

# Managing premenstrual syndrome

Nick Panay

Many women will experience minor physical and emotional changes premenstrually. However, in a few women (approximately 5%), these symptoms are severe enough to interfere with normal activities, and can even lead to a breakdown in interpersonal relationships. Fortunately, various treatments are available (Figure 1).

Premenstrual syndrome (PMS) has been defined as distressing physical, behavioural and psychological symptoms not due to organic disease, which regularly recur during the same phase of each menstrual (ovarian cycle) and which disappear or significantly regress during the remainder of the cycle. Typical psychological symptoms include depression, anxiety, irritability and loss of confidence; physical symptoms include bloating and mastalgia. Figure 2 summarizes the different types of PMS.

## Diagnosing PMS

Correct diagnosis is crucial to the management of PMS. This cannot be accurately established by retrospective recall. It needs to be made by the prospective logging of symptoms by the patient, ideally over two cycles. A symptom questionnaire (which can be downloaded from the NAPS website, see page 39) is the best way of documenting the symptoms. The initial completed questionnaires should be kept to give an objective indication of response to therapy.

**Differential diagnosis:** the questionnaires may reveal a complete absence of cyclicality to the symptoms. If this is the case, other diagnoses should be considered (Figure 3).

- Psychological illness (e.g. depressive illness, chronic fatigue syndrome, anxiety neuroses and manic depressive disorders) may be mistakenly ascribed to PMS by the sufferer or by clinicians. If these conditions are at all suspected then a psychiatric opinion should be sought.

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Agnus castus (Courtesy of SW Missouri State University Herbarium)

- Although it is not necessary to perform routine psychiatric testing (except in studies), the clinician should be sensitive to the fact that the diagnosis can often be difficult to make and may have multiple aetiologies (e.g. secondary PMS).
- Organic illness should be considered. For example, thyroid disease may present with the psychological and physical symptoms of PMS (e.g. low mood, tiredness).

## Lifestyle changes

Patients who seek medical help for symptoms of PMS have usually instituted lifestyle changes and have tried most over-the-counter remedies. However, before any medical treatments are commenced, it is still important to confirm that lifestyle has been optimized.

**Stress:** there is little doubt that severe PMS can be aggravated by social and environmental factors, which can tip people 'over the edge', and that reduction of stress is a great help in ameliorating the symptoms. Stress at work or in relationship difficulties appears to lower the tolerance threshold above which severe symptoms occur. Although in an ideal world steps should be taken to minimize stressors (e.g. by exercise, relaxation), in the real world, sufferers still have to function normally in difficult situations, which often cannot be controlled. Medical therapy can therefore be viewed as an artificial way of raising the threshold in order to minimize the breakthrough of severe symptoms.

**Dietary measures** such as avoidance of carbohydrate binges and limitation of alcohol and caffeine intake are often of benefit. A recent study has suggested that a high intake of calcium and vitamin D (four servings/day of milk or yoghurt) may reduce the risk of PMS,<sup>1</sup> but it is unclear whether these nutrients affect symptom severity in women with established PMS.

## Herbal and other 'complementary' therapies

Some alternatives to traditional therapy are showing promising results in randomized controlled trials.

**Agnus castus:** one randomized placebo controlled study has shown that agnus castus is an effective treatment for women with PMS.<sup>2</sup> The effects were confirmed by the women's self-assessment

**Treatment hierarchy for PMS**

(Cognitive behaviour therapy is also a useful treatment – see text.)

Self-help	Lifestyle change Herbal/complementary therapies	
<b>Primary care</b>	First-line	Combined continuous new generation pill (e.g. Yasmin, Cilest)
	Second-line	Oestradiol patches (100mcg) + oral progestogen (e.g. duphaston 10mg D17-D28 or Mirena) SSRIs (e.g. half cycle citalopram 10-20mg D15-D28)
<b>Specialist treatments</b>	Third-line	GnRH analogues (e.g. goserelin 3.6mg or leuprorelin 3.75mg) + tibolone 2.5mg/day or continuous combined low-dose HRT
	Fourth-line	Hysterectomy with oophorectomy – with adequate HRT (including testosterone replacement)

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and by the investigators' evaluation. Tolerability of agnus castus was good. Patient acceptance was high and side effects were few and mild.

**Red clover** isoflavones can lengthen the follicular phase of the ovarian cycle. This, coupled with benefits for menopausal symptoms, has led to further research on the use of this product in the treatment of PMS in both pre- and perimenopausal women. Data are expected in the next year from the author's unit.

**Vitamin B<sub>6</sub>**: a systematic review of the efficacy of vitamin B<sub>6</sub> for treatment of PMS concluded that there are no high-quality randomized trials.<sup>3</sup> Therefore, there is no rationale for giving daily doses of vitamin B<sub>6</sub> in excess of 100 mg, especially following the recommendation from the Department of Health and the Medicine Control Agency in 1999 to restrict the dose of vitamin B<sub>6</sub> available generally to 10 mg, and to limit the dose sold by pharmacists to less than 50 mg.

