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Premenstrual disorders: Premenstrual syndrome and premenstrual dysphoric disorder

Takashi Takeda

Division of Women's Health, Research Institute of Traditional Asian Medicine, Kindai University School of Medicine, Osaka, Japan

Abstract

Recently, the term premenstrual disorders (PMDs), which includes premenstrual syndrome and premenstrual dysphoric disorder as a continuum, has been proposed. Although the precise etiology of PMDs remains unknown, the involvement of hormonal fluctuations is clear. The brain transmitters, serotonin and γ-amino butyric acid, also seem to be involved. Serotonin reuptake inhibitors and oral contraceptives are the current mainstay of treatment, but these are insufficient. Even the currently used prospective two-period symptom diary is not widely used in actual clinical practice, creating a major problem of discrepancy between research and clinical practice. In this review, I would like to outline the latest information and problems in the etiology, diagnosis, and treatment of PMDs, with an emphasis on promising new therapies.

Key words: allopregnolone, PMDD, PMDs, PMS, serotonin.

INTRODUCTION

Premenstrual symptoms are characterized by a variety of psycho-physical symptoms that are present in the luteal phase before menstruation and impair the quality of life of many women.[1] Epidemiological studies show that the prevalence of premenstrual symptoms, including mild cases, is very high, ranging from 80% to 90%.[2] As diseases with intense premenstrual symptoms, they have been classified as premenstrual syndrome (PMS) in the field of gynecology and as premenstrual dysphoric disorder (PMDD) in the field of psychiatry. In recent years, they have been recognized under the name of premenstrual disorders (PMDs), which encompasses both.[3] The exact pathophysiology of PMDs remains unclear. In this review, I will examine the current status and challenges of diagnosis and treatment in PMDs.

Diagnostic criteria

Although weak premenstrual symptoms can be considered a physiological condition, among biological women of reproductive age, 20–30% are diagnosed with PMS and 1.2–6.4% with PMDD.[1] The American College of Obstetricians and Gynecologists (ACOG)'s PMS diagnostic criteria require one or more affective or somatic symptoms that impair social, work, or school performance for a diagnosis of PMS.[4] PMDD is diagnosed mainly by its psychiatric symptoms, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM). The most updated version is the DSM Fifth Edition, Text Revision.[5] According to these criteria, at least five symptoms including affective symptoms with functional impairment are necessary for diagnosis. In actual clinical practice, premenstrual symptoms may indicate severe impairment of social life, although they do not meet the diagnostic criteria for PMDD. In contrast, the

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Correspondence: Takashi Takeda, Division of Women's Health, Research Institute of Traditional Asian Medicine, Kindai University School of Medicine, 377-2, Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan.
Email: take@med.kindai.ac.jp

diagnostic criteria for PMD proposed by International Society for Premenstrual Disorders (ISPMD) have no restrictions regarding the number of symptoms and match the needs of patients seeking treatment (Figure 1). According to these criteria, ISPMD defines the classic PMS as core PMDs. Among the core PMDs, PMDD is defined as a severe disorder with affective symptoms as the main symptom. It has been found that patients tend to overestimate premenstrual symptoms because they are cyclic, present only in the luteal phase, and resolve after the onset of menstruation.[6,7] Therefore, each of the diagnostic criteria of ACOG, DSM, and ISPMD also requires the inclusion of a symptom diary for two cycles of a prospective menstrual cycle. While prospective evaluation is useful for accurate diagnosis, it may be problematic for the patient to maintain such a diary, which she may find difficult. In a survey of family physicians and gynecologists in the US, only 11.5% of physicians performed a prospective two-cycle symptom.[8] In a recent survey conducted by the Japanese Society of Obstetrics and Gynecology, the prospective two-cycle symptom diary practice rate was 8.4%, a rate as low as in the US. A recent survey of 2512 patients treated for PMDD symptoms reported that 68% of cases were diagnosed with PMDD by a diagnostic method other than a prospective daily chart.[9] These data show that a disconnect exists between research recommendations and actual practice in the diagnosis of PMDD. In the future, it will be necessary to develop new, simpler diagnostic methods, such as biomarker development, to add to the currently practice of diagnosis based upon symptoms.

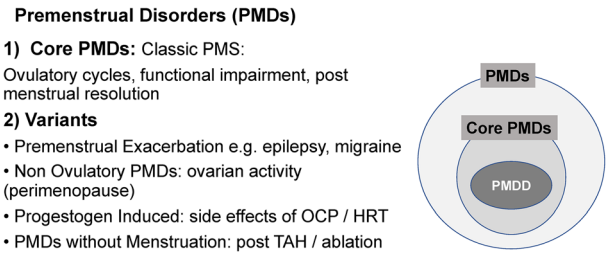

FIGURE 1 Premenstrual disorders. HRT, hormone replacement therapy; OCP, oral contraceptive; PMDD, premenstrual dysphoric disorder; PMDs, premenstrual disorders; PMS, premenstrual syndrome; TAH, total abdominal hysterectomy.

Epidemiology

Due to the complexities of forward-looking diary-based assessments, there are actually few studies on the incidence of PMS and PMDD using rigorous criteria. Studies of community populations have shown that the prevalence of PMS is 20 ~ 30% and that of PMDD is 1.2% ~ 6.4%.[1] In the old days, PMS was a Western culture-specific disease,[10] but data from retrospective studies show that it exists worldwide.[11] One prospective evaluation study conducted in Asia, involving 815 participants in China, has been reported.[12] According to this study, the prevalence of PMS is 21.1% and that of PMDD is 2.1%, which are somewhat lower than that in Western countries. In Japan, only retrospective data exist, but one report showed a lower incidence of PMS (5.3%) and PMDD (1.2%) than the Chinese results.[13] As both studies used the questionnaire using the DSM-based premenstrual symptoms, I could compare the prevalence of each symptom. The most frequent symptoms were different between the patients in the two countries; irritability (91.2%) in China and physical symptoms (81.2%) in Japan.

