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CASE REPORT

Changes in the pharmacokinetics of lurasidone in a pregnant woman with schizophrenia

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Abstract

Background: The population of pregnant women with schizophrenia is increasing. Managing schizophrenia during pregnancy poses unique challenges due to the potential effects of second-generation antipsychotics on maternal mental health and fetal development and changes in drug pharmacokinetics. Evidence on how physiological changes during pregnancy affect the levels of second-generation antipsychotics, particularly lurasidone, is limited. There are no data on effectively managing medications and decreasing side-effects during pregnancy.

Case Presentation: We presented the case of a 34-year-old pregnant woman with schizophrenia who had a stable condition with lurasidone therapy before conception. However, she exhibited worsening psychiatric symptoms during the third trimester of pregnancy. Serial measurements of serum lurasidone levels were performed during late pregnancy. Despite maintaining the same dosage, her serum lurasidone levels significantly decreased during the third trimester (maximum decrease of ~65% compared with baseline) and rapidly increased during the postpartum period, coinciding with an improvement in psychiatric symptoms.

Conclusion: Decreased serum lurasidone levels during pregnancy may increase the risk of symptom worsening in patients with schizophrenia. Hence, clinicians should be knowledgeable about the risk of decreased drug levels and the need for therapeutic monitoring and dosage adjustments during pregnancy to maintain treatment efficacy and maternal and fetal health.

KEYWORDS
antipsychotic therapy, lurasidone, pregnancy, schizophrenia, serum levels

BACKGROUND

Schizophrenia, a chronic disorder with a prevalence of ~1%, usually develops during adolescence or early adulthood and female reproductive years.[1,2] Patients with schizophrenia reportedly have fewer opportunities for pregnancy and childbirth compared with the general female population.[3] However, with the introduction of second-generation antipsychotics and improvements in psychiatric rehabilitation services, the chances of marriage and pregnancy among these patients have increased.[4]

The primary concern among pregnant patients with schizophrenia is the potential impact of antipsychotics on the fetus. Preliminary data have revealed that the risk of congenital malformations associated with antipsychotic exposure during pregnancy is minimal.[5,6] Pregnant women with schizophrenia are at increased risk of obstetric complications, such as hypertensive disorders of pregnancy, preterm

birth, and low-birth-weight infants, which may be influenced by their behavioral characteristics rather than use of antipsychotics.[7] Nevertheless, due to concerns regarding the effect of antipsychotics on fetal development, some patients discontinue their medication. This notion is supported by a report showing that >50% of women who were taking antipsychotics before pregnancy discontinued their treatment during pregnancy.[8]

No studies have specifically focused on the relapse rates of schizophrenia in patients who discontinued taking antipsychotics during pregnancy. However, antipsychotic treatment reduces the rates of relapse and hospitalization in patients with schizophrenia.[9] Therefore, indiscriminate dose reduction or medication discontinuation increases the risk of relapse, leading to pregnancy termination or preterm birth. The 2014 National Institute for Health and Care Excellence guidelines recommended that women who are stable with medications and at high risk of relapse should continually receive antipsychotic treatment during pregnancy.[10]

Based on clinical experience, psychiatric symptoms occasionally worsen during pregnancy despite ongoing treatment. During pregnancy, various physiological changes occur, including increases in blood and body fluid volumes, alterations in hepatic enzyme activity, variations in protein-binding rates, and enhancement in renal blood flow and clearance. These changes can considerably impact the pharmacokinetics of therapeutic drugs.[11,12] An increase in circulating blood volume and renal blood flow leads to the dilution of drugs in the bloodstream and enhances their clearance, resulting in lower blood drug levels. For drugs with a high protein-binding rate, decreased plasma protein levels during pregnancy can increase the proportion of unbound, free drugs. This may enhance the drug's pharmacological effects but can also lead to faster elimination, reducing the duration of its effectiveness.[13] Additionally, >50% of medications are metabolized by cytochrome P450 (CYP) 3A4, whose activity nearly doubles by the end of pregnancy.[11] CYP3A4 primarily metabolizes lurasidone (LUR), and increased CYP3A4 activity during pregnancy may accelerate LUR metabolism.[14] These physiological changes are anticipated to reduce blood LUR levels and diminish its therapeutic effects.

