

# DIAGNOSTIC FORUM

## PREMENSTRUAL SYNDROME

# Diagnosing and managing premenstrual syndrome

Correct diagnosis can only be made by prospective logging of symptoms by the patient. By Mr Nicholas Panay

Premenstrual syndrome (PMS) has been defined as distressing physical, behavioural and psychological symptoms not due to organic disease that 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. Many women will experience minor physical and emotional changes premenstrually. However, when severe (in approximately 5 per cent of women), these symptoms can lead to a breakdown in interpersonal relationships and interference with normal activities.

### DIAGNOSIS AND COMMENCING TREATMENT

Crucial to the management of PMS is the need to make the correct diagnosis. 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 National Association for Premenstrual Syndrome website) is the best way of documenting the symptoms. Questionnaires should be kept up when treatment has started to give an objective indication of response to therapy.

Before any medical treatment is begun, it is important that lifestyle is optimised. Reduction of stress is a great help in ameliorating the symptoms. Also, dietary measures, such as avoiding carbohydrate binges and limiting alcohol and caffeine intake, are often of benefit.

However, in cases of moderate to severe PMS it is important that medical therapy is instituted sooner rather than later. Few treatments for PMS are licensed, though sufficient evidence exists for some for it to be reasonable for a GP to prescribe them for the treatment of PMS from a medicolegal standpoint.

### THE EVIDENCE FOR ALTERNATIVE TREATMENTS

Progesterone and progestogens are not recommended for treating PMS, as there is insufficient evidence for their efficacy. A recent meta-analysis showed no significant benefit for the treatment of severe PMS with progestogens and progesterone.<sup>1</sup>

This is not surprising, since synthetic progestogens have PMS-like side effects. Natural progesterone could have some benefits because it can produce an anxiolytic effect and act as a mild diuretic. However, of the few underpowered studies conducted, only one has shown benefit and better data are needed.<sup>2</sup>

*Agnes castus* is a herbal preparation available over the counter. One randomised, placebo-controlled study has shown that it is an effective treatment for PMS. The effects were confirmed by the women's self-assessment and by the investigators' evaluation. Tolerability was good, patient acceptance was high and side effects were few and mild.<sup>3</sup>

Red clover preparations are also available OTC. Study data show that the follicular phase of the ovarian cycle is lengthened by red clover isoflavones.<sup>4</sup> 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.



PMS is poorly understood and in many cases inadequately managed

A recent meta-analysis of trials investigating the use of vitamin B6 in the treatment of PMS concluded there was insufficient data to recommend its use.<sup>5</sup> Therefore, there is no rationale for giving daily doses of vitamin B6 over 100mg, especially following the recommendation from the Medicines Control Agency in 1999 to restrict the dose of vitamin B6 available generally to 10mg and to limit the dose sold by a pharmacist to less than 50mg.

One study has demonstrated significant improvements for women with severe PMS during treatment with bright white light from a face mask (available OTC).<sup>6</sup> The mechanism of action of light therapy in severe PMS is unknown, and further data are required. Some investigations have linked severe PMS to a disturbance in circadian rhythm;<sup>7</sup> hence, light therapy may act by correcting an abnormal rhythm.

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>8</sup> Tolerance and compliance with the treatment was good. However, the absence of a placebo group in this trial limited the evaluation of the extent of the preparation's effectiveness.

### MEDICAL TREATMENTS

The two main evidence-based medical treatments for moderate to severe PMS are ovulation suppression and SSRIs.

Although the underlying cause of severe PMS remains unknown, cyclical ovarian activity appears to be an important factor. A logical treatment for severe PMS, is to suppress ovulation and thus suppress the cyclical endocrine/ biochemical changes that cause the distressing symptoms.

Although able to suppress ovulation, and used commonly to improve PMS symptoms, the combined oral contraceptive (COC) pill was initially not shown to be of benefit in randomised prospective trials.

A new type of combined pill contains an anti-mineralocorticoid and the anti-androgenic progestogen drospirenone. This is showing considerable promise in the treatment of severe PMS, as it is devoid of progestogenic side effects and has a mild diuretic and anti-androgenic effect. Both

observational and small randomised trial data exist supporting its efficacy.<sup>9</sup>

If the pill is used to treat severe PMS, pill packets should be used back to back (bi-cycling or tri-cycling or continuous use), with a break introduced only if erratic bleeding occurs.

An ovulation-suppressant treatment of proven efficacy in placebo-controlled trials that appears suitable for long-term usage is continuous 17 $\beta$ -oestradiol combined with cyclical progestogen. In one of the first studies, 200 $\mu$ g oestradiol patches were tested against placebo in a cross-over trial and found to be highly effective.<sup>9</sup> Both the physical and psychological symptoms of PMS were reduced by an average 60 per cent. The standard dose is now 100 $\mu$ g, which produces physiological mid-follicular oestradiol levels.

Both the COC pill and transdermal oestradiol are backed by sufficient evidence to allow a GPSI in women's health to prescribe them for PMS from a medicolegal viewpoint.

Oestradiol treatment for PMS requires the use of oral progestogens (norethisterone or dydrogesterone) to prevent endometrial hyperplasia. However, the side effects from progestogens often lead to a reduction in efficacy and treatment discontinuation. The hormone released by the levonorgestrel intrauterine system Mirena acts locally to produce endometrial atrophy, with minimal systemic progestogenic side effects.

### TREATMENTS FOR SPECIALIST HOSPITAL USE

Gonadotrophin releasing hormone (GnRH) analogues and hysterectomy are two management options recommended for hospital specialist use only.

GnRH analogues result in cycle suppression and elimination of pre-menstrual 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 after only six months of therapy.

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

Total abdominal hysterectomy and bilateral salpingo-oophorectomy is the ultimate form of ovulation suppression and the only true cure for PMS, as it stops 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.

### SSRI ANTIDEPRESSANTS

There is now considerable evidence for the beneficial effects of SSRIs in treating PMS, sufficient for a GPSI in women's health to prescribe them for this indication from a medicolegal point of view.

Initial studies with fluoxetine showed it to be efficacious compared with placebo for treating premenstrual dysphoric disorder (PMDD) – the American Psychiatric Association's definition of severe PMS. A wealth of data now exists for the treatment of severe PMS with most SSRIs.<sup>10, 11</sup>

Studies have shown that half-cycle SSRI treatment is as efficacious as continuous administration, thus patients are less likely to develop dependence on this regimen, benefit is immediate and are more likely to accept the treatment, as it can be regarded as being different from that used for psychiatric disorders.

One of the optimum regimens for treatment-resistant PMS is half-cycle citalopram, 20mg per day from day 15 to day 28 of the cycle. This regimen appears to be effective even in women whose previous SSRI treatment has failed.

**TABLE 1: STEP-WISE MANAGEMENT FOR PMS**

First line*	<b>Continuous new generation COC pill (eg, Yasmin, Cilest).</b>
Second line*	Transdermal oestradiol (100 $\times$ g) plus oral progestogen (eg, duphaston 10mg on days 17 to 28, or Mirena), <b>or</b> SSRI (eg, half-cycle citalopram 10-20mg on days 15 to 28).
Third line	<b>GnRH analogues (eg, goserelin 3.6mg or leuprorelin 3.75mg) and tibolone 2.5mg/day or continuous combined low-dose HRT.</b>
Fourth line	Total abdominal hysterectomy and bilateral salpingo-oophorectomy plus HRT (including testosterone).

\*Indicates suitability for use in primary care

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