Although the highest percentage of those receiving medical care are reported to be in their 30s,[14] many studies reported that PMDs are also recognized in adolescents.[15–17] One report from Japan indicates that the severity of PMDs is higher in adolescents than in adults, based on comparisons using the same survey instrument.[16] PMDs are not only a negative impact on academics, but also an important issue for the performance of female athletes, many of whom are teenagers at the midpoint of their careers.[18–21]

Along with PMDs, menorrhagia, the most common symptom associated with menstruation, is known to begin around 6 to 12 months after menarche.[22] There is a correlation between the severity of menstrual pain and premenstrual symptoms, and perhaps the two influence each other.[23] A study of Japanese high school students aged 15 to 19 years showed that they began to notice premenstrual symptoms at a median age of 15 years (IQR: 14–16 years). From menarche, the median age was 2 years, and this value was inversely correlated with age at menarche ($\rho = -0.47$, $p < 0.001$). A Cox proportional hazards regression analysis showed that early menarche (≤11) was significantly associated with a lower cumulative risk of developing premenstrual symptoms (OR: 0.73 [95% CI 0.58 to 0.91]). This means that while menstrual pain begins to appear with the establishment of the

ovulatory cycle after menarche, premenstrual symptoms are influenced not just by endocrine factors, but perhaps by social factors as well. One can speculate about the pathophysiological differences between the two.

Screening and diagnostic questionnaires

To avoid recall bias, as mentioned above, a prospective two menstrual cycle symptom record is necessary for accurate diagnosis, but it is also complicated. Although a detailed interview of the patient is necessary, the use of screening tools for PMDs is helpful for an efficient examination. In a survey of family physicians and gynecologists in the United States, 23.0% of physicians performed a screening questionnire.[8] The Premenstrual symptom screening tool (PSST) is a screening tool originated from the DSM-IV PMDD criteria.[15,24] The PSST was translated from English to many languages, such as German,[25] Portuguese,[26] Arabic,[27] and so on. The PMDD scale in Japanese is essentially the Japanese version of PSST.[28] Despite its general use around the world, the original English version has not been adequately validated for reliability, and psychometric properties have not been adequately analyzed.[13] The PSST consists of 12 symptoms listed in the DSM-IV criteria for PMDD, with "Insomnia or hypersomnia" divided into "Insomnia" and "Hypersomnia" as separate symptoms. The PSST also includes five items on functional impairment; in total, 17 items are included in the PSST. Recently, an analysis using item response theory (IRT) was reported for the PSST.[29] The IRT complements the traditional classical test theory (CTT) and allows a more detailed examination of individual survey items such as the quality.[30] According to this report, "Insomnia" is a dimension independent of PMDs. In the PSST, there seems to be no significance in separating "insomnia" and "hypersomnia" into individual items.

On the other hand, the PSQ is a screening tool developed in Japan independently of the PSST, and consists of 14 items in total, including 11 premenstrual symptoms listed in the DSM-IV criteria and three items to evaluate the degree of social disability caused by these symptoms.[13] The PSQ exists only in Japanese and is used in many epidemiological and clinical studies.[14,23–30] The PSQ is essentially the short form of the PSST and has been confirmed to be in agreement with the PMDD scale, the Japanese version of PSST.[31] Furthermore, the PSQ has been adequately validated for reliability, and psychometric properties have been shown to be sound. More recently, the short-form of the PSQ (PSQ-S), consisting of nine items from the PSQ was developed and analyzed by CTT and IRT.[32] In CTT, the PSQ-S showed the same ability as the PSQ in the aspect of reliability, structural validity, and concurrent validity. Moreover, IRT showed that the all nine items in the PSQ-S performed well. Even though the PSQ-S reduced the number of questions from the PSQ to 64.3%, the maximum information content was maintained at 87.5%, indicating that the PSQ-S is useful as a shortened version of the PSQ.

After interview and use of a validated screening tool, an accurate diagnosis requires a prospective symptom assessment of two menstrual cycles. The Diary Record of Severity of Problems (DRSP) is the most universally used diary for recording symptoms, based on the DSM-IV PMDD criteria, worldwide, and is included in the UK's Green Top Guidelines.[33] The original English version has been adequately tested for reliability validity, but psychometric properties have not been fully examined.[34] For Asian languages, Chinese and Japanese versions have been created and validity and reliability have been examined.[35–40] Two types of questionnaires exist in the Japanese version: the DRSP-J[36–38] and the J-DRSP,[39,40] which were developed independently. The Chinese version of the DRSP and DRSP-J showed strong evidence of validity and reliability as compared with the original DRSP. As for the J-DRSP, it has the disadvantage that test–retest reliability is somewhat problematic, especially in the follicular phase. As to the structural validity of DRSP-J, confirmatory factor analysis (CFA) showed that a two-factor model (Mood and Behavior/Physical) was an acceptably good fit.[38] Conversely, J-DRSP showed poor fit for CFA The short form of J-DRSP was shown to be a relatively good fit, but only two evaluation methods were used.[40]

Etiology

Although the precise etiology of PMDs is remains unknown, there is no doubt about the involvement of hormonal fluctuations, as symptoms do not appear before menarche, during pregnancy, or after menopause. In PMDD patients, the administration of leuprolide, a Gonadotropin-releasing hormones (GnRH) agonists, which suppresses ovulation, suppresses premenstrual symptoms, but estrogen and progesterone replacement has been reported to cause a recurrence of premenstrual symptoms.[41] Under the same circumstances, it has been reported that premenstrual symptoms are more pronounced in the first

month of hormone replacement and less pronounced later, when hormone levels have stabilized.[42] This fact indicates the importance of hormonal fluctuations in the etiology of PMDs.

