PMS: diagnosis, aetiology, assessment and management

REVISITING… PREMENSTRUAL SYNDROME

Carol A. Henshaw

Abstract This article reviews our understanding of the epidemiology and aetiology of premenstrual syndrome and premenstrual dysphoric disorder, and its assessment and management. It also addresses the concerns of the feminist community and the views of women themselves about this condition and its management. Service provision in the UK for women with these problems is unfocused and greatly varying, and they might be better assessed and treated by psychiatrists.

Moira Connolly’s article on premenstrual syndrome can be viewed and downloaded free from the APT website (http://apt.rcpsych.org), via the article search link.

Some 6 years ago, an article appeared in APT on the epidemiology, aetiology, assessment and management of premenstrual syndrome (Connolly, 2001). That article gave a detailed discussion of the diagnosis and assessment of women with premenstrual syndrome, so I will not repeat it here. Instead, I review advances in understanding since that time and address the concerns of the feminist community and the views of women themselves about this condition and its management. I recommend to readers a themed supplement of Psychoneuroendocrinology (2003: 28, S3, pp. 1–55), which contains four comprehensive reviews of different aspects of premenstrual syndrome and a recent treatment algorithm (Halbreich, 2005).

What is premenstrual syndrome?

Premenstrual syndrome can be broadly defined as any constellation of psychological and physical symptoms that recur regularly in the luteal phase of the menstrual cycle, remit for at least 1 week in the follicular phase and cause distress and functional impairment. There is no single precise definition of the syndrome, but it is generally accepted that, in order to be clinically significant, the symptoms should be of at least moderate intensity and cause functional impairment. Severe symptoms that are predominantly dysphoric and cause severe impairment are referred to as premenstrual dysphoric disorder. Women with clinically significant premenstrual symptoms tend to have a specific symptom profile that recurs in each cycle but may vary in severity in response to environmental stressors or other health problems.

A diagnosis of discrimination?

Although these diagnoses are accepted by researchers and clinicians, the existence of these disorders continues to be debated. Some, particularly psychologists writing from a feminist perspective, still see the diagnostic label as continuing the oppression of women by the medical profession. Only 5 years ago Chrisler & Caplan (2002) described premenstrual syndrome as a ‘form of social control and victim blame’. They expressed concerns that women with premenstrual dysphoric disorder recorded in their medical record might be seen as unfit mothers in child custody cases and as unsuitable candidates for positions of authority or political office, thus leading to increased bias and discrimination against women. In the 1980s, premenstrual syndrome was accepted as a cause of diminished responsibility in two prominent UK murder trials, fuelling the popular notion that hormonal changes can turn women into dangerous criminals (Raitt & Zeedyk, 2002: pp. 109–134).

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A culture-based construct?

In December 2003, Eli Lilly removed premenstrual dysphoric disorder from the indications for fluoxetine in the UK, Austria, Greece and Portugal. The reasons given were that it is not listed as a condition in ICD–10, remains a research diagnosis in DSM–IV, is not a well-established disease entity within Europe and that women with less severe symptoms might erroneously receive a diagnosis of premenstrual dysphoric disorder and inappropriate treatment (Moynihan, 2004).

Chrisler & Caplan also described premenstrual syndrome as culture-bound and recognised predominantly by women and researchers in Western countries. Many of the participants in early studies were indeed women attending specialist or private services in the West, but more recently community studies have been undertaken that include women from wider social groupings. Wittchen et al (2002) carried out a large epidemiological study of young women aged 14–29 in Germany using structured diagnostic interviews. They found the 12-month prevalence of premenstrual dysphoric disorder to be 5.8% (consistent with the rates of 3–10% found in several other studies); a further 18.6% were found to have sub-threshold symptoms (which might fit a diagnosis of premenstrual syndrome). Lifetime rates for comorbid anxiety disorders (especially post-traumatic stress disorder), mood disorders, somatoform disorders and nicotine dependence were high, with only 26.5% having no other mental disorder. The diagnosis remained stable over 48 months and participants with premenstrual dysphoric disorder were more likely than those without to develop a new-onset depressive disorder. They also had higher utilisation of health services and higher rates of self-harm, suggesting that considerable morbidity is associated with this diagnosis.

A community study of women aged 36–44 in the USA (Cohen et al, 2002) found similar rates of premenstrual dysphoric disorder. The diagnosis was associated with a lower educational level, a history of major depression, smoking and working outside the home. Broadly similar prevalences have now been reported in widely differing countries and cultures, including Iceland (Sveinsdottir & Marteinsdottir, 1991), Mexico (Marvan, et al, 1998) and Saudi Arabia (Rasheed & Al-Sowilem, 2003), although a Japanese study reported lower rates (Takeda et al, 2006).

