Mini Review

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Premenstrual disorder and the adolescent: clinical case report, literature review, and diagnostic and therapeutic challenges

Abstract

Objective: The aim of this paper is to present a case with premenstrual dysphoric disorder and to review the diagnosis from an adolescent medicine approach, discussing why diagnosis and treatment must be distinct for this age group and different from the adult approach.
Introduction: Premenstrual disorder is a periodic, recurrent, debilitating condition with either physical and/or psychological symptoms that occur during the late luteal phase of the menstrual cycle.
Case: We report the case of a 16-year-old female diagnosed with premenstrual disorder.
Discussion: Physical signs, behavioral changes, and mood disturbances that occur before menstruation have long been recognized in women, but how well is the disorder defined for adolescents? Due to the unique characteristics of teens, do the current diagnostic criteria appropriately represent this population?

Keywords: adolescent; premenstrual dysphoric disorder (PMDD); premenstrual syndrome (PMS).

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Introduction

Premenstrual symptoms are physical, emotional, and behavioral symptoms that repeatedly occur in a cyclic fashion preceding menstruation and then disappear after the menstrual period. These symptoms do not interfere with one's personal, social, and professional life (1). By contrast, a woman with a premenstrual disorder, such as premenstrual syndrome (PMS), has premenstrual symptoms that do have a substantial impact on quality of life, with resultant impairment of education/work, interpersonal relationships, and home life (2). Some patients with severe psychological symptoms and a greater dysfunction of social and professional activities also fulfill the American Psychiatric Association (APA) criteria for premenstrual dysphoric disorder (PMDD) (3). However, it is crucial to establish the correct diagnosis using clearly defined criteria, especially for the adolescent population. In this work, we present a case of PMDD with an initial mistaken diagnosis of major depression causing noncompliance with the treatment and avoiding the therapeutic alliance between the mental health therapist and the adolescent. We will also discuss the features of this disorder unique to the adolescent population.

Case

A 16-year-old female presented to the Adolescent Medicine Clinic with heavy bleeding during her periods, with additional symptoms of anxiety, sadness and unexplained crying spells, which had been occurring for the past 6 months. Her symptoms usually occurred a few days before the onset of her menses and improve by day 3. She had also noticed severe bloating, abdominal pain, and back pain during these periods. She had missed many school days as she also lacked interest in usual daily activities and stayed in bed all day, or locked herself in the bathroom spending a majority of her time crying. She had previously been seen by a child and adolescent psychiatrist and was diagnosed with major depression and started on Fluoxetine a month previously. However, she refused to take the medicine just as much as she refused

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the diagnosis of depression. She stated that she knew she was not depressed and was angry that nobody believed her. Menarche occurred at age 12 years. Her menses were regular, although she stated an increased flow with normal duration. Her past medical history and physical exam were unremarkable. Due to the complaint of heavy bleeding, complete blood count was ordered and revealed no anemia with a hemoglobin level of 13.2 g/dL. Psychosocial evaluation revealed no history of substance use/abuse and no weight issues. Family history revealed depression in the mother and no other mental health issues.

We explained the diagnosis of PMDD to the patient and how it was different from depression. We did not ask her to keep track of her symptoms using a menstrual calendar as we felt she would not come back and needed immediate help and assistance. We decided to start her on continuous Fluoxetine 20 mg/day again and also added a cyclic treatment with ethinyl estradiol and drospirenone containing combined oral contraceptive drug to suppress the ovulation. During the next visit 1 month later, the patient's symptomatology was minimally relieved; she stated that although she felt better, she was still not her usual self, but bleeding had significantly decreased. She was re-evaluated 2 months later and stated that all of her symptoms had disappeared. Written consent was obtained from the patient and her parents for the publication of this case.

Discussion

According to the classification made by the International Society for Premenstrual Disorders, the key characteristic of PMS is the timing of symptoms, which occur only during all or part of the 2 weeks leading up to menstruation, the luteal phase of the menstrual cycle. Symptoms disappear by the end of menstruation and do not recur before ovulation, giving the patient a symptom-free interval of at least 1 week. PMS is cyclical and occurs in most menstrual cycles. Symptoms must be prospectively rated for at least two cycles. Substantial impairment of daily activities at work or school, social activities and hobbies, and interpersonal relationships is a key feature. The criteria do not require specific symptoms to be present and, although well over 200 have been reported, some are considered key or characteristic symptoms (4).

