Menstruation-related Syndrome: Clinical relations and treatment

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Abstract

Mental and physical conditions associated with the menstrual cycle are often left untreated unless they become severe or are accompanied by psychiatric concomitants, by which time treatment may be ineffective. This paper introduces the pathophysiology and treatment of premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) and offers comments and conclusions based on a discussion of their relation to atypical psychosis. Menstruation-related syndrome (MRS) is a group of diseases in which the menstrual cycle is related to various mental and physical symptoms and influences the clinical course. Although specific abnormalities of gonadal hormones are not apparent, serotonin dysfunction is thought to be present because selective serotonin reuptake inhibitors are effective for premenstrual dysphoric disorder. MRS and atypical psychosis have many similar pathophysiologic and clinical features. I propose a new clinical classification of all menstruation-related conditions which provides a contrast between MRS and atypical psychosis.

Key words Menstruation-related syndrome, Premenstrual syndrome, Premenstrual dysphoric disorder, Atypical psychosis

Introduction

A variety of conditions associated with the menstrual cycle produce mental changes or physical changes or both. Although biological and sociopsychological factors are clearly involved in the pathogenesis of these conditions is unclear, these factors are often discussed separately because of the obscure definitions and concepts associated with them. The concept of menstrual psychosis (also known as cyclic psychosis and considered a type of atypical psychosis) has been used in the field of psychiatry, but different diagnoses have been given to cases with the same pathologic features.

To eliminate confusion, operational diagnoses based on the International Classification of Diseases, 10th revision (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)¹ have been introduced, but a group of diseases with short, cyclic, morbid phases were eventually excluded because of the difficulties of diagnosis. This exclusion has led to further confusion.

Premenstrual syndrome (PMS), ovulatory disorders, and climacteric syndrome have been investigated on the basis of endocrine function (hypothalamic-pituitary system), age, parity, level of activity, and nutritional status. However, mental or physical symptoms are experienced by many women during the menstrual cycle, they tend to be regarded as common or trivial problems not requiring medical attention and are therefore left untreated.

In contrast, because premenstrual dysphoric disorder (PMDD) is considered a severe condition, diagnostic criteria are provided in DSM-IV and have gradually attracted attention. In addition to PMS/PMDD and menstrual psychosis, a
A variety of psychosomatic medical conditions are associated with menstrual disorders. Because I do not consider these menstruation-related conditions to be independent clinical entities, I have suggested establishing a separate field of medicine to address menstruation-related conditions by defining, classifying, and specifying the subjects of research. For this reason, I have defined menstruation-related syndrome (MRS) as a condition in which menstruation is closely involved in the pathophysiology and symptom formation of these disease entities and results in both mental and physical symptoms. With this definition, I have attempted to clarify the pathology of the various conditions that are related to menstruation and have not yet been fully clarified and to develop treatments for them.

This paper outlines the clinical position and treatment of MRS and compares it with so-called atypical psychosis, which is thought to have similar pathophysiological features.

### Clinical Position of MRS

The conditions I have included in MRS are listed in Table 1. Although conditions 9 through 11 are also found in male patients, they are included in this table as reflecting the broad sense of MRS because most patients are women and these symptoms are closely related to menstruation.

If attention is focused on the mental symptoms of these conditions, a clinical picture of atypical psychosis-like disease usually, but not always, emerges. An atypical psychosis-like condition is characterized by abrupt onset; a complex of disturbances of consciousness and affective and psychomotor disorders; and a periodic, transient course. Clinical symptoms vary widely from reduced alertness and bradykinesia to an abnormal sleep-wakefulness cycle, abnormal eating patterns, depression, impatience, irritability, impulsivity, excitation, hyperkinesia, mania, and hallucination, and paranoia.

Table 2 shows the proposed reclassification of MRS, with attention focused on the mental symptoms and the menstrual cycle. Initially, the overall clinical picture was regarded as fitting the atypical psychosis-like disease group. This classification may require some explanation.

1. **MRS in the narrow sense**
   1) PMS and PMDD are the main axes of this syndrome and represent the main topics of this paper. Their symptoms and treatments will be described later.
   2) Periodic psychosis (synchronous with the menstrual cycle) is characterized by the common features of atypical psychosis-like disease. Periodic psychosis is classified both under MRS in the narrow sense and as a type of atypical psychosis, as described later (section 2). Periodic psychosis is included in both categories because not all cases show synchronicity with the menstrual cycle.
   3) Mental symptoms in patients with puerperal mental disorders have been cited as typical features of atypical psychosis-like disease.
   4) Some patients with climacteric disorder exhibit

