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Relapse of psychiatric symptoms after discontinuation of antipsychotics in pregnant women with schizophrenia: a retrospective study

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ABSTRACT

This study aimed to examine the effect of discontinuation of antipsychotic medication on the relapse of psychiatric symptoms in pregnant women with schizophrenia. We investigated the medical records of all consecutive pregnant women with schizophrenia who continuously visited and delivered their children at Chiba University Hospital from January 2007 to January 2019. We retrospectively assessed the scores on the Clinical Global Impression of Change scale (CGI-C) during the period when psychiatric symptoms changed most during the pregnancy. A CGI-C score of 5 or more was defined as a relapse. Twenty-eight patients consisting of the maintained treatment group (n = 18) and the discontinuation group (n= 10) were recruited. During pregnancy, the relapse rate in the maintained treatment group (16.7%) was significantly lower than that in the discontinuation group (90.0%). This study demonstrates a high relapse rate in pregnant women discontinuing their antipsychotic medication, as well as during the non-pregnancy period.

Keywords: antipsychotics, pregnancy, relapse, schizophrenia

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Introduction

Antipsychotic medications play a crucial role in treating schizophrenia, and a stable treatment regimen prevents relapse of psychotic symptoms [1]. A systematic review and meta-analysis revealed that continued antipsychotic treatment for patients with schizophrenia largely reduces relapse rates after 1 year, compared to placebo [1]. However, pregnancy is likely to cause discontinuation of medical treatment in female patients with psychiatric diseases [2].

The typical age of onset for schizophrenia ranges between late adolescence and early thirties [3], highly overlapping with childbearing age. Recently, not a few women with schizophrenia experience pregnancy and childbirth [4]. Although only one previous study has reported that two-thirds of women with schizophrenia with psychiatric symptoms, and a history of psychotic episodes, discontinued psychiatric visits during their pregnancy [5], few studies have investigated the relationship between continuation/discontinuation of antipsychotics and relapse rates of psychiatric symptoms in pregnant women with schizophrenia. There is one previous report suggesting that the estimated rate of relapse due to discontinuation of medication treatment is 65% in pregnant women with schizophrenia, specifically with reference to the data of non-pregnant people with schizophrenia [6].

The aim of this study was, thus, to investigate the effect of continuation/discontinuation of antipsychotic medication on relapse of psychiatric symptoms in female patients with schizophrenia during the pregnancy period. To examine this, we conducted a retrospective survey using a medical-record review method.

Subjects and Methods

Study design and participants

This was a retrospective cohort study investigating the medical records of all consecutive pregnant women seen at Chiba University Hospital from January 2007 to January 2019, who met the diagnostic criteria for schizophrenia according to the DSM-5, and were continually treated and delivered their children at the hospital.

Ethical considerations

The protocol used in the present study was reviewed and approved by the Ethics Committee of the Graduate School of Medicine at Chiba University (ID: 3387). Using the opt-out method, all pertinent information about this study was disclosed on the website of the Department of Psychiatry, Graduate School of Medicine, Chiba University. This study was conducted in accordance with tenets of the Declaration of Helsinki.

Assessment of psychiatric symptoms

Psychiatric symptoms were assessed retrospectively with The Clinical Global Impression of Severity scale (CGI-S) and Clinical Global Impression of Change scale (CGI-C) from medical records before and during pregnancy. The period of the CGI-S was immediately before pregnancy. In this study, we used the CGI-C to evaluate the psychiatric symptoms changed most during the pregnancy. A score of 5 or more on the -C was defined as "relapse".

Groups of participants

We divided the participants in this study into the following two groups: (1) The maintained treatment group, in which participants continued to take antipsychotic medication throughout pregnancy, including following a dose reduction strategy; (2) the discontinuation group, in which patients discontinued use of antipsychotics immediately after confirmation of the pregnancy.

Maternal and neonatal data

With regard to maternal and neonatal outcomes, the data obtained from the medical records provided the following information: (1) pregnancy complications; (2) labor complications; (3) neonatal complication.

Primary and secondary outcomes

The primary outcome measure of this study was to identify the differences in relapse rates of psychiatric symptoms, during the pregnancy, due to medication discontinuation. The secondary observations were the maternal/neonatal outcomes.

Statistical analyses

Statistical analyses were performed using SPSS, Version 19.0 (SPSS Inc., Chicago, IL, USA). Fisher's exact tests were used for comparing categorical variables, including the primary outcome. Student's t-test was performed for all continuous variables. The statistical significance was set at $p < 0.05$.