As far as neurotransmitters are concerned, two have been proposed to be involved in the pathology of PMDs: serotonin and γ-amino butyric acid (GABA).[43] Serotonin is a well-known etiologic factor in mood and anxiety disorders as well as PMS.[44] Serotonin is activated by estrogen, so serotonin levels are physiologically low before menstruation.[45,46] With regard to serotonin reuptake inhibitors (SSRI), which are antidepressants, the fact that they are considered in the first-line treatment for PMS/PMDD supports the importance of serotonin in the etiology of PMDs.[4,33] Removal of tryptophan, a precursor of serotonin, from the diet has been reported to cause premenstrual symptoms, which further suggests serotonin involvement in etiology.[47] Neuro-imaging is a very advanced method in neuroscience to evaluate neurotransmission in the brain, and has been applied to PMDD.[48] A report using neuroimaging showed a difference in the serotonin receptor 1A availability between PMDD patients and control women from the follicular to the luteal phase.[49]

Another neurotransmitter, GABA, is known to have inhibitory effects on the central nervous system.[50] Allopregnanolone (ALLO), a metabolite from progesterone, is a potent positive allosteric modulator of $GABA_A$ receptor and acts as a neuroactive steroid (Figure 2).[51] ALLO is metabolized from progesterone with 5-alpha reductase. Both progesterone and ALLO increase in the luteal phase and rapidly decrease around menstruation. An animal model of PMDD created by rapid progesterone depletion reported enhanced anxiety behavior and altered GABA receptor function.[52,53] With regard to blood levels of ALLO in humans, it has been reported that in the luteal phase, these are decreased in PMDD patients compared with those in controls.[54,55] Dutasteride, a 5-alpha reductase inhibitor showed significant improvement in PMDD symptoms in a preliminarily placebo-controlled randomized controlled trial (RCT).[56] This study indicates that fluctuations in ALLO are involved in the etiology of PMDD. For an ALLO antagonist, Sepranolone, the placebo-controlled phase 2 trial showed fairly promising results, but did not differ significantly from placebo in efficacy on the primary endpoint.[57] Further study is needed to confirm its applicability to humans.

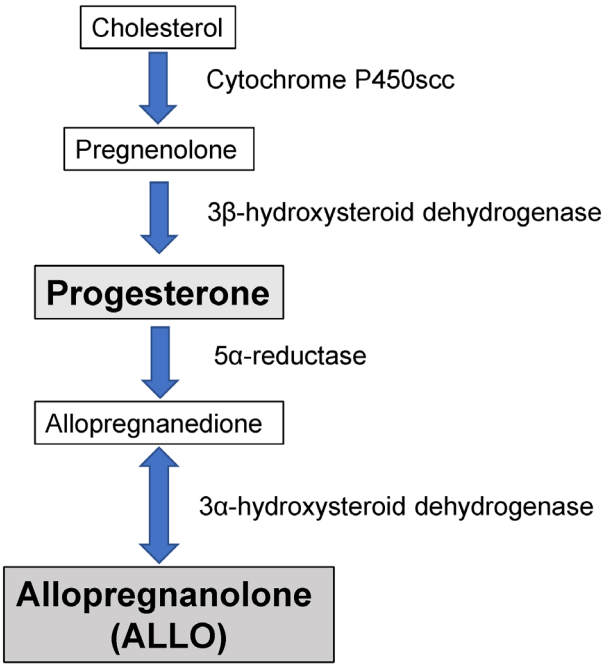

FIGURE 2 Progesterone synthesis and metabolism route

Several reports using neuro-imaging showed some relationships between PMDD and GABAergic system in brain.[58,59] Proton magnetic resonance spectroscopic findings of cortical GABA showed that GABA levels decreased from the follicular to the luteal phase in normal subjects, whereas they increased in PMDD patients.[58]

Brain derived neuro trophic factor (BDNF), which is essential for nerve cell growth, is thought to interact with serotonin systems in mood disorders.[60] The association of lower levels of BDNF and BDNF *Val66Met* polymorphism with increased risk for depression has been reported.[61,62] PMDD patients with BDNF *Val66Met* polymorphism have lower front-cingulate cortex activation in the luteal phase compared with controls with the *Met* allele.[63] Serum BDNF levels in the luteal phase are higher in PMDD patients than in controls, and conversely lower in PMS patients.[64,65] Thus, further research is needed on the relationship between PMDs and BDNF.

The gut microbiota-brain axis has been the focus of much attention, and many studies have been conducted on psychiatric disorders, including depression, and gut microbiota.[66–70] A study comparing the gut microbiota of PMDs patients and healthy controls showed that certain characteristics of the gut

microbiota were associated with premenstrual symptoms.[71] Linear discriminant effect size analysis showed that organisms such as *Parabacteroides*, *Butyricicoccus*, and *Megasphaera* were decreased in patients with PMDs. *Parabacteroides* is a GABA-producing bacterium, and *Butyricicoccus*, and *Megasphaera* contribute to BDNF production via butyric acid production. The gut microbiota may be involved in PMDs via brain transmitters.

Treatments

Usually, five types of treatments are used: (1) nonpharmacologic, (2) antidepressants, (3) hormone therapy, (4) vitamin and complementary medicine, and (5) surgery.

Nonpharmacologic treatments

It is a good alternative when symptoms are mild, or when premenstrual symptoms are present but do not meet the diagnostic criteria for PMS or PMDD. Because it is less invasive, it is positioned as the first step in treatment.