**St John's Wort**: extensive trial data exist for St John's Wort as an antidepressant. In a small pilot study of women with severe PMS, treatment resulted in a significant improvement of symptoms.<sup>4</sup> Tolerance and compliance with the treatment were good. However, the absence of a placebo group in this trial limited the evaluation of efficacy.

**Light mask**: one study showed significant improvements for women with severe PMS during treatment with bright white light from a face mask. The mechanism of action of light therapy in severe PMS is unknown and further data are required. Some investigations have linked severe PMS to disturbance in circadian rhythms and hence light therapy may act by correcting abnormal circadian rhythms.

**Natural progesterone**: a recent meta analysis showed no significant benefit for the treatment of severe premenstrual syndrome with progestogens and progesterone.<sup>5</sup> This is not surprising. Synthetic progestogens actually have PMS-like side effects! Natural progesterone could actually have some benefits as it can have an anxiolytic effect and acts as a mild diuretic. However, of the few

underpowered studies conducted, only one has shown benefit and better data are needed.

**Ovulation suppression**

Although the underlying cause of severe PMS remains unknown, cyclical ovarian activity appears to be an important factor. A logical treatment for severe PMS, therefore, is to suppress ovulation and the ensuing cyclical endocrine/biochemical changes that cause the distressing symptoms. Several drugs are capable of performing this function, but they are not without their own side effects, which may influence the efficacy of the treatment or the duration for which they may be given.

**The combined oral and contraceptive pill**: although able to suppress ovulation, and used commonly to improve PMS symptoms, the combined pill was initially not shown to be of benefit in randomized prospective trials. This is probably because it was used with a pill-free week and because the daily progestogen in the second-generation pills caused PMS-type symptoms of its own accord. A new type of combined contraceptive pill (*Yasmin*) contains an anti-mineralcorticoid and anti-androgenic progestogen, drospirenone. This is showing considerable promise in the treatment of PMS as it is devoid of progestogenic side effects and has a mild diuretic and anti-androgenic effect. There are now both observational and small randomized trial data supporting its efficacy.<sup>6</sup> If the pill is used to treat severe PMS, pill packets should be used back to back (bicycling/tricycling or continuously) and a break introduced only if erratic bleeding occurs.

**Progestogens**: as mentioned above, the data from randomized studies and meta analyses do not support the use of either progesterone or synthetic progestogens in the treatment of severe PMS.<sup>5</sup> Depo medroxyprogesterone acetate (*Depo Provera*), etonorgestrel rod (*Implanon*) and anovulation suppression 'progestogen-only pill' (*Cerazette*) all have ovulation suppressant activity and as such would be expected to have greater treatment efficacy. However, cyclical symptoms are often replaced with continuous low-grade symptoms due to the PMS-like side effects of synthetic progestogens. Data regarding efficacy are therefore either absent

or at best contradictory.

**Transdermal estradiol (oestradiol):** continuous 17β-estradiol combined with cyclical progestogen is an ovulation suppressant treatment of proven efficacy in placebo-controlled trials. It was first administered as a 100 mg implant and proved to be highly effective compared with a placebo. The drawback is that the implants last for a long period of time, which has twofold implications if treatment is to be discontinued.

- Fertility is suppressed and may take 24 months to be restored as the implant wears off, so implants may not be appropriate for younger age groups.
- Progestogens must continue to be taken for at least 18 months until the stimulatory oestrogenic effects on the endometrium have ceased.

In one of the first patch studies, 200 µg estradiol was tested against a placebo in a crossover trial and found to be highly effective. Both the physical and psychological symptoms of PMS were reduced by an average of 60%. The standard dose is now 100 µg, which produces physiological mid-follicular estradiol levels.<sup>7</sup>

**Progestogen intolerance** – estradiol treatment for PMS requires the use of oral progestogens (e.g. norethisterone or dydrogesterone), to prevent endometrial hyperplasia. However, the side effects from progestogens often lead to a reduction in efficacy and treatment discontinuation. Progestogen intolerance can be reduced by using less androgenic progestogens and/or a shorter duration of progestogen. However, an improvement in treatment efficacy using less oral progestogen must be balanced with the risks of endometrial hyperplasia. The hormone released by the levonogestrel intrauterine system *Mirena* acts locally to produce endometrial atrophy, with minimal systemic progestogenic side effects.<sup>8</sup>

**Danazol:** cycle suppression may be achieved using danazol, an androgenic steroid. A study has demonstrated benefit for several symptoms,<sup>9</sup> but due to masculinizing side effects, especially at higher, cycle-suppressing doses, it is not commonly used.

**Gonadotrophin-releasing hormone (GnRH) analogues** have been successfully employed to suppress gonadal steroid production in conditions such as breast cancer and endometriosis. GnRH analogue usage results in cycle suppression and elimination of premenstrual symptoms. However, because symptoms return with ovarian function, therapy would have to be continued indefinitely; this is precluded by significant trabecular bone loss, which can

occur with only 6 months of therapy. The use of GnRH analogues with add-back HRT or tibolone, however, is a useful option,<sup>10</sup> both to prevent vasomotor symptoms and bone loss; bone mineral density should be monitored in women using analogues for more than 6 months.