LUR is considered an effective drug with a high safety profile, making it a potentially suitable option during pregnancy, especially considering the risk of obstetric complications based on its side-effect profile.[14] The risk of LUR-related fetal congenital abnormalities does not significantly differ from that of the general population.[6] However, current data are limited, and research on its use during pregnancy is scarce.[15] This report presented new data on the pharmacokinetics of LUR during pregnancy and the postpartum period in women with schizophrenia. The clinical implications of changes in drug pharmacokinetics for the mother and fetus were examined.

CASE PRESENTATION

A 34-year-old woman with no significant medical or developmental history was diagnosed with schizophrenia. At 18 years of age, she began experiencing delusions and believed that her house was "bugged" and that people were speaking ill of her. Accordingly, she was diagnosed with schizophrenia at a local clinic. Initially, she responded well to her antipsychotics and lived independently with a part-time job. At 29 years of age, she moved in with her partner and discontinued her medication, resulting in symptom relapse. Her condition stabilized with LUR (60 mg), showing a Positive and Negative Syndrome Scale (PANSS) score[16] of 35. She got married at 33 years of age and then conceived her first child.

At ~27th week of pregnancy, she presented with delusions again and believed that she possessed supernatural abilities. Thus, we increased her LUR dosage to 80 mg at 29 weeks of gestation, and her previously worsening psychiatric symptoms stabilized.

At 34 weeks of pregnancy, her symptoms rapidly worsened, leading to hallucinations and severe agitation. She could not recognize her pregnancy or the presence of a fetus, necessitating inpatient management.

Despite continuous treatment with LUR (80 mg), her psychiatric symptoms did not improve (PANSS score: 86). The decline in her psychiatric condition was suspected to be related to decreased blood LUR levels. At 35 weeks of gestation, she provided written informed consent for measuring blood LUR levels. Serum LUR samples were collected at a steady state (22–24 h after dosing). Blood drug levels were measured using liquid chromatography–tandem mass spectrometry, a standard analytical technique in therapeutic drug monitoring (TDM) for various antipsychotics with high precision and accuracy in measuring drug levels.[17] Analysis was performed using a modified version of previously published methods.[18] The limits of detection and quantification were 0.01 ng/mL and 0.02 ng/mL, respectively (Table 1). At 35 weeks of gestation, her serum LUR level was 3.6 ng/mL. After consulting with the obstetrics team, it was determined that vaginal delivery could be extremely challenging considering her psychiatric condition. Hence, a cesarean section was performed at 36 weeks and 5 days of gestation. At 2 days postdelivery, the patient's blood LUR levels increased, reaching 10.2 ng/mL. At 1 week postdelivery, her blood LUR levels further increased to 11.3 ng/mL. During this period, her psychiatric symptoms showed signs of improvement (PANSS score: 63) and she was discharged home. At 4 months postpartum, she maintained a stable psychiatric condition (PANSS score: 34), with a blood LUR level of 10.4 ng/mL, indicating that it had returned to baseline level starting 2 days postdelivery (Table 2). The infant outcomes were favorable without congenital abnormalities.

DISCUSSION

This study revealed that the patient's blood LUR levels at 35 weeks of pregnancy, when psychiatric symptoms were most severe, had significantly decreased by ~65.0% compared with those during the postpartum period. These findings align with previous research indicating that blood levels of various antipsychotics decline as pregnancy advances into its later stages.[19] The worsening of psychiatric symptoms at 27 weeks of pregnancy, which improved with

TABLE 1 SRM transitions, LLOD, and LLOQ of analytes and IS from plasma standards.

Analyte	MW	SRM transition (*m/z*)			Retention time (min)	LLOD (ng/mL)	LLOQ (ng/mL)
Lurasidone	492.68	493.3	→	166.0	3.13	0.01	0.02
Diazepam-d_5 (IS)	289.77	290.2	→	154.1	3.43		

Abbreviations: IS, internal standard; LLOD, lower limit of detection; LLOQ, lower limit of quantification; MW, molecular weight; *m/z*, mass-to-charge ratio; SRM, selected reaction monitoring.

TABLE 2 Perinatal serum lurasidone concentrations and PANSS scores.

		During pregnancy		Postpartum		
	Pre-pregnancy	2nd trimester	3rd trimester			
Perinatal period, weeks	BL	27	35	2 D	7 D	5 M
Lurasidone daily dose, mg	60	60	80	80	80	80
Serum concentration levels, ng/mL	NM	NM	3.6	10.3	11.3	10.4
PANSS score	35	80	86	80	63	34

Abbreviations: BL, baseline; D, day; M, month; NM, not measured; PANSS, Positive and Negative Syndrome Scale.

higher doses of LUR, indicates changes in LUR distribution at this time. Thus, the worsening of psychiatric symptoms observed in late pregnancy was partly attributed to altered LUR distribution resulting from physiological changes during pregnancy, including heightened CYP3A4 activity.