What makes the diagnosis of PMS difficult for all age groups is that there are no objective diagnostic tests. Furthermore, according to the Royal College of Obstetricians and Gynaecologists' (RCOG) guidelines, diagnosis depends on prospectively recording symptoms over two cycles, using a tool such as the Daily record of severity of problems tool (5). This may cause a problem for physicians working with adolescents. Studies have shown that adolescents rarely ask for professional help even when it is necessary (6). An interesting study showed that although 80% of women enrolled experienced mood and physical symptoms associated with their menstrual cycle and 50% reported an effect on functioning at work, only one-fourth of the women sought treatment (7). Asking a patient like the one in our case to go home and record her symptoms for 2 months would have probably resulted in her seeking help somewhere else or not at all. Although we agree that recording of symptoms is important for an accurate diagnosis, it is highly possible for an adolescent to delay the start of treatment. A question we raise is that "With good history taking or the use of a screening tool, would it be possible to skip the embarking on 2 months of data collection?" Table 1 shows how to take a detailed history in a patient with PMS.

Another question we raise is "Should we adapt the 'two cycles' criteria for adolescents as is accepted in adult women"? The problem would be that the ovarian cycle is not predictable like that of an adult female. It is well known that menstrual cycles are often irregular due to anovulatory cycles, and this is considered normal after the first few years of menarche. Then, with the maturation of hypothalamus-hypophysis-ovarian axis, ovulation starts and both PMS and dysmenorrhea symptoms may be seen thereafter (8). The timing of the start of ovulatory cycles is also not predictable for an adolescent and may differ in a wide range of years. As the transition from anovulatory cycles to ovulatory cycles may vary for every adolescent girl, and because this timing is important to attribute some defined symptoms to PMS, is the criterion stating that symptoms must occur prospectively for at least 2 months applicable for an adolescent with an irregular cycle?

Another problem causing either under diagnosis or over diagnosis of a patient with PMS lies in the co-occurrence of the syndrome with the psychosocial maturation period of adolescence. As previously stated, PMS begins after ovulation and for most adolescents, this occurs during mid-adolescence (14–16 years). Mid-adolescence is a period of more frequent and intense conflict between parents and teenagers and is also known as the most difficult period of psychosocial maturation. During this period, conflicts become more prevalent as the adolescent exhibits less interest in parents and more interest in friends. During this stage of development, such characteristics as individuality and striving for independence can increase these conflicts. Struggling with establishing one's identity and self-image and being accepted by

Table 1 History of an adolescent with PMS.

	Questions
Menstrual history	What are the dates of menarche and the last menstrual period? Describe the frequency, duration, heaviness, regularity, and cases of dysmenorrhea.
History of premenstrual symptom	What is the nature of the symptoms (predominantly physical or psychological)? What part of the menstrual cycle do they occur? Has the patient experienced a week of symptom-free follicular phase? How long have these symptoms been occurring?
Severity of symptoms	Describe the level of impairment the symptoms have caused, their effects on work, school, hobbies, social activities, family, partner, work colleagues. How much distress has the patient experienced? Has there been any suicidal ideation?
Medication history	Is the patient being treated with hormones? For example, combined or progestogen-only contraception, progestogens, hormonal replacement therapy. Does the patient have an underlying medical problem so that symptoms become worse before menstruation?
Medical diagnosis	Does she have other medical diagnoses, particularly gynecological diagnoses, such as heavy menstrual bleeding, endometriosis, pelvic pain, dyspareunia, or cervical smear abnormalities?

friends feels extremely important for the teen. Separation from familial ideals and values and a more intense involvement with peers may also lead to confusion and conflict. Mood swings and labiality, to an extent, would be accepted as normal psychological and behavioral patterns for this period (9). If anger outbursts and/or anxiety spells, as well as sudden mood changes due to struggles of adolescence coincide with the luteal stage of the premenstrual cycle, it may be misinterpreted as the psychological symptoms PMS.

This again is another reason why physicians working with adolescents should be skeptical of the RCOG guidelines, which advise that symptoms should be observed for only two cycles. On the contrary, the psychosocial developmental characteristics of this age may cause a delay in the diagnosis of PMS, because a physician may interpret these symptoms as being normal for this age group. Such factors must be ruled out in the differential diagnosis. It is for this reason that the health care providers who evaluate such adolescents must ensure that they take detailed psychosocial histories of the adolescents.

There is a wide variation in estimates of the prevalence of PMS, which most probably stems from different diagnostic criteria. However, it has been estimated that 15%–20% of women of reproductive age have PMS with significantly impaired functioning, and a further 3%–8% have PMDD (10). However, how well is the adolescent population represented? We were unable to find valid population-based data on the prevalence in adolescents and very few studies have examined the occurrence of premenstrual symptoms among adolescents. Indeed, there are only a few studies and case reports of this condition in this age group in the current literature (11, 12). A previous study aimed to investigate the frequency of PMS associated symptoms in adolescent girls who applied to the clinic for other reasons. Adolescents were given a questionnaire on criteria for PMS, dysmenorrhea, and regularity of menstrual cycle. Modified Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria were used for the diagnosis of PMS. An outstanding 61.4% met the DSM-IV criteria for PMS, while 49.5%, 37.1%, and 13.4% had mild, moderate and severe PMS, respectively. The most common symptom of PMS was negative effect, particularly in the form of stress (87.6%) and anxiety (87.6%) (13). A study by Cleckner-Smith et al. (14) aimed to examine the prevalence and severity of premenstrual symptoms in adolescents and compare these according to age (13- to 15-year-olds and 16- to 18-year-olds). All participants reported at least one premenstrual symptom of minimal severity, 88% reported their symptoms as moderate, 73% as severe, and 56% as extreme. The symptoms most commonly reported were food cravings, breast swelling, abdominal discomfort, mood swings, stressed feeling, and dissatisfaction with appearance. The younger adolescents had significantly less intense symptoms than the older adolescents.