Effects of premenstrual syndrome

Although the symptom profiles of premenstrual syndrome and premenstrual dysphoric disorder have been recognised for years, only recently has the level of functional impairment been systematically examined. Women with premenstrual dysphoric disorder report impaired social adjustment and reduced perceived quality of life, which, unsurprisingly, are at their worst during the luteal phase. They also differ from unaffected women during the asymptomatic follicular phase, although for most factors these differences do not cause impairment. The severity of luteal phase impairment is similar to that seen in women with dysthymia and, in some domains, approaches that of major depressive disorder. This is not surprising, given that in clinical practice it is not unusual to find a woman with premenstrual dysphoric disorder who experiences suicidal ideation each luteal phase. Pearlstein et al (2000) found that women with premenstrual dysphoric disorder scored worse than women with dysthymia on the parental factor of the Social Adjustment Self Report Scale, a finding consistent with data from a large telephone survey in which symptomatic women reported highest functional impairment at home (Hylan et al, 1999). However, the impairment in occupational function is also significant. In Hylan et al’s study, 8–16% of symptomatic women had missed work in the preceding year because of premenstrual syndrome and 5–8% of those who had ever missed work had been absent for more than 14 days in the past year. Even symptomatic women who do not seek treatment for premenstrual syndrome appear to use more healthcare services in general and missed work more often than asymptomatic women.

The above epidemiological studies confirm the findings of the earlier work, which studied more select populations: women with premenstrual dysphoric disorder have higher lifetime rates of affective disorder, but the precise relationship between premenstrual syndrome/premenstrual dysphoric disorder and mood disorders remains unclear. Premenstrual syndrome differs from depression in its wider symptom profile, including physical symptoms such as bloating, mastalgia and headache. The most commonly reported psychological symptom is irritability rather than depressed mood. Although premenstrual symptoms respond well to selective serotonin reuptake inhibitors (SSRIs), the onset of the depression is more rapid than that of major depression and may well involve different mechanisms. A good review of psychiatric morbidity in premenstrual syndrome and premenstrual dysphoric disorder is given by Kim et al (2004).

Women’s views

Qualitative studies of women’s opinions regarding premenstrual syndrome have revealed that they believe most of their gender to experience
premenstrual changes, which in at least 50% of cases warrant a diagnosis of premenstrual syndrome. They feel that general practitioners are ill equipped to deal with these problems. Women tend to report a wider variety of symptoms, including many physical symptoms than they consider other women to have and say that men complain about far fewer symptoms in their partners and focus on the negative mood changes (Sveinsdóttir et al, 2002). However, in many of these studies few or none of the women had moderate or severe premenstrual symptoms or had consulted a health professional for such symptoms. It is not clear whether the experiences of more severely affected women differ, as there are few qualitative studies on this population. One study of Turkish women with premenstrual dysphoric disorder found that they had more negative attitudes towards menstruation than controls (Yücil & Polat, 2003). Many women believe that the symptoms of premenstrual syndrome have a biological cause and reject situational attributions for their distress. Thus, they blame ‘this thing that takes over me’ for any interpersonal problems, abuse, violence and other negative outcomes of their actions during the luteal phase of the menstrual cycle (Swann & Ussher, 1995).

Aetiology

Genetic vulnerability

Twin, family and adoption studies (references available from the authors) suggest that there is a genetic component to premenstrual syndrome, but they vary in how closely it is thought to be related to neuroticism and the heritable component of major depression. There is some agreement that the estimated heritability is around 30–35%. Unfortunately, most of these studies relied on retrospective reporting of symptoms, which is known to be unreliable.

It is now clear that premenstrual syndrome and premenstrual dysphoric disorder involve an abnormal response to a normal hormonal environment as symptoms appear to be dependent on ovulation (they do not appear in anovulatory cycles). The gonadal steroids or some other factor produced by the corpus luteum in the second half of the menstrual cycle are the likely triggers. As not all women are affected there must also be some underlying vulnerability.

Studies attempting to elucidate the pathophysiology of the syndrome concentrate on three main areas: the hypothalamic–pituitary–adrenal (HPA) axis, the γ-aminobutyric acid (GABA) system and the serotonergic system.

The HPA axis

Dysregulation of the HPA axis is associated with major depression and it is therefore not surprising that it has also been investigated in relation to premenstrual syndrome. Basal plasma and urinary free cortisol do not appear to distinguish women with premenstrual syndrome from controls nor do circadian patterns. The results of studies examining cortisol responses to stressors or stimulation have been conflicting and in several studies women with premenstrual syndrome have failed to show the HPA axis abnormalities characteristic of major depression.