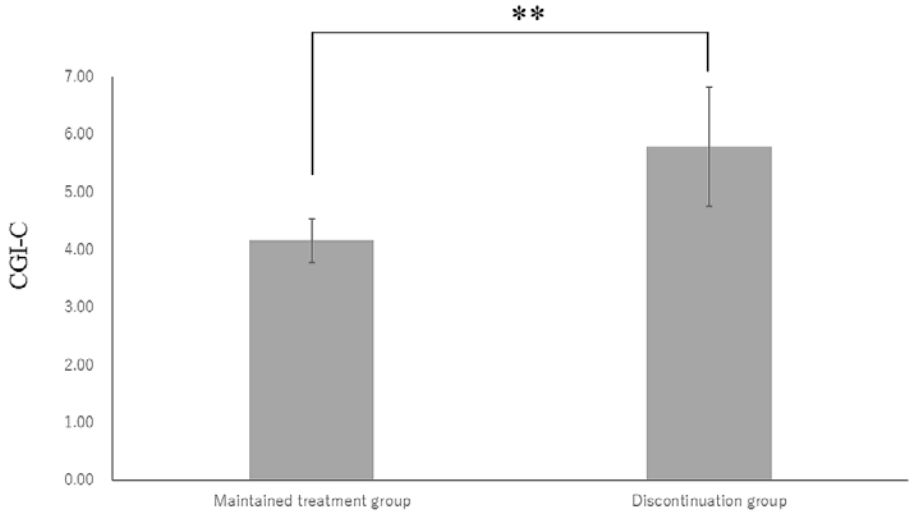

Figure 1. The Clinical Global Impression of Change scale (CGI-C) scores observed during pregnancy in the two groups.
The scores of the CGI-C in the discontinuation group are higher than those of the maintained treatment group. Error bars represent standard deviation of the mean. $^{**}p < 0.01$.

Results

Participant characteristics

A total of 28 pregnant women with schizophrenia were recruited during the survey period. Below are the demographic characteristics of all participants of this study. The pregnant women with schizophrenia were classified into the maintained treatment group (mean [SD], age 33.1 [4.3] years; n = 18), and the discontinuation group (mean [SD], age 34.2 [2.7]; n = 10). Regarding use of antipsychotics, aripiprazole was used most frequently, followed by olanzapine. There were no significant differences among the two groups in the CGI-S score and the chlorpromazine (CP)-equivalent daily dose, before pregnancy.

Relapse during the pregnancy

CGI-C scores in the discontinuation group were significantly higher than those in the maintained treatment group (t (10.40) = -4.82, $p < 0.01$; Figure 1). Additionally, during pregnancy, the relapse rate of psychiatric symptoms in the maintained treatment group (16.7 %) was significantly lower than that in the continuation group (90.0%) (Fisher's exact test, two-tailed, $p < 0.001$). In the maintained group, three patients were assessed as "in relapse" having a score of ≥ 5 on the CGI-C scale, during pregnancy.

Regarding antipsychotic medication use during pregnancy, of ten patients in the discontinuation group, eight resumed antipsychotic medication due to relapse in symptoms, and two were without antipsychotics until delivery. Among the eight patients who resumed antipsychotic treatment, three required a higher dosage of antipsychotics (as CP-equivalent) compared to the dose taken before pregnancy. The mean (SD) CP-equivalent doses in the patients are the following: 406.3 (259.7) mg/day before pregnancy, 337.5 (298.5) after reintroduction, respectively. There is no significance between before and after reintroduction of medication.

Maternal Outcomes

Maternal and fetal/neonatal outcomes during the perinatal period are summarized in Table 1. Gestational diabetes mellitus (GDM) was the most commonly observed adverse maternal outcome (5/28, 17.9%) in this study. Of five patients with GDM, three were in the maintained treatment group. Of these patients, two patients were treated with olanzapine, and one with aripiprazole. Emergent caesarean sections were performed for two patients in the maintained treatment group (one was due to arrest of labor, and the other due to non-reassuring fetal status with decreased fetal heart rate at the beginning of delivery), and for one in the discontinuation group due to preterm prelabor rupture of membranes.

Fetal/Neonatal Outcomes

Regarding adverse fetal/neonatal outcomes, one patient who was continuously treated with olanzapine,

Table 1. Maternal and fetal/neonatal outcomes

	Maintained treatment group (n = 18)	Discontinuation group (n = 10)
Maternal outcomes, n (%)		
Gestational diabetes mellitus	3 (16.7)	2 (20.0)
Caesarean section	6 (33.3)	2 (20.0)
Elective CS	3 (16.7)	1 (10.0)
Emergent CS	3 (16.7)	1 (10.0)
Oligohydramnios	1 (5.6)	1 (10.0)
Arrest of labor	2 (11.1)	0 (0.0)
Preterm prelabor rupture of membranes	0 (0.0)	1 (10.0)
Breech presentation	1 (5.6)	0 (0.0)
Neonatal outcomes, n (%)		
Preterm birth (< 37 weeks)	0 (0.0)	1 (10.0)
Low birth weight infant (< 2500 g)	2 (5.6)	1 (10.0)
Fetal growth restriction	0 (0.0)	1 (10.0)
Non-reassuring fetal status*	1 (5.6)	0 (0.0)
Congenital anomaly**	1 (5.6)	0 (0.0)
Neonatal withdrawal syndrome	1 (5.6)	0 (0.0)
Apgar ≤ 7 at 1 min	2 (11.1)	1 (10.0)
Apgar ≤ 7 at 5 min	0 (0.0)	0 (0.0)
Neonatal jaundice	1 (5.6)	1 (10.0)
Immunological hemolytic jaundice	0 (0.0)	1 (10.0)
NICU admission, n (%)	9 (50.0)	5 (50.0)
Length of hospitalization in NICU*** days (SD)	7.1 (6.2)	5.4 (3.8)