**Total abdominal hysterectomy and bilateral salpingo-oophorectomy** is the ultimate form of ovulation suppression and the only true cure for PMS, as this removes the ovarian cycle completely. The procedure is only rarely performed for this indication, as a lesser alternative can usually be found. Preoperative GnRH analogues are a useful test of whether hysterectomy/oophorectomy will be successful in treating symptoms. It is essential that adequate hormone therapy is given (including consideration of testosterone replacement) to prevent simply replacing one set of symptoms with another. Women who have had a hysterectomy with ovarian conservation will often continue to have cyclical symptoms in the absence of menstruation.

### Selective serotonin re-uptake inhibitors (SSRIs)

Studies have shown that the serotonin uptake and content of platelets is significantly lower in the premenstrual phase in patients diagnosed with PMS, compared with controls. There is now considerable evidence for the beneficial effects of serotonin re-uptake inhibitors in treating PMS.

- Initial studies with fluoxetine showed it to be efficacious compared to placebo for treating premenstrual dysphoric disorder (PMDD) – the American Psychiatric Association’s definition of severe PMS. One of these studies led to the licensing of *Prozac* 20 mg/day for the treatment of PMDD. Although the product licence has recently been withdrawn, there are sufficient data to justify entirely the use of fluoxetine for PMS.
- There now exists a wealth of data from other randomized controlled trials for the treatment of severe PMS with most types of SSRIs.

**Half-cycle treatment** – interestingly, randomized studies have shown that half-cycle SSRI treatment is as efficacious as continuous administration.<sup>11</sup> The importance of this is that patients are less likely to develop dependence on this regimen, benefit is immediate and patients are more likely to accept the treatment as it can be regarded as being different to the regimens used for psychiatric disorders. One of the optimum regimens for treatment resistant PMS is half-cycle citalopram, 20 mg per day from day 15 to day 28 of the cycle. This regimen appears to be effective even in women

### The various forms of premenstrual syndrome (PMS)

<b>Primary PMS</b>	PMS symptoms leading up to menstruation but completely relieved when bleeding starts
<b>Secondary PMS</b>	Background psychopathology with incomplete relief of symptoms when bleeding starts
<b>Mild PMS</b>	Does not interfere with personal/social and professional life
<b>Moderate PMS</b>	Interferes with personal/social and professional life but still able to function and interact although may be suboptimally
<b>Severe PMS (treatment resistant)</b>	Unable to interact personally/socially/professionally – withdraws from social and professional activities
<b>PMDD</b>	Premenstrual dysphoric disorder. American Psychiatric Association's definition of severe PMS

whose previous SSRI treatment has failed.<sup>12</sup>

### Cognitive behavioural therapy (CBT)

A recent study examined the relative effectiveness of cognitive behavioural therapy (ten sessions), fluoxetine (20mg daily) and combined therapy (CBT plus fluoxetine), in women with premenstrual dysphoric disorder.<sup>13</sup> This was a randomized treatment trial lasting 6 months; follow-up was undertaken 1 year post-treatment. Significant improvement occurred in all 3 treatment groups after 6 months' treatment. Fluoxetine was associated with a more rapid improvement, however, at follow-up, CBT was associated with better maintenance of treatment effects compared with fluoxetine. There appeared to be no additional benefit of combining the treatments and no difference in efficacy between the treatment groups. The difficulty with this treatment modality is accessing the few places where it is carried out. ♦

### Treatment dilemmas

#### How long should treatment be continued?

None of the treatments (except bilateral oophorectomy) are 'cures'. Patients should therefore be counselled that the symptoms may well return when treatment is discontinued, and treatment should be seen as relatively long-term (minimum of 12 months) rather than as a 'quick fix'. Studies suggest that the benefits of treatment with oestrogen patches continue to increase up to 14 months from the start of therapy.<sup>14</sup> Multiple treatments may be required, with breaks taken to assess symptom severity or to achieve pregnancy (which is an excellent treatment in itself). Even if patients are made aware that symptoms may return after discontinuation of therapy, they are often prepared to accept this in the knowledge that they could have 6 to 12 symptom-free months during which they can put their affairs straight and repair their relationships.

#### When stopping, should treatment be 'tailed off'?

Discontinuation of therapy with oestrogen patches and SSRIs should be tailed off gradually, by halving and then quartering the dosage over 3 to 6 months, rather than allowing the patient to go cold turkey.

#### How should a non-responder be managed?

The diagnosis of PMS should be reconsidered where the patient has failed to respond to multiple treatments. Suspicion regarding the correct diagnosis is raised particularly with failure to respond to GnRH analogues, which completely suppress the cycle, or if persistence of 'cyclical' symptoms is reported after bilateral oophorectomy with unopposed continuous oestrogen therapy. As mentioned previously, the presence of symptoms in the absence of an ovarian cycle is highly suggestive of background psychopathology or organic disease. A psychiatric and/or medical opinion should be sought, and appropriate investigations instituted (e.g. thyroid function tests, prolactin), if they have not already been performed.

### REFERRAL

For referral of research patients, tel: 0208 383 4172

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