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## Special Feature Article

### Psychiatric Preconception Care for Patients with Mental Illnesses: Daily Clinical Practice Recommendations

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#### Abstract

Preconception care refers to health care promotion to support future pregnancies for women and couples. In psychiatry, preconception care prepares women with mental illness for pregnancy, and this article focuses on two aspects of daily clinical practice. First, reviewing patient lifestyle is important. Appropriate weight maintenance, cessation of tobacco and alcohol consumption, keeping a well-balanced diet, and stress avoidance can lead to having healthier children. The second is adjusting psychotropic medications. Antipsychotics and antidepressants show no teratogenic or developmental effects; however, as these findings are for single agents, medications should be kept as simple as possible. Valproic acid should not be prescribed to women of childbearing potential because of increased risk of teratogenicity and effects on child development. Lithium carbonate should also be used with caution, but is now known to be dose-dependent, and below 600 mg per day does not increase risk. Sharing information about lifestyle and medications with the patient and family when discussing future pregnancies may enable them to feel more comfortable going forward with pregnancy.

**Keywords:** preconception care, pregnancy, teratogenicity, shared decision making

## Introduction

For women with mental illness, pregnancy and childbirth can cause various anxieties. In daily clinical practice, women of childbearing age may ask questions, such as: “Will the medication I'm currently taking affect my pregnancy?” or “My husband says I should stop taking my medication if I get pregnant. What should I do?” Furthermore, many doctors have experienced the surprise and panic of being told: “Doctor, I am pregnant. I have stopped taking my medication. What should I do now?”

In recent years, the idea of “preconception care” has been gaining traction. Preconception care involves discussing pregnancy, childbirth, and the postpartum period with the woman herself, her partner, and her family before conception, sharing information, and providing opportunities for women to conceive and give birth safely and appropriately. This article introduces the basics of preconception care and outlines its fundamental aspects for patients with mental illness. For detailed information on preconception care for women with mental illness, please refer to: ‘Clinical Practice Guidelines for Pregnant Women with Comorbid or Potentially Comorbid

Mental Illness: General Principles,’ published by the Japanese Society of Psychiatry and Neurology and Japan Society of Obstetrics and Gynecology.

## I. What is Preconception Care?

The term “conception” means “pregnancy or fertilization.” Therefore, preconception care simply means “care provided before pregnancy.” Here, we present the widely used definitions and objectives provided by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC). WHO defines preconception care as “providing medical, behavioral (individual), and social support to women and couples before pregnancy,” with the objective of “improving the health of women and couples and reducing behavioral, individual, and social factors that increase problems during childbirth or compromise the health of the child.”<sup>23)</sup> CDC defines preconception care as “medical care given by healthcare providers to women and men, focusing on factors known to increase the likelihood of having a healthy child.”<sup>8)</sup> In Japan, the “Basic Policy on the Comprehensive Promotion of Measures Concerning the Provision of Maternal and Child Healthcare, etc.” was formulated in 2021. Within this

policy, preconception care is defined as follows: “efforts targeting women and couples to promote health management for future pregnancy.”<sup>11)</sup>

## II. Reasons Preconception Care is Needed

Attention to preconception care first arose from interventions for patients with diabetes. For women with diabetes, when glycemic control was initiated before pregnancy, the rate of major congenital malformations in infants was 1.2%, whereas when glycemic control began during pregnancy, the rate increased to 10.9%.<sup>9)</sup> This is a representative example showing that intervention before pregnancy increases the likelihood of having a healthier child. Furthermore, it has been suggested that smoking cessation before and during pregnancy could prevent 5–7% of perinatal deaths and 23–24% of sudden infant deaths.<sup>23)</sup> Additionally, approximately 40% of women worldwide experience unintended pregnancies.<sup>18)</sup> These findings clearly indicate that paying attention to daily lifestyle habits before, rather than after, becoming pregnant contributes to the health of future children. The National Center for Child Health and Development made the Preconception Care Checklist publicly available.<sup>10)</sup> This checklist includes versions for both women and men. Items commonly recommended for

both sexes include maintaining a healthy weight, smoking cessation, limiting alcohol consumption, following a well-balanced diet, managing stress, preventing infections, and receiving vaccinations.