### Table 1 Diseases in the broad-based category of MRS

<table>
<thead>
<tr>
<th>No.</th>
<th>Disease</th>
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<tbody>
<tr>
<td>1</td>
<td>Perimenarche syndrome</td>
</tr>
<tr>
<td>2</td>
<td>Pubertal periodic psychosis</td>
</tr>
<tr>
<td>3</td>
<td>Premenstrual tension syndrome (PMS)</td>
</tr>
<tr>
<td>4</td>
<td>Premenstrual dysphoric disorder (PMDD)</td>
</tr>
<tr>
<td>5</td>
<td>Periodic psychosis (synchronous to menstrual cycles)</td>
</tr>
<tr>
<td>6</td>
<td>Puerperal mental disorders</td>
</tr>
<tr>
<td>7</td>
<td>Climacteric disorder</td>
</tr>
<tr>
<td>8</td>
<td>Ovulation disorders (e.g., those related to the hypothalamus-pituitary system and PCOS)</td>
</tr>
<tr>
<td>9</td>
<td>Atypical psychosis (including periodic psychosis)</td>
</tr>
<tr>
<td>10</td>
<td>Eating disorder</td>
</tr>
<tr>
<td>11</td>
<td>Seasonal affective disorder</td>
</tr>
<tr>
<td>12</td>
<td>Others</td>
</tr>
</tbody>
</table>

### Table 2 Menstruation-related syndrome from the aspect of based on classification of the atypical psychosis-like disease group

<table>
<thead>
<tr>
<th>No.</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Menstruation-related syndrome (MRS) (narrow sense)</td>
</tr>
<tr>
<td>1)</td>
<td>PMS, PMDD</td>
</tr>
<tr>
<td>2)</td>
<td>Periodic psychosis (synchronous to menstrual cycles)</td>
</tr>
<tr>
<td>3)</td>
<td>Puerperal mental disorders</td>
</tr>
<tr>
<td>4)</td>
<td>Climacteric disorder</td>
</tr>
<tr>
<td>5)</td>
<td>Others (e.g., PCOS)</td>
</tr>
<tr>
<td>2</td>
<td>Atypical psychosis</td>
</tr>
<tr>
<td>1)</td>
<td>Periodic psychosis</td>
</tr>
<tr>
<td>2)</td>
<td>Acute transient psychotic disorder</td>
</tr>
<tr>
<td>3)</td>
<td>Schizoaffective disorder</td>
</tr>
<tr>
<td>4)</td>
<td>Catchall category</td>
</tr>
<tr>
<td>3</td>
<td>Organic mental disorders</td>
</tr>
</tbody>
</table>
a clinical picture of atypical psychosis-like disease. This type of disorder may develop after bilateral ovariectomy.

5) Other disorders of MRS in the narrow sense include polycystic ovary syndrome (PCOS). Although no symptoms are diagnostic for this PCOS, the clinical picture is occasionally that of an atypical psychosis-like disease. Attention should also be paid to eating disorders and seasonal affective disorders.

2. Atypical psychosis

The concept of atypical psychosis was developed in Japan. Although this condition is not limited to women, female patients outnumber male patients by 7 or 8 to 1, and attention has focused on the co-existence of PMS or endocrine disease. Because of this focus, several neuroendocrinologic studies have been performed and have found vulnerability in the diencephalic-hypothalamic system. This finding explains why atypical psychosis is included MRS when broadly defined (Table 1). However, the symptoms of atypical psychosis-like disease suggest that this condition also occurs in men. Therefore, the diagnosis of atypical psychosis has come to be applied to a wide spectrum of cases. Because atypical psychosis also occurs in men, it cannot be classified solely under the category of MRS. Thus, a separate category that represents the conventional diagnosis of atypical psychosis has been differentiated from narrowly defined MRS.

Atypical psychosis can be subclassified as 1) periodic psychosis (a subgroup closer to MRS); 2) acute transient psychotic disorder, a diagnosis described in DSM-IV and ICD-10, corresponding to atypical psychosis; 3) schizoaffective disorder; and 4) a catchall category (unspecified atypical clinical picture). In fact, the techniques of operational diagnosis are not appropriate for diagnosing a disease group with this clinical picture. For this reason, the conventional diagnosis of atypical psychosis seems to be more suitable and more useful because it is based on symptoms and disease stage.

3. Organic mental disorder

Mental symptoms in patients with symptomatic mental disorders and organic brain damage form the clinical picture of an atypical psychosis-like disease.

The above explanation presents the clinical picture of MRS from the viewpoint of the clinical picture of atypical psychosis-like disease. Although this classification may be flawed and controversial, a more clinically realistic tool was the goal of this classification, which is based on conventional and operational diagnostic techniques. I intend to review and improve this classification from the perspective of evidence-based medicine.

PMS/PMDD

1. History of the diagnosis of PMS/PMDD

After Frank proposed the concept of PMS in 1931, the diagnostic criteria for this condition were first presented in the DSM-III-R in 1987 as late luteal phase dysphoric disorder (LLPDD), a mental disorder not otherwise specified. This condition was classified as premenstrual dysphoric disorder (PMDD) in DSM-IV and as PMS in ICD-10 in 1994.

