Premenstrual Syndromes - An Approach to Diagnosis and Treatment

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Abstract

This article discusses the differences between *premenstrual syndrome* and *premenstrual dysphoric disorder* and outlines a treatment approach.

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INTRODUCTION

The premenstrual syndromes are characterised by physical and/or affective symptoms that occur in the luteal phase of the menstrual cycle. Symptoms and severity of symptoms vary and therefore the impact of these syndromes on psychosocial and economical aspects is difficult to quantify and generalise.

CLINICAL MANIFESTATIONS

Premenstrual syndrome (PMS) will affect about 25% of women with a regular menstrual cycle, depending on the strictness of criteria. Physical and behavioural symptoms can occur.

Premenstrual dysphoric disorder (PMDD) is a more severe type of PMS where the psychological and behavioural symptoms of labile and depressed mood, anger, irritability and internal tension are prominent. PMDD occurs in about 5% of women with regular cycles.[1]

Table 1: Common symptoms of premenstrual syndrome.

COMMON PHYSICAL SYMPTOMS OF PMS
Abdominal bloating
Extreme fatigue
Breast tenderness
Headache
Also: acne, dizziness, palpitations,

COMMON BEHAVIOURAL SYMPTOMS OF PMS
Labile mood
Irritability
Tensions
Depressed mood
Also: anger, increased appetite, easy crying, forgetfulness

While over 150 symptoms have been ascribed to PMS, the most common symptoms are listed in tables 1 and 2. To accurately diagnose these disorders, recognized criteria should be used as many women suffer from other underlying disorders exacerbated pre-menstrually and should not be treated as PMS.[2]

DIAGNOSTIC CRITERIA

The criteria of the American College of Obstetricians and Gynecologists for PMS are widely used (table 2). These criteria describe affective and somatic symptoms in a cyclical fashion with a severity criterion of identifiable social or economic dysfunction.[3]

For the diagnosis of PMDD the most widely used criteria is that of the DSM-IV (table 3).

Only affective symptoms are required with prospective confirmation, correct timing and a severity clause.[4]

PATHOGENESIS

Ovarian steroid hormone fluctuations are clearly needed to precipitate the symptoms. On the other hand it is also clear that these cyclical changes are not solely responsible for either the mood changes or the systemic manifestations of the syndrome and disorder. Susceptible symptomatic women have levels comparable to levels found in asymptomatic women.[5]

Interaction between the ovarian steroid hormones and neurotransmitters seems to play a major role, with serotonin currently most implicated. While susceptibility to both mood disorders

Table 2: The diagnostic criteria of the American College of Obstetricians and Gynecologists for premenstrual syndrome.

DIAGNOSTIC CRITERIA FOR PREMENSTRUAL SYNDROME
* At least one of the following affective and somatic symptoms must be reported during the five days before menses in each of the three prior menstrual cycles:
Affective Symptoms - Depression - Angry outbursts - Irritability - Anxiety - Confusion - Social Withdrawal
Somatic Symptoms - Breast tenderness - Abdominal bloating - Headache - Swelling of extremities
* These symptoms are relieved within 4 days of the onset of menses without recurrence until at least cycle day 13.
* The symptoms are present in the absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol use.
* The symptoms occur reproducibly during two cycles of prospective recording.
* The patient suffers from identifiable dysfunction in social or economic performance.

Table 3: The DSM IV diagnostic criteria of the Amercian Psychiatric Association. (Diagnostic and Statistical Manual Edition IV)

RESEARCH CRITERIA FOR PREMENSTRUAL DYSPHORIC DISORDER

A) In most menstrual cycles during the past five year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week post menses, with at least one of the symptoms being either of the first four:

1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
2. Marked anxiety, tension, feelings of being "keyed up" of "on edge"
3. Marked affective liability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
4. Persistent and marked anger or irritability or increased interpersonal conflicts
5. Decreased interest in usual activities (e.g., work, school friends, hobbies)
6. Subjective sense of difficulty in concentrating
7. Lethargy, easy fatigability, or marked lack of energy
8. Marked change in appetite, overeating, or specific food cravings
9. Hypersomnia or insomnia
10. A subjective sense of being overwhelmed or out of control
11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating", weight gain

B) The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C) The disturbance is not merely an exacerbation of the symptoms of another disorder, such as Major Depressive Disorder, Panic Disorder, Dysthymic Disorder, or a Personality Disorder (although it may be superimposed on any of these disorders).

D) Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

and PMS and PMDD are strongly inherited, predisposition to other mood disorders do not seem to predict PMS/PMDD.[6]

Steroid hormone fluctuations indeed cause cyclical change in the opoid system (beta-endorphin), the GABA system and the serotonin system centrally.[7,8] It appears that the fluctuations caused in these neurotransmitters are accentuated in women suffering symptoms of PMS/PMDD, pointing towards increased biological sensitivity to cyclical change.[9,10]

This genetically determined biological vulnerability is most likely also affected by personal and social factors influencing the severity of symptoms. Several recent studies, however, have challenged the importance of external factors like psychosocial stress.[11,12]

TREATMENT

Premenstrual symptoms are common and do not need treatment, the premenstrual syndrome (PMS), however is less common and more frequently would need intervention. The premenstrual dysphoric disorder (PMDD) is much less common and would mostly need treatment. Because these disorders are not easy to diagnose, the symptoms frequently not easy to quantify, the response to treatment is also not easy to measure. Patients would commonly perceive their symptoms as varying substantially from month to month and this makes the response to treatment even more difficult to judge.

It would be important to explain to patients who present with this syndrome complex that the problem is not caused by an abnormality in hormone secretion. It is also important to point out that this problem is not as easily treatable as pneumonia where one can use a course of antibiotics that solves the disease permanently. The treatment plan would virtually always be a long-term plan.

Different treatment options will be discussed with the evidence for prescribing these therapies.

Serotonin Reuptake Inhibitors

This group of drugs probably have the best evidence for being effective in this syndrome. The efficacy of particularly fluoxetine has been documented in quite a number of studies. The typical positive response rate is as high as 75%, with the usual prescribed dosage 20mg per day. A higher dose is not more effective and significantly increases the side effects. It is also important to note from these trials that both the affective and somatic symptoms improve on this drug and that the response is maintained over the long term.[13, 14] Fluoxetine is approved by the FDA for PMDD but not by the European drug regulators because of their concern with lack of strict diagnostic criteria in certain trials and their concern with possible inappropriate prescribing practices. There are also publications to support the use of other SRI's such as paroxetine and citalopram.

Only administering the drugs during the luteal phase is also supported by placebo controlled trials and might well be the better option to reduce side-effects and cost. The drug would typically be given from about day 14 to the first day of menstruation.[15] Physical symptoms might not respond as well on the intermittent regime as continuous use.

Antidepressants not belonging to the group of SRI's such as MAOI's and the tricyclic antidepressants are unfortunately not effective in this condition. The same is true for lithium. These drugs do not fare better than placebo in trials and should not be used.

Benzodiazepines

Alprazolam may be beneficial in women with PMS but does not seem to work well in patients that suffer from PMDD. It would not be the first drug to use and the addictive potential is real.[16,17,18]

Oral Contraceptives

Inducing anovulation should alleviate the symptoms of this disease but several studies failed to show any improvement using some of the older formulations. There are however more than one placebo controlled trial where the newer progestogen drosperinone was used. In both the contraceptive formulations that contain drosperinone (with 24 and 21 day active tablets) statistically significant beneficial effects have been shown.[19,20]

GnRH analogues

By inducing anovulation with these agents a woman is relieved from all hormonal fluctuations and PMS/PMDD will improve. It is more effective in preventing physical and irritability symptoms than depressive symptoms. Unfortunately side effects such as flushing and emotional sequelae are common. Add-back therapy to control the hypo-estrogenic symptoms will give protection against the flushing and bone

loss but still does not make this a viable option in the long term. It could however be used to predict the effect of surgical oophorectomy.[21,22,23]

Danazol
Danazol does improve the symptoms but only once high enough dosages are used to suppress ovulation. Unfortunately the androgenic side effects are too severe at these dosages for most patients.

Spironolactone
This steroid like diuretic should have the best likelihood to be effective but results of trials are at best ambiguous.

Exercise
It is difficult to investigate this option in a blinded manner but trials and observational data suggest a beneficial effect. Exercise should be recommended.

Calcium
There are studies that show a beneficial response on calcium supplementation if 600mg twice daily is used. Other studies show a dose related association between intake and severity of symptoms.[24]

Other Supplements
The response on vitamin B6 is at best not dramatic but it might well be worth trying.[25] Magnesium supplementation has even less convincing scientific evidence but small trials have described modest improvements. Vitamin E supplementation at 400IU per day was described in small studies to improve the physical and affective symptoms.

Evening Primrose oil, gingko biloba and essential free fatty acids really have no evidence to show their efficacy and progesterone has been shown not to work.

SUGGESTED APPROACH TO MANAGEMENT:
In patients where the diagnosis has been established and the woman is symptom free in the follicular phase, it would be important to quantify her symptoms. If the situation is manageable the patient should be advised to exercise in a scheduled program with significant intensity. Vitamin B6 should probably be offered as it might work and is harmless as long as doses not more than 100mg per day is used.

If distress is judged to be severe SRI's should be offered. About 30% of patients will not respond to SRI's and it might be worth while increasing the dose, changing to a 2nd SRI or switching from luteal phase therapy to continuous therapy. A few patients will have significant side effects such as nausea, headache, poor libido and anorgasmia.

Drosperinone containing contraceptives should frequently be used and in recalcitrant cases alprazolam, spironolactone and calcium supplements might offer some relief. As an absolute last resort and when GnRH has been successful in alleviating symptoms removal of the uterus and ovaries should be contemplated.

See CPD Questionnaire, page 39

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