A study reported that the blood quetiapine and aripiprazole levels significantly decreased during pregnancy compared with baseline levels because they are metabolized by CYP3A4 and CYP2D6, which are activated during this period.[19] However, only a few studies have measured blood LUR levels during pregnancy. Only one case report has documented blood LUR levels in a patient with bipolar II disorder during pregnancy,[15] confirming a decrease in blood LUR levels during pregnancy (~57% lower than those measured postpartum), accompanied by worsening of depressive and anxiety symptoms. Studies with larger sample sizes should be conducted to validate these findings.

The American Society of Clinical Psychopharmacology guidelines have recommended therapeutic blood concentration ranges for neuropsychiatric drugs, emphasizing the use of TDM in clinical practice.[17] Currently, there are no guidelines for TDM of antipsychotics during pregnancy. In a systematic review examining changes in pharmacokinetic and serum levels of antidepressants between pregnant and nonpregnant individuals, the lack of specific guidelines for using antidepressants during pregnancy has been emphasized,[12] highlighting the importance of individualized monitoring and careful management when using antidepressants in pregnant patients. The psychiatric symptoms of our patient worsened, leading to hospitalization due to concerns regarding maternal and fetal well-being and delivery via cesarean section. These findings underscore the importance of stabilizing psychiatric symptoms during pregnancy to ensure maternal and fetal safety.

It is important to understand at what stage of pregnancy the drug levels begin to decline and how maternal serum levels normalize during the postpartum period. Previous case reports have shown that the trough serum quetiapine levels in the early, late, and postpartum periods were 42%, 55%, and 53% lower than baseline levels, respectively.[19] Another study revealed that serum quetiapine levels returned to baseline levels within the first few weeks of the postpartum period,[20] consistent with the findings of the current study. In pregnancies complicated with schizophrenia, it is essential to measure baseline serum levels in advance and monitor any changes in psychiatric symptoms and blood levels throughout the pregnancy and postpartum to ensure maternal and fetal safety during delivery.

When examining factors related to worsening mental symptoms, it is essential to consider variables beyond the decline in blood drug levels. During pregnancy, rapid fluctuations in hormones, such as estrogen and progesterone, can influence brain neurotransmitters, potentially contributing to the destabilization of mental symptoms.[12] Lifestyle and physical stressors during pregnancy can heighten anxiety and stress, potentially affecting mental health symptoms.[12] Effectively managing pregnant patients with comorbid schizophrenia requires careful attention and follow-ups to address the impact of various physiological changes during pregnancy, including hormonal fluctuations, as well as the impact of environmental changes.

CONCLUSION

As the population of pregnant women with schizophrenia increases, guidelines for monitoring serum antipsychotic levels should be established to maintain the therapeutic efficacy of drugs and prevent adverse effects during pregnancy. Personalized management is essential for pregnant women with schizophrenia, considering the physiological changes occurring during pregnancy. However, the guidelines for adjusting dosages of antipsychotics based on TDM during pregnancy and comprehensive mental and social support for these women are still lacking. Therefore, large-scale studies should be

conducted to improve perinatal mental health care in patients with schizophrenia.

AUTHOR CONTRIBUTIONS

Mihoko Kawai, the corresponding author, confirms that all authors contributed to the conception, design, data acquisition, analysis, and manuscript drafting. All authors reviewed and approved the final version, agreeing to take responsibility for the accuracy and integrity of the work. Although all authors contributed, specific responsibilities were as follows: As the principal investigator, Mihoko Kawai, had full access to all data and ensured data integrity and analysis accuracy. Mihoko Kawai developed the study concept and design, recruited the patient along with Ryosuke Aratake and Tadashi Ogawa, created the table, and drafted the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available from the authors upon request.

ETHICS APPROVAL STATEMENT

This study aligns with the Declaration of Helsinki and was approved by the Ethics Committee of Aichi Medical University.

PATIENT CONSENT STATEMENT

Written informed consent and a signed release were obtained from the patient.

CLINICAL TRIAL REGISTRATION

N/A

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