PMDD has been moved from DSM-IV Appendix B, "Criteria Sets and Axes Provided for Further Study", to the main body of DSM-V under the chapter on depressive disorders (15). According to the DSM-V, symptoms must occur during the final week before menstruation, but do not need to be present most of the time. Symptoms are not required to remit within a few days of menstruation, but should improve and should be minimal (if not absent) in the week following menstruation. Mood labiality and irritability are the leading two symptoms. Symptoms cause clinically significant distress or interference with activities at work or school or at home, or both. One positive change in the criteria is that the clinically significant distress or activities at home are now being considered. However, an

area that has been overlooked in DSM-V is that the criteria still only focus on severe psychological symptoms while placing relatively little importance on physical symptoms. From a clinician's perspective, this may exclude some girls with debilitating symptoms who do not meet these specific criteria.

During history taking or after the evaluation of a diary, if the patient gives no reference to a symptom-free period it is also important to consider alternative medical diagnosis, such as anemia, autoimmune disorders, hypothyroidism, diabetes mellitus, seizure disorders, endometriosis, chronic fatigue syndrome, collagen vascular disease, eating disorders, substance use, or psychological illnesses, including major depression, dysthymia generalized anxiety, panic disorder, and bipolar illness in the differential diagnosis of PMS (16).

The goals of treatment are limitation or reduction of symptoms and improvement of social and educational functioning. However, one of the most important approaches to treatment is that management should be tailored according to the severity and type of symptoms as well as to the patient's age and preferences.

For patients with less severe symptoms, changes in lifestyle have been shown to be effective, including regular, frequent (every 2–3 h), small balanced meals rich in complex carbohydrates; regular exercise; smoking cessation; alcohol and caffeine restriction; and regular sleep (17). Supplements such as calcium, vitamin B6 and vitamin D have also been shown to be superior to placebo. The only herbal supplement that has been shown to be effective in small placebo-controlled trials is the fruit extract of *Vitex agnus castus* (18).

Pharmacotherapy for PMS can be divided into two groups: hormonal and non-hormonal. The major problem concerning the pharmacological treatment of PMS in adolescents is that randomized controlled trials of teens have yet to be performed.

As mentioned earlier, it is important that treatment is tailored according to the patients' needs. A good example for this is that 100 mg/day of spironolactone has been given to a patient with predominantly physical symptoms in the luteal phase in a randomized placebo-controlled study, resulting in reduced abdominal bloating, swelling, breast discomfort, and mood symptoms (19). However, this study was performed in adults.

Serotonin is a neurotransmitter that has been implicated in the pathophysiology of PMS (20). Changing the balance of serotonin enhances mood. Selective serotonin reuptake inhibitors (SSRIs) are a group of drugs that work by inhibiting its absorption, thus increasing its availability. Currently, SSRIs are more commonly used for the treatment of depression and anxiety (21). During the menstrual cycle, levels of serotonin show discrepancy under the effect of estrogen and progesterone (20). Study designs using placebo-controlled trials have shown that SSRIs or serotonin and noradrenaline reuptake inhibitors are effective in reducing both mood and physical symptoms (22). Furthermore, SSRIs are effective in improving not only psychological symptoms, such as irritability, depression and dysphoria, but also physical symptoms, such as bloating, breast tenderness, and appetite changes. Another interesting finding is that compared with the treatment for depression, the onset of effects occur much more promptly (23).