Many efficacy studies, including three RCTs, have been conducted on cognitive behavioral therapy (CBT).[72] In an RCT comparing the SSRI fluoxetine, CBT alone, and a combination of both, there was no significant difference in efficacy between the three groups after 6 months treatment.[73] Interestingly, the CBT group showed a significantly lower recurrence rate during follow-up.

With regard to lifestyle improvements, better eating habits and adequate exercise will be adopted. Dietary intervention with complex carbohydrates (elevating serum tryptophan) in the luteal phase improved PMS mood and appetite symptoms compared with placebo food by RCT.[74]

Antidepressants

There is strong evidence for the use of SSRIs for the treatment of PMDD[75] and they are considered a first line of treatment.[4,33,76] Unlike the treatment of depression, the efficacy of SSRIs administered after the onset of symptoms has been reported in the case of PMDD, assuming a different mechanism of action.[77]

Hormone therapy

The purpose of hormonal treatment is to suppress ovulation., Oral contraceptives (OCPs) were the first drugs to be used. OCPs containing drospirenone and ethinyl estradiol significantly improved PMDD symptoms.[78] Continuous dosing regimens are advantageous for improving premenstrual symptoms because they eliminate the hormone-free period compared with regimens with classical withdrawal periods.[33] There are reports suggesting the effectiveness of sequential dosing.[79,80]

GnRH agonists suppress ovulation and improve the PMS symptoms.[81,82] Low estrogen status results in symptoms of vasomotor symptoms, bone loss, and vaginal atrophy, similar to those seen after menopause, requiring estrogen add-back. Because of this invasive nature of the treatment, GnRH agonists are not first-line drugs and are indicated for SSRIs and OCPs invalid cases.[33]

Vitamins and complementary medicine

A variety of alternative medicines are being used around the world, but the evidence is limited.[33]

Among them, vitamin B6 (pyridoxine) has been extensively studied and moderate benefit was reported in 100 mg of pyridoxine treatment for premenstrual symptoms.[83] In the RCOG guidelines, vitamin B6 is listed as one of the first choices in the treatment algorithm.[33]

Calcium carbonate supplementation with 1200 mg daily was reported to be effective compared with placebo for premenstrual symptoms.[84] However, this effect was only weak compared with that of fluoxetine.[85]

Vitex agnus castus (chasteberry) is widely used in Europe and has been the subject of numerous studies, with a meta-analysis of 17 trials reporting efficacy compared with placebo.[86]

In Japan, Kampo, a type of herbal medicine, has traditionally been used in general practice. In a survey of Japanese obstetricians and gynecologists, the frequency of use of Kampo medicine as a first-line treatment for PMDs was 19%, ranking second after OCPs. Kampo medicines are available as extracted powder manufactured as industrial products by pharmaceutical companies, and can be prescribed in the same way as Western medicines. Kampo medicines have a high degree of uniformity of ingredients, and in the field of obstetrics and gynecology, their efficacy in the treatment of menopausal symptoms was examined using a placebo-controlled trial.[87] The only efficacy studies for PMDD have been preliminarily conducted using one of the Kampo formula *Kamisyoyosan*.[88] *Kamisyoyosan* has been reported to act on the brain serotonin system in a mouse model of depression,[89] making it a promising therapeutic agent for PMDs.

Surgery

Surgical intervention, total hysterectomy and bilateral adnexectomy, is a permanent treatment limited to cases of recurrence of intense symptoms.[90]

EXPECTED NEW TREATMENTS

The ALLO targeting strategy, such as a 5-alpha reductase inhibitor (Dutasteride) and ALLO antagonist (Sepranolone) are promising.[56,57] These drugs are under development, with no indications in other diseases, and further validation of their efficacy and safety is needed before they can be put into practical use.

Ulipristal Acetate (UPA), a progesterone receptor modulator, which functions as a progesterone antagonist, has been shown to be effective for PMDD symptoms by double-blind, placebo-controlled, randomized, comparative studies.[91] Since continuous UPA administration suppresses ovulation, the therapeutic effect on PMDD is predictable. UPA differs from GnRH agonists in that estradiol concentrations are maintained at levels corresponding to the follicular phase.[92] Therefore, it has the advantage that symptoms of deficient ovarian function are not observed. UPA has been commercialized as a treatment for uterine fibroids and may have potential application as a treatment for PMDD.[93]

Vitamin B6 is consist of three forms, pyridoxine, pyridoxal, and pyridoxamine. Among them only pyridoxamine has an amino group and is characterized by the fact that it acts with reactive carbonyl compounds (RCOs) to eliminate their action.[94] Since RCOs act to degrade serotonin and GABA, pyridoxamine may help maintain these brain transmitters by removing the effects of RCOs. Furthermore, pyridoxamine acts to promote the synthesis of serotonin and GABA,[95] which may act to increase the concentration of these brain transmitters more effectively than pyridoxine and pyridoxal.[96] Considering that pyridoxine treatment for premenstrual symptoms have moderate benefit,[83] pyridoxamine would be more effective than pyridoxine. A placebo-controlled, double-blind, comparative study is underway in Japan to evaluate the therapeutic effect of pyridoxamine on PMS/PMDD.

CONCLUSIONS

There is a discrepancy between actual clinical practice and research recommendations when it comes to the diagnosis of PMS/PMDD, and it is necessary to develop simpler diagnostic methods such as disease markers. SSRIs and drospirenone containing OCPs have strong supporting evidence for their efficacy in the treatment of PMDs. However, these drugs may be ineffective in some cases, or may not be taken due to contraindications or side effects. In the future, the development of minimally invasive therapies such as drugs for ALLO and pyridoxamine will also be pursued.