The GABA system

Other researchers have looked at the role of progesterone, GABA and neuroactive steroids (or neurosteroids). Sundström Poromaa et al (2003) carried out a comprehensive review of GABA, progesterone and premenstrual dysphoric disorder. Allopregnanolone is a neuroactive metabolite of progesterone that has anaesthetic and anxiolytic properties. It binds with high affinity to the GABA-A receptor. Dysregulation of allopregnanolone and GABA systems may play a role in premenstrual syndrome and recent studies support this hypothesis. Levels of allopregnanolone appear to fall after antidepressant treatment, and falls in this metabolite are associated with improved depression and reduced appetite changes (Freeman et al, 2002a). Proton magnetic resonance spectroscopy has been used to examine cortical GABA levels in premenstrual dysphoric disorder. A reduction in cortical GABA levels during the follicular phase has been found in women with premenstrual dysphoric disorder compared with controls. Cortical GABA levels declined across the menstrual cycle in healthy women, whereas those with premenstrual dysphoric disorder experienced an increase from the follicular phase to the mid- and late-luteal phases. Oestradiol and progesterone were positively associated with GABA levels in women with premenstrual dysphoric disorder (Epperson et al, 2002), who also show abnormal motor cortex excitability during the luteal phase (Smith et al, 2003).

The serotonergic system

Considerable evidence supports the involvement of the serotonergic system in the pathophysiology of premenstrual syndrome, not least the fact that SSRIs are effective in treating the symptoms. Inhibition of serotonergic activity by acute tryptophan depletion has been shown to aggravate symptoms of premenstrual dysphoric disorder. Furthermore, metergoline, a serotonin-selective antagonist that
blocks serotonin (5-HT) receptors (particularly 5-HT$_1$A and 5-HT$_2$A) also provokes a return of symptoms in women with premenstrual dysphoric disorder treated with fluoxetine (Roca et al, 2002).

**Endogenous opioids**

Women with premenstrual dysphoric disorder appear to have lower pain thresholds and lower pain-tolerance times than controls. They have a heightened sensitivity to ischaemic pain at all phases of the cycle, but rate this pain as being more intense and more unpleasant in the luteal phase. Compared with controls they have lower β-endorphin levels throughout the cycle (Straneva et al, 2002). All of these findings suggest that endogenous opioids may be involved.

**Summing up**

It is likely that all these neurotransmitter systems are involved, but the nature of their complex interactions and any common pathways that may give rise to premenstrual symptoms are not yet understood. The review by Halbreich (2003) is probably the most comprehensive and up to date available.

**Assessment**

It is well recognised that 20–50% of women who experience premenstrual symptoms will not show them on prospective daily rating and some who do not present with symptoms will show changes when prospectively rated. It can be difficult to differentiate on history alone between brief recurrent depression, dysthymia and premenstrual exacerbation of a depressive disorder. Hence, prospective daily rating of at least two menstrual cycles is required to confirm the diagnosis.

Various scales are available, but for clinical use it is best to choose one that the patient can complete quickly and the doctor can easily read and assess during a clinic. The vast majority are in English (often American English) and, despite international studies, very few have been validated in other languages. Haywood et al (2002) have reviewed most of the currently available measures, commenting on their strengths and weaknesses. One of the easiest to use in clinical settings is the Calendar of Premenstrual Experiences (COPE). The woman rates 22 items (physical and behavioural) on a four-point scale (0, symptom not present; 4, symptom severe). It has high test–retest reliability, which is useful in a prospective measure. Its criterion validity was assessed in clinical and community samples and it correctly identified women in the premenstrual syndrome group from those in the control group in 104 out of 108 cycles (a 2.8% false-negative rate with no false positives). Above all, it is simple to use and score, although some American terms (e.g. ‘hot flashes’) might require explanation.

The lack of evidence for any abnormality of serum hormone levels underlines the fact that it is rarely necessary to check hormone levels in women referred for premenstrual problems (although they frequently request this and often attribute their difficulties to hormone imbalances). Take note of menstrual cycle phase when assessing mental state.

Symptoms may have been present for several years, perhaps since menarche, but women often present when they have other stressors and chronic difficulties in their lives. Harmful use of alcohol and other substances is not uncommon and some will have psychiatric comorbidity. Some present when they experience heavy or irregular menstrual bleeding or pelvic pain. A gynaecologist should see such women before psychiatric assessment, in order to exclude other pathologies.