## III. Preconception Care in the Psychiatric Field

In the psychiatric field, where pharmacotherapy is often required, understanding the effects of medications on pregnancy allows clinicians to provide appropriate information. Below, we give an overview of schizophrenia, depression, and bipolar disorder, describing the effects of each disorder on pregnancy and impacts of their respective treatments.

### 1. Schizophrenia

The impact of schizophrenia itself on pregnancy has yet to be clearly established. However, reduced social functioning associated with schizophrenia has been reported to increase the risk of obstetric complications. Meta-analyses indicate that women with schizophrenia have a higher risk of obstetric complications (including gestational hypertension, fetal growth restriction, preterm birth, low birth weight, low Apgar scores, congenital anomalies, stillbirth, neonatal death, and sudden infant death syndrome).<sup>13)</sup> However, these

risks are influenced by factors such as advanced maternal age, smoking during pregnancy, and limited prenatal care. It is highly likely that behavioral characteristics associated with the disorder (such as difficulty quitting smoking and low proactive attendance at prenatal checkups) have a greater impact on the risk than the disorder itself.

Regarding the effects of antipsychotic medications on pregnancy, large database studies have shown that antipsychotics do not significantly increase the risk of major congenital malformations in the fetus.<sup>6)</sup> Furthermore, guidelines from the National Institute for Health and Care Excellence (NICE) indicate that antipsychotics do not increase the risk of preterm birth.<sup>16)</sup> Conversely, multiple meta-analyses reported that antipsychotic use during pregnancy increases the risk of gestational diabetes.<sup>12)22)</sup> Therefore, when prescribing antipsychotics during pregnancy, it is advisable to discuss the need to manage the gestational diabetes risk while preventing excessive weight gain in advance with the patient. In Japan, haloperidol and bromperidol are contraindicated during pregnancy. Currently, second-generation antipsychotics are the mainstay of schizophrenia treatment, and given the availability of various antipsychotics, it

is unlikely that haloperidol or bromperidol would need to be prescribed to pregnant women. However, it should be noted that these drugs are contraindicated according to their package inserts.

## 2. Depression

There is no consensus on whether depression itself increases the risk of common obstetric complications. However, untreated depression has been reported to increase the risk of preterm birth and fetal growth restriction, suggesting that a depressive state may affect fetal development.<sup>7)</sup> Furthermore, depression during pregnancy has been reported to affect maternal-fetal attachment, with more severe depression associated with weaker attachment to the fetus.<sup>14)</sup> Furthermore, depressive states during pregnancy are known risk factors for postpartum depression, and they may affect fetal development, maternal-fetal attachment, and postpartum depressive symptoms.

Regarding the teratogenicity of antidepressants, most studies have focused on selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed class of antidepressants. Summarizing current evidence, although an association between SSRIs and congenital anomalies cannot be completely ruled out, any increased risk

is limited to approximately 1.2-fold. Regarding paroxetine, although earlier reports suggested more frequent occurrences of congenital heart defects compared with other antidepressants, recent findings indicate that the incidence is not significantly higher than with other SSRIs. A meta-analysis by Gao, S.Y. et al. demonstrated a significant increase in the risk of major malformations and congenital heart disease associated with paroxetine use during pregnancy. However, when the analysis was limited to patients with psychiatric disorders, comparing those who used paroxetine with those who did not, no significant increase in the risk of either major malformations or congenital heart disease was observed.<sup>3)</sup>

Furthermore, several studies suggested that exposure to antidepressants may increase the risk of autism spectrum disorder (ASD) in children. However, recent studies consistently showed that while an apparent association between antidepressant use and ASD is observed before adjusting for confounding factors, this association disappears after adjustment, indicating the lack of an association between antidepressant exposure and the risk of ASD in children.<sup>15)19)</sup>

### 3. Bipolar Disorder

The effects of depressive episodes on pregnancy and the fetus have already been discussed, whereas the effects of manic episodes on pregnancy and the fetus remain unclear. In bipolar disorder, the effects of pharmacotherapy, as discussed in the next section, are more significant.