Meanwhile, different methods of dosing have been tested, including a continuous method where the SSRI is taken every day throughout the menstrual cycle, the luteal/intermittent method where the SSRI is taken only during the luteal phase of the menstrual cycle (i.e., from estimated ovulation to menstruation), or the semi-intermittent method wherein SSRI is taken every day, with a low SSRI dose during the follicular phase of the menstrual cycle and a higher dose in the luteal phase. It is also important to mention that intermittent use of SSRIs does not cause SSRI withdrawal symptoms. Another proposed method starting SSRI at the onset of PMS symptoms and continued until the onset of menstruation (24). A Cochrane database review evaluating the use of SSRIs for PMS suggests that both intermittent and continuous dosing regimens are effective in reducing symptoms (25). The choice of type of administration should be based on the preference of the patient and certain factors, such as whether the menstrual cycle is predictable, and compliance of a different treatment regime should be discussed with the patient. Adolescents have difficulty taking medication regularly and this is also something that should be considered. Although adult studies have shown the effectiveness of SSRIs, to date, no data has been published regarding adolescents and SSRI use for PMS treatment in this group. An unpublished pilot study with 11 teens between 15 and 19 years reported that the Penn Daily Symptom Report scores decreased 41% in the SSRI group and 28% in the placebo group. However, no significant difference between the groups was statistically shown and this was attributed to the lack of statistical power with this very small sample size (25). Another major problem concerns the prescription of these drugs. In certain countries, such as our own, Adolescent Medicine specialists (e.g., pediatricians, gynecologists) are not licensed to prescribe SSRI regardless of the diagnosis. SSRIs are licensed in the US, but not in Europe, for the management of PMDD even by a psychiatrist.

Other psychotropic drugs used for PMS are anxiolytics. Studies have shown that anxiolytics are more effective than placebo but less effective than SSRIs; furthermore, because the side effects are greater, this makes them a less advantageous option when compared with SSRIs (26). The second type of pharmacotherapy is hormonal treatment. Although the pathogenesis behind PMS is complex and the exact causal mechanism is poorly understood, the one certain contributing factor is the cyclical ovarian activity, as PMS does not occur before ovulatory cycles, in pregnancy, or after the menopause and symptoms occur in the luteal phase (27). Thus, a treatment that suppresses ovulation and eliminates the luteal phase should, in theory, be an ideal treatment method. However, studies that originally used the OCP showed an opposite effect to what was primarily expected; furthermore, patients were found to be susceptible to negative moods (28) and physical symptoms, such as bloating and water retention were reported (29). Further studies have shown that certain factors, such as type, formulation and dose of progestogen and estrogen, schedule of administration and length of pill-free intervals, all have an effect on the treatment's efficacy to reduce or eliminate PMS (30). The predominantly physical effects, such as bloating, breast tenderness and water retention, are due to the estrogen component, whereas the psychological effects are due to the progestin derived from 19-nor testosterone (31). For this reason, a lower dose of estrogen combined by a progestin not derived from testosterone seems a better approach.

Drospirenone is a progestin derived from 17-α-spironolactone; it differs from 19-nortestosterone-derived progestins in that it has antimineralocorticoid and antiandrogenic activity (32). The first report that used drospirenone was a study by Freeman et al. (33) wherein patients received 3 mg drospirenone and 30 mg ethinyl estradiol in a 21/7 regimen. The Calendar of Premenstrual Experiences scale was used to evaluate the patients, and the study found that symptoms improved in only three areas: appetite, acne and food cravings. However, when patients were also evaluated with the Beck Depression Inventory and Profile of Mood States, those treated with drospirenone showed greater improvement. They concluded that the treatment was beneficial for the treatment of PMDD (33). Preceding this study, a different dosage with 3 mg drospirenone and 20 mg ethinyl estradiol in a 24/4 regimen was evaluated. The study by Yonkers et al. (34) showed a significant reduction in both total and individual symptom scores. Similarly, a multicenter, double-blind, placebo-controlled, cross-over study by Pearlstein et al. (35) also showed a significant decrease in daily Record of Severity of Problems scores for the group using drospirenone/ethinyl estradiol when compared with the group that used placebo. Based on the findings of these studies, drospirenone 3 mg and ethinyl estradiol 20 μg in the 24/4 regimen has been approved by the Food and Drug Administration in the US for the treatment of PMDD, but is not licensed under this indication in Europe. Similar to the other drugs used for PMS and PMDD, no studies with drospirenone have been conducted with adolescents.

Various treatments, such as the use of drugs (e.g., gonadotrophin-releasing hormone agonist, high doses of transdermal estrogen) and even surgery (e.g., bilateral oophorectomy and hysterectomy) have been suggested to be effective in the treatment of PMS (32). These treatments are not suitable for a growing and developing adolescent, as they would compromise pubertal development and bone health. Thus, these treatments were not discussed in this paper.

We present this adolescent case report to highlight the fact that an adolescent may suffer from serious PMDD. We use this opportunity to conclude that future studies concerning both diagnosis and treatment of PMS/PMDD, which strictly focus on the adolescent population, is extremely important. The future research areas would include the development of a tool and/or a set of criteria that would enable accurate diagnosis of PMS/PMDD in adolescents. These should take both pubertal and psychological developmental features of adolescence into consideration. Further studies regarding pharmacotherapy, which focus solely on adolescents, are also essential, especially for patients with functional impairment.

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