CONFLICT OF INTEREST

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References

1. Yonkers KA, Simoni MK. Premenstrual disorders. *Am J Obstet Gynecol*. 2018;**218**:68–74.
2. Angst J, Sellaro R, Merikangas KR, Endicott J. The epidemiology of perimenstrual psychological symptoms. *Acta Psychiatr Scand*. 2001;**104**:110–6.
3. O'Brien PM, Bäckström T, Brown C, Dennerstein L, Endicott J, Epperson CN, et al. Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: the ISPMD Montreal consensus. *Arch Womens Ment Health*. 2011;**14**:13–21.
4. Hofmeister S, Bodden S. Premenstrual syndrome and premenstrual dysphoric disorder. *Am Fam Physician*. 2016;**94**:236–40.
5. Association AP. *Diagnostic and statistical manual of mental disorders: DSM-5*. TR. Arlington: American Psychiatric Association; 2022.
6. Dr Fau R, Roy-Byrne P, Roy-Byrne P. Premenstrual syndromes: overview from a methodologic perspective. *Am J Psychiatry*. 1984;**141**:163–72.
7. Henz A, Ferreira CF, Oderich CL, Gallon CW, Castro JRS, Conzatti M, et al. Premenstrual syndrome diagnosis: a comparative study between the daily record of severity of problems (DRSP) and the premenstrual symptoms screening tool (PSST). *Rev Bras Ginecol Obstet*. 2018;**40**:20–5.
8. Craner JR, Sigmon ST, McGillicuddy ML. Does a disconnect occur between research and practice for premenstrual dysphoric disorder (PMDD) diagnostic procedures? *Women Health*. 2014;**54**:232–44.
9. Hantsoo L, Sajid H, Murphy L, Buchert B, Barone J, Raja S, et al. Patient experiences of health care providers in premenstrual dysphoric disorder: examining the role of provider specialty. *J Womens Health (Larchmt)*. 2022;**31**:100–9.
10. Johnson TM. Premenstrual syndrome as a Western culture-specific disorder. *Cult Med Psychiatry*. 1987;**11**:337–56.

11. Dennerstein L, Lehert P, Heinemann K. Epidemiology of premenstrual symptoms and disorders. *Menopause Int*. 2012; **18**:48–51.
12. Qiao M, Zhang H, Liu H, Luo S, Wang T, Zhang J, et al. Prevalence of premenstrual syndrome and premenstrual dysphoric disorder in a population-based sample in China. *Eur J Obstet Gynecol Reprod Biol*. 2012;**162**:83–6.
13. Takeda T, Tasaka K, Sakata M, Murata Y. Prevalence of premenstrual syndrome and premenstrual dysphoric disorder in Japanese women. *Arch Womens Ment Health*. 2006;**9**: 209–12.
14. Osborn E, Wittkowski A, Brooks J, Briggs PE, O'Brien PMS. Women's experiences of receiving a diagnosis of premenstrual dysphoric disorder: a qualitative investigation. *BMC Womens Health*. 2020;**20**:242.
15. Steiner M, Peer M, Palova E, Freeman EW, Macdougall M, Soares CN. The premenstrual symptoms screening tool revised for adolescents (PSST-A): prevalence of severe PMS and premenstrual dysphoric disorder in adolescents. *Arch Womens Ment Health*. 2011;**14**:77–81.
16. Takeda T, Koga S, Yaegashi N. Prevalence of premenstrual syndrome and premenstrual dysphoric disorder in Japanese high school students. *Arch Womens Ment Health*. 2010;**13**: 535–7.
17. Lu D, Aleknaviciute J, Bjarnason R, Tamimi RM, Valdimarsdóttir UA, Bertone-Johnson ER. Pubertal development and risk of premenstrual disorders in young adulthood. *Hum Reprod*. 2021;**36**:455–64.
18. Czajkowska M, Drosdzol-Cop A, Gałązka I, Naworska B, Skrzypulec-Plinta V. Menstrual cycle and the prevalence of premenstrual syndrome/premenstrual dysphoric disorder in adolescent athletes. *J Pediatr Adolesc Gynecol*. 2015;**28**: 492–8.
19. Takeda T, Imoto Y, Nagasawa H, Muroya M, Shiina M. Premenstrual syndrome and premenstrual dysphoric disorder in Japanese collegiate athletes. *J Pediatr Adolesc Gynecol*. 2015;**28**:215–8.
20. Takeda T, Imoto Y, Nagasawa H, Takeshita A, Shiina M. Stress fracture and premenstrual syndrome in Japanese adolescent athletes: a cross-sectional study. *BMJ Open*. 2016;**6**: e013103.
21. Takeda T, Ueno T, Uchiyama S, Shiina M. Premenstrual symptoms interference and equol production status in Japanese collegiate athletes: a cross-sectional study. *J Obstet Gynaecol Res*. 2018;**44**:488–94.
