch. Gynecol. Obstet*., 2011, *283*, 141.

[11] Gentile S.: "Antipsychotic therapy during early and late Pregnancy, A systematic review". *Schizophrenia Bulletin*, 2010, *36*, 518.

[12] Yaeger D., Smith H.G., Altshuler L.L.: "Atypical antipsychotics in the treatment of schizophrenia during pregnancy and the postpartum". *Am J Psychiatry*., 2006, *163*, 2064.

[13] Iqbal M.M.. Sobhan T., Ryals T.: "Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant". *Psychiatr Serv*., 2002, *53*, 39.

[14] Vigod S.N., Gomes T., Wilton A.S., Taylor V.H., Ray J.G.: "Antipsychotic drug use in pregnancy: high dimensional, propensity

matched, population based cohort study". *BMJ*, 2015, *350*, h2298.
[15] Kieviet N., Dolman K.M., Honig A.: "The use of psychotropic medication during pregnancy: how about the Newborn?". *Neuropsychiatr Dis Treat*., 2013, *9*, 1257.
[16] Ranning A., Munk Laursen T., Thorup A., Hjorthoj C., Nordentoft M.: "Serious mental illness disrupted caregiving for children: a nationwide, register-based cohort study". *J. Clin. Psychiatry*., 2015, *76*, 1006.

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