**Management**

**SSRIs**

Once the diagnosis is confirmed as premenstrual syndrome or premenstrual dysphoric disorder, a treatment plan must be negotiated with the woman. In recent years a number of systematic reviews have helped to clarify effective and ineffective interventions for premenstrual symptoms (Box 1) and there are now expert guidelines for the use of SSRIs (Steiner et al, 2006).

The efficacy of SSRIs in the treatment of both physical and psychological symptoms of premenstrual syndrome (Dimmock et al, 2000) has been confirmed and studies have shown that these drugs also reduce functional impairment. The onset of improvement is more rapid than that in SSRI treatment of depressive disorder. Treatment can be given throughout the menstrual cycle, but several studies now support dosing during the luteal phase alone, as this appears to be equally efficacious (Freeman et al, 2004). One randomised controlled trial (RCT) has found 90 mg enteric-coated fluoxetine given twice during the luteal phase both efficacious and well tolerated (Miner et al, 2002) and similar data now exist for controlled-release paroxetine. However, neither of these formulations is currently available in the UK. Women with irregular cycles can find intermittent dosing difficult, so it is not suitable for all. It may be useful in particular for women concerned about taking medication continuously (see below). There is RCT evidence to support the use of venlafaxine.
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Box 1 Treatments for premenstrual syndrome and premenstrual dysphoric disorder: effectiveness determined from systematic literature reviews

Effective interventions
- SSRIs
- Gonadotrophin-releasing hormone analogues
- Interventions of doubtful or uncertain efficacy
- Vitamin B6
- Bright-light therapy

Interventions that improve mastalgia only
- Danazol
- Evening primrose oil

Interventions that have no effect on premenstrual symptoms
- Progesterone and progestogens

‘Natural’ remedies

Many women have concerns about taking antidepressants, often believing them to be addictive. They may fail to start taking them or stop prematurely. Sometimes this is because of side-effects (mostly sexual dysfunction), but many also cite a wish to deal with problems ‘naturally’ and are increasingly using complementary or alternative therapies to manage premenstrual syndrome. The evidence to support their efficacy is, as yet, very limited. Stevinson & Ernst (2001) undertook a systematic review of complementary and alternative therapies. The poor methodology of some of the studies they identified posed problems and many could not be included in the review. They had to conclude that such therapies are of doubtful efficacy. Similar difficulties beset a meta-analysis of bright-light therapy (Krasnik et al, 2005). Extract of the berries of the shrub Vitex agnus-castus (agnus castus) has been shown to be as efficacious as fluoxetine in treating overall symptoms of premenstrual dysphoric disorder, with fluoxetine being superior for psychological symptoms and agnus castus for physical symptoms (Atmaca et al, 2003). There is also RCT evidence supporting calcium supplementation. Other interventions, such as exercise, other herbal medicines and mind–body approaches, are supported by some evidence. For a comprehensive review of complementary and alternative therapies for premenstrual syndrome see Girman et al (2003). As mentioned above, a proprietary herbal remedy containing pollen extract, pollen and pistil) can shorten cycle length (Winther & Hedman, 2002).

Evening primrose oil (Budeiri et al, 1996) is efficacious for premenstrual mastalgia but not for premenstrual syndrome in general. Luteal phase danazol is also efficacious for premenstrual mastalgia but not for other premenstrual symptoms.

Suppression of ovulation

Systematic reviews have shown progesterone and progestogens to be efficacious (Wyatt et al, 2001) in treating premenstrual symptoms. Oral contraceptives can improve, aggravate or have no effect on them and it is difficult to predict the response. Oral contraceptives do, however, suppress ovulation. Monophasic pills are probably more efficacious than biphasic or triphasic formulations, which may create an artificial cycle and provoke symptoms similar to those of premenstrual syndrome. They can be worth trying in a woman who has not had problems with them previously, particularly if she has irregular cycles that she wishes to regulate (after pathology has been excluded) and needs contraception. Several studies have shown a new oral contraceptive that

Comorbidity

Women with mood disorders (unipolar or bipolar) or anxiety disorders may experience significant mood changes in the premenstrual period. Titrating the dose of existing medication up at that time and reducing to a baseline level once menses have occurred is a possible strategy. This might also be a useful approach for women with premenstrual syndrome or premenstrual dysphoric disorder and comorbid mood or anxiety disorders, who need to stay on medication but find the addition of premenstrual symptoms problematic.

(Freeman et al, 2001) and one study suggesting that citalopram might work in cases resistant to other SSRIs (Freeman et al, 2002b). Buspirone is of doubtful efficacy in premenstrual irritability and nefazodone appears to be inefficacious (Landen et al, 2001). Fluoxetine has been found to alter the duration of the menstrual cycle, either shortening or lengthening cycles (Steiner et al, 1997) (a proprietary herbal remedy has also been found to shorten cycle length: see below). The significance of this and the mechanisms involved are not known.