Regarding pharmacotherapy, the NICE guidelines recommend switching mood stabilizers to second-generation antipsychotics whenever possible.<sup>16)</sup> Mood stabilizers have significant effects on pregnancy. Lithium carbonate is known to increase the incidence of congenital heart disease, and is contraindicated in Japan according to the package insert. However, recent systematic reviews and meta-analyses indicated that the risk increases only when 600 mg/day or more is used during the first trimester; under other conditions, the risk does not increase.<sup>2)</sup> The NICE guidelines state that in pharmacotherapy for bipolar disorder during pregnancy, switching to second-generation antipsychotics is the standard approach. However, in cases where antipsychotics are ineffective but lithium carbonate is effective, they specify that lithium carbonate taken during the first trimester may cause congenital heart disease in the child, that the risk is not yet fully understood, and that blood lithium levels should be monitored more frequently than usual

during pregnancy and postpartum.<sup>16)</sup> Indeed, cases where only lithium carbonate is effective are encountered. From these perspectives, in preconception care for women taking lithium carbonate, it is crucial to fully explain that it is contraindicated based on the Japanese package insert, while also introducing international guidelines such as the NICE guidelines and recent findings, and engaging in shared decision-making with the patient and family. Management of lithium carbonate may change in the future. Concerning valproic acid, multiple meta-analyses have shown that the risk of major congenital malformations increases to approximately three times the baseline level.<sup>1)21)</sup> Furthermore, it is known to affect not only major malformations but also child development. Network meta-analyses indicate that valproic acid causes delays in cognitive development, increased autism spectrum disorder, and delayed language development in children.<sup>20)</sup> There are also indications that it increases the risk of developing attention deficit hyperactivity disorder (ADHD).<sup>4)</sup> Developmental delays are more likely to occur when valproic acid is taken at high doses (800–1,000 mg/day or more) during pregnancy.<sup>5)</sup> For these reasons, valproic acid should be avoided in women with childbearing potential. Morphological, congenital

anomalies are also known to be associated with carbamazepine, showing a dose-dependent relationship: approximately 3% at doses below 400 mg/day, 5% at 400–1,000 mg/day, and 8% at 1,000 mg/day or higher.<sup>15)</sup> Conversely, no increased risk of congenital anomalies has been observed with lamotrigine.<sup>21)</sup> Furthermore, developmental delays in children have not been noted with either carbamazepine or lamotrigine.<sup>20)</sup>

#### **IV. Preconception Care Psychiatrists Can Provide in Routine Clinical Practice**

In summary, preconception care that psychiatrists can provide in routine clinical practice includes reviewing lifestyle habits and managing psychotropic medications.

##### **1. Reviewing Lifestyle Habits**

Maintaining a healthy weight, quitting smoking, limiting alcohol consumption, following a balanced diet, and avoiding excessive stress are practices that enhance overall quality of life, not only during pregnancy. It is advisable to share with patients, their partners, and families that these everyday practices are key points for having a healthier baby.

##### **2. Adjusting Psychiatric Medications**

Antipsychotics and antidepressants have been shown to cause no clear harm during pregnancy or breastfeeding. In fact, because uncontrolled psychiatric symptoms during pregnancy can negatively affect the postpartum mother-infant relationship, it is important to emphasize the merit of achieving stable mental health before pregnancy. However, most studies investigating the effects of psychiatric medications on pregnancy have focused on single-agent use. Therefore, it is important to simplify the medication regimen as much as possible. For bipolar disorder, valproic acid and lithium carbonate should be avoided whenever possible, and treatment should be conducted with second-generation antipsychotics or lamotrigine. If treatment with second-generation antipsychotics or lamotrigine is ineffective, lithium carbonate at a dose of 600 mg/day or lower may be considered after thorough discussion with the patient and family regarding its potential effects on pregnancy.

### Conclusion

This article has presented preconception care. By ensuring that all relevant parties have accurate knowledge and discussing matters from before and during pregnancy, women with mental illness can be supported at

all times while maintaining mental stability and experiencing the joys of motherhood. Note that some patients and/or their families may not agree with medication changes or other aspects of preconception care. The advantage of preconception care is that it provides sufficient time, as it is conducted before pregnancy. When encountering such cases, the author strives to engage in careful, thorough discussions. Phrases such as: "There is no need to rush. Let us prepare to welcome a healthy baby," contribute to supportive psychotherapy and exemplify preconception care that can be uniquely provided by psychiatrists.

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### Conflict of Interest

Kiyotaka Nemoto: (Lecture fees) Eli Lilly Japan K.K., Otsuka Pharmaceutical Co., Ltd.

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