22. ACOG Committee Opinion No. 760: dysmenorrhea and endometriosis in the adolescent. *Obstet Gynecol*. 2018;**132**: e249–58.
23. Kitamura M, Takeda T, Koga S, Nagase S, Yaegashi N. Relationship between premenstrual symptoms and dysmenorrhea in Japanese high school students. *Arch Womens Ment Health*. 2012;**15**:131–3.
24. Steiner M, Macdougall M, Brown E. The premenstrual symptoms screening tool (PSST) for clinicians. *Arch Womens Ment Health*. 2003;**6**:203–9.
25. Bentz D, Steiner M. SIPS MG: screening instrument for premenstrual symptoms. The German version of premenstrual symptoms screening tool to assess clinically relevant disturbances. *Nervenarzt*. 2012;**83**:33–9.
26. Câmara RA, Köhler CA, Frey BN, Hyphantis TN, Carvalho AF. Validation of the Brazilian Portuguese version of the premenstrual symptoms screening tool (PSST) and association of PSST scores with health-related quality of life. *Braz J Psychiatry*. 2017;**39**:140–6.
27. Mahfoud Z, Emam R, Anchassi D, Omran S, Alhaj N, al-Abdulla S, et al. Premenstrual dysphoric disorder in Arab women: validation and cultural adaptation of the Arabic version of the premenstrual screening tool. *Women Health*. 2019;**59**:631–45.
28. Miyaoka Y, Akimoto Y, Ueda K, Ujiie Y, Kametani M, Uchiide Y, et al. Fulfillment of the premenstrual dysphoric disorder criteria confirmed using a self-rating questionnaire among Japanese women with depressive disorders. *Biopsychosoc Med*. 2011;**5**:5.
29. Śliwerski A, Koszałkowska K. The influence of depression on biased diagnosis of premenstrual syndrome and premenstrual dysphoric disorder by the PSST inventory. *Life (Basel)*. 2021;**11**:1278.
30. Jabrayilov R, Emons WHM, Sijtsma K. Comparison of classical test theory and item response theory in individual change assessment. *Appl Psychol Measur*. 2016;**40**:559–72.
31. Takeda T, Yoshimi K, Yamada K. Psychometric testing of the premenstrual symptoms questionnaire and the association between perceived injustice and premenstrual symptoms: a cross-sectional study among Japanese high school students. *Int J Womens Health*. 2020;**12**:755–63.
32. Takeda T, Yoshimi K, Kai S, Inoue F. Development and psychometric testing of a new short-form of the premenstrual symptoms questionnaire (PSQ-S). *Int J Womens Health*. 2022;**14**:899–911.
33. Management of premenstrual syndrome: Green-top Guideline; No. 48. *BJOG*. 2017;**124**(3):e73–e105.
34. Endicott J, Nee J, Harrison W. Daily record of severity of problems (DRSP): reliability and validity. *Arch Womens Ment Health*. 2006;**9**:41–9.
35. Wu L, He Z, Zhao H, Ma D, Zhang S, Deng H, et al. Chinese version of daily record of severity of problems: reliability and validity. *J Adv Nurs*. 2013;**69**:449–56.
36. Takeda T, Shiina M, Chiba Y. Effectiveness of natural S-equol supplement for premenstrual symptoms: protocol of a randomised, double-blind, placebo-controlled trial. *BMJ Open*. 2018;**8**:e023314.
37. Takeda T, Shiina M, Yamada K. Development of the Japanese version of the daily record of severity of problems (DRSP): translation and linguistic validation. *Clin Gynecol Obstet (in Japanese)*. 2019;**73**:807–11.
38. Takeda T, Kai S, Yoshimi K. Psychometric testing of the Japanese version of the daily record of severity of problems among Japanese women. *Int J Womens Health*. 2021;**13**:361–7.
39. Ikeda Y, Egawa M, Hiyoshi K, Ueno T, Ueda K, Becker CB, et al. Development of a Japanese version of the daily record of severity of problems for diagnosing premenstrual syndrome. *Womens Health Rep (New Rochelle)*. 2020;**1**:11–6.
40. Ikeda Y, Egawa M, Okamoto K, Mandai M, Takahashi Y, Nakayama T. The reliability and validity of the Japanese version of the daily record of severity of problems (J-DRSP) and development of a short-form version (J-DRSP [SF]) to assess symptoms of premenstrual syndrome among Japanese women. *Biopsychosoc Med*. 2021;**15**:6.
41. Schmidt PJ, Nieman LK, Danaceau MA, Adams LF, Rubinow DR. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. *N Engl J Med*. 1998;**338**:209–16.