2. Differences between PMS and PMDD

The major symptoms of PMS, which are seen in 50% to 70% of menstruating women, include various types of pain, such as breast pain and lower back pain, and other physical symptoms, such as swelling and weight gain. Mild depression, irritability, and sleep disorder may also occur. PMDD is considered to be a severe type of PMS, present in 2% to 8% of patients with PMS. The symptoms of PMDD include physical symptoms and mood disorders. Characteristic symptoms are marked depression, anxiety, emotional lability, difficulty concentrating, altered eating behavior, sleep disorders (hypersomnia or insomnia), and various types of pain. The most important symptom is tendency for uncontrollable anger (a feeling of being out of control). Like patients with depression, patients with PMDD have behavioral difficulties, both social (including work) and interpersonal.

3. Pathophysiology of PMDD

Despite years of endocrinologic research on PMDD, there is no clear evidence that abnormal hormone regulation plays a role. Schmidt et al. have reported that an abnormal reaction to the normal secretion of gonadal steroid hormones, e.g., hyperreactivity of receptors and neurotransmitters, is responsible for PMDD. Among the possible mechanisms, abnormality in the
serotonergic nervous system has long been the most likely theory, for the following reasons.
1) Serotonin suppresses the major symptoms of PMDD, i.e., irritability, tendency for uncontrollable anger, depression, abnormal appetite (hyperphagia), and sleep disorders (hypermornia or insomnia).
2) Studies of serotonin dysfunction in PMDD have shown decreases in serotonin reuptake by and content of platelets.
3) Serotonergic agents are clinically effective. As documented in several case reports and clinical trials, both selective serotonin reuptake inhibitors (SSRIs) and serotonin agonists produce improvements in symptoms which could be blocked by serotonin antagonists.6,7
Thus, serotonin dysfunction triggered by gonadal steroid hormones has been suggested to result in psychological, physical, and behavioral disorders.

4. Treatment of PMDD
The main methods of treatment for PMDD are the inhibition of ovulation and the use of antidepressants (e.g., SSRIs).
(1) Psychotropic drugs
i) Efficacy of antidepressants
Clinical studies have shown that SSRIs (e.g., citalopram, fluoxetine, paroxetine, sertraline, and fluvoxamine) and the tricyclic serotonergic agent clomipramine are significantly more effective than placebo in patients with PMDD. These agents are also more effective than nonserotonergic drugs. These drugs usually act quickly on the predicted disease phase. These agents are effective at low doses for both mental and physical symptoms. Discontinuation of SSRI therapy allows symptoms to return. However, intermittent administration is also effective.
ii) Anxiolytic drugs
Alprazolam and buspirone (5HT1a agonist) are particularly effective for treating irritability.
(2) Ovulation inhibition
Ovulation inhibition, considered the definitive treatment, eliminates an important trigger of PMDD. Various types of ovulation-inhibitors are available: gonadotropin-releasing hormone agonists, such as leuprolide, goserelin, and nafarelin; danazol, a gonadotropin antagonist; and estrogen/progesterone oral contraceptives. However, ovulation-inhibitors can induce climacteric symptoms. Therefore, ovulation inhibition is indicated only for patients who have severe symptoms that justify this risk. Thus far, however, the results of ovulation inhibition therapy have been mixed, with inconsistent or disappointing outcomes and even the worsening of symptoms.
(3) Other agents
Although the efficacy of SSRIs suggests that the serotonergic agent fenfluramine will also be useful, another effective drug, the dopaminergic agent bromocriptine, promotes, rather than inhibits, ovulation.8 Although opposing methods may be effective in regulating ovulation, ovulation inhibition seems to be effective in patients with periodic psychosis and psychopathic symptoms. The fact that fenfluramine and bromocriptine are effective despite opposing actions (ovulation inhibition and promotion, respectively) implies that this group of analogous diseases has a complicated pathophysiology.9–11 Other agents recently reported to be useful include calcium, vitamin B6, and Chinese herbal remedies, such as kamishoyosan, tokishakuyakusan, and keishibukuryogan.
(4) Treatments other than drug therapy
Sociopsychological support includes such therapies as cognitive behavioral therapy, group therapy, aerobic exercise, and dietary therapy with a carbohydrate-rich diet. In addition, I have previously reported the efficacy of phototherapy, in which the patient is exposed to bright lights during the luteal phase. If the treatment is done in the follicular phase, ovulation is inhibited.

Conclusion
Conditions with both mental and physical components which occur in association with the menstrual cycle often remain untreated if they are mild. Even if these conditions are severe, treatment may be withheld because they are regarded as a normal part of menstruation. If psychotic features are present, treatment will be started. However, the condition may be resistant to conventional chemotherapy or to ovulation inhibition, which is generally considered a definitive treatment. Unexpectedly, no specific abnormality in gonadal hormones is present.
Atypical psychosis, a concept that grew out of periodic psychosis, came to include cases in men after initial studies of cases in women progressed to include peripheral complaints. As a result, the concept and definition of atypical psychosis
has become increasingly unclear. No specific endocrine abnormalities are apparent in these conditions. However, after the vulnerability of the hypothalamic-pituitary system was discovered, research on these conditions has decreased. I intend to focus on core cases and study the pathophysiology and treatment of MRS.

References