* This case had decreased fetal heart rate at the beginning of delivery.
**This case had congenital duodenal atresia and distorted common bile duct at birth.
***The newborn with the congenital anomaly was excluded from the days count, owing to being the extreme outlier.
Abbreviations: CS, Caesarean section; NICU, neonatal intensive care unit; SD, standard deviation.

(1.25 mg per day, in the maintained treatment group) delivered a newborn with poor neonatal adaptation syndrome (PNAS), who experienced transient tachypnea and mild hypoxemia with SpO2 = 86% on room air; these symptoms dissipated 5 hours later. Although there were 3 newborns with Apgar score ≤ 7 at 1 min, none of them had Apgar score ≤ 7 at 5 min (Table 1). However, there was one serious case of congenital duodenal atresia, obstructive jaundice due to distorted common bile duct, and associated MRSA sepsis in a neonate born to a patient in the maintained treatment group. After surgery and vancomycin administration, the newborn recovered and was discharged at the age of 102 days. Other common fetal/neonatal complications included low birth weight and neonatal jaundice (Table 1). Fifteen participants in the maintained treatment group and seven in the discontinuation group, had no maternal or neonatal complications during the perinatal period.

Discussion

In the present study, the relapse rate in pregnant women with schizophrenia who discontinued antipsychotic medication during pregnancy was 90%; in contrast, women who continued medication showed a relapse rate of 16.7%. After placebo treatment, the relapse rate at one-year follow-up was 64% in patients with schizophrenia [1], suggesting that the present findings are considered to be natural consequences of medication discontinuation. Thus, prior to pregnancy, female patients with schizophrenia and their families should be informed about the importance of maternal mental health during pregnancy to promote better outcomes for both mothers and their offspring.

GDM was the most commonly observed adverse maternal event among the participants, regardless of antipsychotic medication use. Use of atypical antipsychotics in pregnancy is associated with an increased risk of GDM due to the metabolic side ef-

fects of some antipsychotics, such as olanzapine and quetiapine [7]. Considering that GDM can lead to an increased risk of "large-for-gestational-age" infants, neonatal hypoglycemia and type 2 diabetes/ metabolic syndrome in their offsprings [8], special attention should be paid to prevent GDM in pregnant patients with schizophrenia and their offsprings.

Gastrointestinal defects, such as congenital duodenal atresia and malformed common bile duct, were observed in one newborn infant whose mother continued antipsychotic medication during pregnancy. Recent systematic reviews and meta-analysis reported that fetal exposure to antipsychotics is associated with an increased risk of major congenital malformations, although this conclusion is still debated [9,10]. The present study did identify low birth weight and PNAS in infants, which are consistent with previous studies reporting increased risks of low birth weight [11] and PNAS or neonatal withdrawal syndrome in the newborns of mothers treated with antipsychotics [12].

There are two major limitations to this study. First, this study was designed as a retrospective chart review with a small sample. Second, this study did not include a group of healthy pregnant women as a comparison group. To resolve these issues, future studies with a larger sample size and comparison group of healthy subjects are needed.

In conclusion, this study demonstrated a high relapse rate of psychiatric symptoms in women with schizophrenia who discontinue antipsychotic medication during pregnancy, and this was seen during non-pregnancy periods as well.

CONFLICTS OF INTEREST

Dr. Tasuku Hashimoto has received a research support from Sodegaura Satsukidai hospital; Dr. Kanahara has received honoraria from Otsuka Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Janssen Pharmaceutical K.K. and Meiji Seika Pharma. Co., Ltd.; Professor Masaomi Iyo has received consultant fees from Eli Lilly Japan K. K., Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Abbott Japan Co., Ltd., and Janssen Pharmaceutical K.K., and has reported honoraria from Janssen Pharmaceutical K.K., Eli Lilly Japan K.K., Otsuka Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd., Ono Pharmaceutical Co., Ltd., GlaxoSmithKline K.K., Takeda Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., MSD K.K., Eisai Co. Ltd., Daiichi-Sankyo Co. Ltd., Novartis Pharma K.K., Teijin Ltd., Shionogi & Co., Ltd., Hisamitsu Pharmaceutical Co., Inc., and Asahi Kasei Corporation. The other authors have no conflicts of interest to disclose.

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