42. Schmidt PJ, Martinez PE, Nieman LK, Koziol DE, Thompson KD, Schenkel L, et al. Premenstrual dysphoric disorder symptoms following ovarian suppression: triggered by change in ovarian steroid levels but not continuous stable levels. *Am J Psychiatry*. 2017;**174**:980–9.
43. Nevatte T, O'Brien PM, Bäckström T, Brown C, Dennerstein L, Endicott J, et al. ISPMD consensus on the management of premenstrual disorders. *Arch Womens Ment Health*. 2013;**16**:279–91.
44. Lin SH, Lee LT, Yang YK. Serotonin and mental disorders: a concise review on molecular neuroimaging evidence. *Clin Psychopharmacol Neurosci*. 2014;**12**:196–202.
45. McQueen JK, Wilson H, Fink G. Estradiol-17 beta increases serotonin transporter (SERT) mRNA levels and the density of SERT-binding sites in female rat brain. *Brain Res Mol Brain Res*. 1997;**45**:13–23.
46. Bertrand PP, Paranavitane UT, Chavez C, Gogos A, Jones M, van den Buuse M. The effect of low estrogen state on serotonin transporter function in mouse hippocampus: a behavioral and electrochemical study. *Brain Res*. 2005;**1064**: 10–20.
47. Menkes DB, Coates DC, Fawcett JP. Acute tryptophan depletion aggravates premenstrual syndrome. *J Affect Disord*. 1994;**32**:37–44.
48. Dubol M, Epperson CN, Lanzenberger R, Sundström-Poromaa I, Comasco E. Neuroimaging premenstrual dysphoric disorder: a systematic and critical review. *Front Neuroendocrinol*. 2020;**57**:100838.
49. Jovanovic H, Cerin A, Karlsson P, Lundberg J, Halldin C, Nordström AL. A PET study of 5-HT1A receptors at different phases of the menstrual cycle in women with premenstrual dysphoria. *Psychiatry Res*. 2006;**148**:185–93.
50. Foster AC, Kemp JA. Glutamate- and GABA-based CNS therapeutics. *Curr Opin Pharmacol*. 2006;**6**:7–17.
51. Schüle C, Nothdurfter C, Rupprecht R. The role of allopregnanolone in depression and anxiety. *Prog Neurobiol*. 2014;**113**:79–87.
52. Schneider T, Popik P. An animal model of premenstrual dysphoric disorder sensitive to antidepressants. *Curr Protoc Neurosci*. 2009;**9**:31.
53. Li Y, Pehrson AL, Budac DP, Sánchez C, Gulinello M. A rodent model of premenstrual dysphoria: progesterone withdrawal induces depression-like behavior that is differentially sensitive to classes of antidepressants. *Behav Brain Res*. 2012; **234**:238–47.
54. Rapkin AJ, Morgan M, Goldman L, Brann DW, Simone D, Mahesh VB. Progesterone metabolite allopregnanolone in women with premenstrual syndrome. *Obstet Gynecol*. 1997; **90**:709–14.
55. Monteleone P, Luisi S, Tonetti A, Bernardi F, Genazzani AD, Luisi M, et al. Allopregnanolone concentrations and premenstrual syndrome. *Eur J Endocrinol*. 2000;**142**:269–73.
56. Martinez PE, Rubinow DR, Nieman LK, Koziol DE, Morrow AL, Schiller CE, et al. 5α-reductase inhibition prevents the luteal phase increase in plasma allopregnanolone levels and mitigates symptoms in women with premenstrual dysphoric disorder. *Neuropsychopharmacology*. 2016;**41**:1093–102.
57. Bixo M, Ekberg K, Poromaa IS, Hirschberg AL, Jonasson AF, Andréen L, et al. Treatment of premenstrual dysphoric disorder with the GABAA receptor modulating steroid antagonist Sepranolone (UC1010): a randomized controlled trial. *Psychoneuroendocrinology*. 2017;**80**:46–55.
58. Epperson CN, Haga K, Mason GF, Sellers E, Gueorguieva R, Zhang W, et al. Cortical gamma-aminobutyric acid levels across the menstrual cycle in healthy women and those with premenstrual dysphoric disorder: a proton magnetic resonance spectroscopy study. *Arch Gen Psychiatry*. 2002;**59**:851–8.
59. Liu B, Wang G, Gao D, Gao F, Zhao B, Qiao M, et al. Alterations of GABA and glutamate-glutamine levels in premenstrual dysphoric disorder: a 3T proton magnetic resonance spectroscopy study. *Psychiatry Res*. 2015;**231**:64–70.
60. Martinowich K, Lu B. Interaction between BDNF and serotonin: role in mood disorders. *Neuropsychopharmacology*. 2008; **33**:73–83.
61. Elfving B, Buttenschøn HN, Foldager L, Poulsen PHP, Andersen JH, Grynderup MB, et al. Depression, the Val66Met polymorphism, age, and gender influence the serum BDNF level. *J Psychiatr Res*. 2012;**46**:1118–25.
62. Harrisberger F, Smieskova R, Schmidt A, Lenz C, Walter A, Wittfeld K, et al. BDNF Val66Met polymorphism and hippocampal volume in neuropsychiatric disorders: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2015;**55**: 107–18.
63. Comasco E, Hahn A, Ganger S, Gingnell M, Bannbers E, Oreland L, et al. Emotional fronto-cingulate cortex activation and brain derived neurotrophic factor polymorphism in premenstrual dysphoric disorder. *Hum Brain Mapp*. 2014;**35**: 4450–8.
64. Oral E, Kirkan TS, Yildirim A, Kotan Z, Cansever Z, Ozcan H, et al. Serum brain-derived neurotrophic factor differences between the luteal and follicular phases in premenstrual dysphoric disorder. *Gen Hosp Psychiatry*. 2015;**37**: 266–72.
65. Cubeddu A, Bucci F, Giannini A, Russo M, Daino D, Russo N, et al. Brain-derived neurotrophic factor plasma variation during the different phases of the menstrual cycle in women with premenstrual syndrome. *Psychoneuroendocrinology*. 2011;**36**: 523–30.
66. Aizawa E, Tsuji H, Asahara T, Takahashi T, Teraishi T, Yoshida S, et al. Possible association of Bifidobacterium and lactobacillus in the gut microbiota of patients with major depressive disorder. *J Affect Disord*. 2016;**202**:254–7.
67. Morais LH, HLT S, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. *Nat Rev Microbiol*. 2021;**19**:241–55.
68. Tian P, Wang G, Zhao J, Zhang H, Chen W. Bifidobacterium with the role of 5-hydroxytryptophan synthesis regulation alleviates the symptom of depression and related microbiota dysbiosis. *J Nutr Biochem*. 2019;**66**:43–51.
69. Sanada K, Nakajima S, Kurokawa S, Barceló-Soler A, Ikuse D, Hirata A, et al. Gut microbiota and major depressive disorder: a systematic review and meta-analysis. *J Affect Disord*. 2020;**266**:1–13.
70. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci*. 2012;**13**:701–12.
71. Takeda T, Yoshimi K, Kai S, Ozawa G, Yamada K, Hiramatsu K. Characteristics of the gut microbiota in women with premenstrual symptoms: a cross-sectional study. *PLoS One*. 2022;**17**:e0268466.