Symptoms will return in the first cycle after SSRI therapy is discontinued, but there are no long-term safety profile data available for premenstrual syndrome beyond 12 months. Advice to women must therefore be based on the safety profile of SSRIs in the long-term management of unipolar depression.
contains drospirenone and ethinylestradiol to be efficacious in treating premenstrual symptoms, including premenstrual dysphoric disorder.

The suppression of ovulation, for example by using gonadotrophin-releasing hormone analogues (GnRHa), is an efficacious means of abolishing premenstrual syndrome (Wyatt et al., 2004), but has been limited to more severely affected women because of the problems caused by ‘add-back’ hormone replacement therapy (HRT). This is used to control menopausal symptoms resulting from down-regulation and to prevent reduction in bone density but some women find that HRT recreates cyclical premenstrual syndrome-like symptoms. The use of GnRHa with tibolone (a synthetic compound structurally related to noretinodel, which has weak oestrogenic, progestogenic and androgenic properties) may now be a way around this problem.

**Psychological interventions**

Earlier studies (e.g. Christensen & Oei, 1995; Blake et al., 1998) have shown cognitive therapy to be an efficacious intervention for premenstrual syndrome and superior to information-focused therapy and group awareness. Coping-skills training is superior to relaxation training. More recently, an RCT has compared cognitive–behavioural therapy (CBT) with fluoxetine and a combination of the two (Hunter et al., 2002). Both CBT and fluoxetine were efficacious on their own, and combining them conferred no additional benefit. As might be expected, fluoxetine had a more rapid onset of action, but at the 1-year follow-up CBT was found to be superior. Other strategies, such as support groups, have a very limited evidence base. There is a wide range of self-help books of variable quality that women may find helpful and organisations such as the National Association for Premenstrual Syndrome (Box 2) provide information and support.

**Ignoring the evidence base**

Studies in both the USA and UK have shown a disparity between the evidence base and what is being prescribed by clinicians. Anecdotal reports from patients indicate that they are often prescribed drugs that do not appear to be effective. A doctor writing in a well-respected women’s magazine recently responded to a reader who wrote enquiring about treatments for her premenstrual syndrome by saying that there was very little that would help and recommending drugs now known to be ineffective. Progestogens and progesterone were still the most commonly prescribed drugs in primary care in the 1990s, although the number of prescriptions for SSRIs was increasing (Wyatt et al., 2002).

**The psychiatrist’s role**

Service provision in the UK is patchy and carried out by a variety of different professionals, including gynaecologists, psychiatrists, nurses and psychologists. This reflects the range of symptoms and interventions. Assuming they screen out women with menstrual problems (who should see a gynaecologist first), psychiatrists are well placed to assess and treat women with premenstrual syndrome. They generally have more time than a gynaecologist has to assess a new patient, routinely examine psycho-social stressors and are able to distinguish between premenstrual syndrome and other mood disorders. The use of rating scales is not foreign to them; they are familiar with antidepressants and psychological therapies and can knowledgeably discuss methods of ovulation suppression in order to negotiate a treatment plan with which a woman is happy.

**Declaration of interest**

None.

**References**

*Recommended further reading.*


MCQs

1 The following are known to be effective interventions for premenstrual syndrome or premenstrual dysphoric disorder:
   a sertraline
   b progesterone
   c cognitive analytic therapy
   d nefazodone
   e evening primrose oil.

2 The pathophysiology of premenstrual syndrome is unlikely to involve:
   a the HPA axis
   b endorphins
   c the serotonergic system
   d the noradrenergic system
   e GABA.

3 The assessment of a woman presenting with premenstrual symptoms should include:
   a family psychiatric history
   b day-21 progesterone level
   c prospective rating of symptoms over one menstrual cycle
   d levels of luteinising hormone and follicle-stimulating hormone
   e a screen for substance misuse.

4 Premenstrual dysphoric disorder:
   a affects more than 10% of women of reproductive age
   b is not associated with smoking
   c is associated with an increased risk of a new-onset anxiety disorder
   d is associated with a past history of depression
   e is associated with a lifetime comorbidity of other psychiatric disorder in less than 5% of cases.

5 The functional impairment in premenstrual dysphoric disorder:
   a is less severe than that found in dysthymia
   b is limited to interpersonal relationships
   c is not improved by treatment with SSRIs
   d leads 20–30% of sufferers to miss work
   e is greater at home than in work settings.

**MCQ answers**

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