72. Lustyk MK, Gerrish WG, Shaver S, Keys SL. Cognitive-behavioral therapy for premenstrual syndrome and premenstrual dysphoric disorder: a systematic review. *Arch Womens Ment Health*. 2009;**12**:85–96.
73. Hunter MS, Ussher JM, Browne SJ, Cariss M, Jelley R, Katz M. A randomized comparison of psychological (cognitive behavior therapy), medical (fluoxetine) and combined treatment for women with premenstrual dysphoric disorder. *J Psychosom Obstet Gynaecol*. 2002;**23**:193–9.
74. Sayegh R, Schiff I, Wurtman J, Spiers P, McDermott J, Wurtman R. The effect of a carbohydrate-rich beverage on mood, appetite, and cognitive function in women with premenstrual syndrome. *Obstet Gynecol*. 1995;**86**:520–8.
75. Marjoribanks J, Brown J, O'Brien PM, Wyatt K. Selective serotonin reuptake inhibitors for premenstrual syndrome. *Cochrane Database Syst Rev*. 2013;**2013**:CD001396.
76. Ismaili E, Walsh S, O'Brien PMS, Bäckström T, Brown C, Dennerstein L, et al. Fourth consensus of the International Society for Premenstrual Disorders (ISPMD): auditable standards for diagnosis and management of premenstrual disorder. *Arch Womens Ment Health*. 2016;**19**:953–8.
77. Yonkers KA, Kornstein SG, Gueorguieva R, Merry B, Van Steenburgh K, Altemus M. Symptom-onset dosing of sertraline for the treatment of premenstrual dysphoric disorder: a randomized clinical trial. *JAMA Psychiat*. 2015;**72**:1037–44.
78. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. *Cochrane Database Syst Rev*. 2012;**2**:Cd006586.
79. Coffee AL, Kuehl TJ, Willis S, Sulak PJ. Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. *Am J Obstet Gynecol*. 2006;**195**:1311–9.
80. Machado RB, Pompei LM, Badalotti M, Ferriani R, Cruz AM, Nahas E, et al. Effects of an extended flexible regimen of an oral contraceptive pill containing 20 μg ethinylestradiol and 3 mg drospirenone on menstrual-related symptoms: a randomised controlled trial. *Eur J Contracept Reprod Health Care*. 2017;**22**:11–6.
81. Mezrow G, Shoupe D, Spicer D, Lobo R, Leung B, Pike M. Depot leuprolide acetate with estrogen and progestin add-back for long-term treatment of premenstrual syndrome. *Fertil Steril*. 1994;**62**:932–7.
82. Mortola JF. Applications of gonadotropin-releasing hormone analogues in the treatment of premenstrual syndrome. *Clin Obstet Gynecol*. 1993;**36**:753–63.
83. Wyatt KM, Dimmock PW, Jones PW, Shaughn O'Brien PM. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ (Clin Res Ed)*. 1999;**318**:1375–81.
84. Thys-Jacobs S, Starkey P, Bernstein D, Tian J. Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual syndrome study group. *Am J Obstet Gynecol*. 1998;**179**:444–52.
85. Yonkers KA, Pearlstein TB, Gotman N. A pilot study to compare fluoxetine, calcium, and placebo in the treatment of premenstrual syndrome. *J Clin Psychopharmacol*. 2013;**33**:614–20.
86. Verkaik S, Kamperman AM, van Westrhenen R, Schulte PFJ. The treatment of premenstrual syndrome with preparations of Vitex agnus castus: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2017;**217**:150–66.
87. Takamatsu K, Ogawa M, Obayashi S, Takeda T, Terauchi M, Higuchi T, et al. A multicenter, randomized, double-blind, placebo-controlled trial to investigate the effects of kamishoyosan, a traditional Japanese medicine, on menopausal symptoms: the KOSMOS study. *Evid Based Complement Alternat Med*. 2021;**2021**:8856149.
88. Yamada K, Kanba S. Effectiveness of kamishoyosan for premenstrual dysphoric disorder: open-labeled pilot study. *Psychiatry Clin Neurosci*. 2007;**61**:323–5.
89. Shimizu S, Ishino Y, Takeda T, Tohyama M, Miyata S. Antidepressive effects of kamishoyosan through 5-HT1Areceptor and PKA-CREB-BDNF signaling in the hippocampus in postmenopausal depression-model mice. *Evid Based Complement Alternat Med*. 2019;**2019**:9475384.
90. Casson P, Hahn PM, van Vugt DA, Reid RL. Lasting response to ovariectomy in severe intractable premenstrual syndrome. *Am J Obstet Gynecol*. 1990;**162**:99–105.
91. Comasco E, Kopp Kallner H, Bixo M, Hirschberg AL, Nyback S, de Grauw H, et al. Ulipristal acetate for treatment of premenstrual dysphoric disorder: a proof-of-concept randomized controlled trial. *Am J Psychiatry*. 2021;**178**:256–65.
92. Whitaker LH, Williams AR, Critchley HO. Selective progesterone receptor modulators. *Curr Opin Obstet Gynecol*. 2014;**26**:237–42.
93. Rabe T, Saenger N, Ebert AD, Roemer T, Tinneberg H-R, de Wilde RL, et al. Selective progesterone receptor modulators for the medical treatment of uterine fibroids with a focus on ulipristal acetate. *Biomed Res Int*. 2018;**2018**:1374821.
94. Mori Y, Kakuta T, Miyakogawa T, Takekoshi S, Yuzawa H, Kobayashi H, et al. Effect of scavenging circulating reactive carbonyls by oral pyridoxamine in uremic rats on peritoneal dialysis. *Ther Apher Dial*. 2016;**20**:645–54.
95. Sherif FM, Ahmed SS. Basic aspects of GABA-transaminase in neuropsychiatric disorders. *Clin Biochem*. 1995;**28**:145–54.
96. Itokawa M, Miyashita M, Arai M, Dan T, Takahashi K, Tokunaga T, et al. Pyridoxamine: a novel treatment for schizophrenia with enhanced carbonyl stress. *Psychiatry Clin Neurosci*. 2018;**72**:35–44.