

Tackling premenstrual syndrome

This Bulletin discusses the management of premenstrual syndrome (PMS), and the evidence for various treatments that have been proposed for this condition.

In the late eighteenth century, PMS was considered to be a state occurring in affluent city women, who had idle lifestyles, read lascivious novels and ate copious amounts of food.¹ Even during the last century, PMS was described as 'a desire to find relief by foolish actions difficult to restrain'.² Has our understanding of PMS moved on from this?

What is PMS?

PMS consists of emotional, behavioural and physical symptoms that regularly recur, specifically during the luteal phase (i.e. the second half) of the menstrual cycle, and resolve by the end of menstruation.^{3,4} The commonest symptoms include:⁴

- **Emotional and behavioural symptoms**, such as depression, irritability, lability, anxiety, loss of self-control, poor concentration, change in libido, aggression or violence, food cravings, and fatigue.
- **Physical symptoms**, such as headache, mastalgia (breast pain/tenderness), breast swelling, backache, weight gain, abdominal bloating, acne, swollen fingers and ankles, and gastrointestinal disturbance.

Some women with severe PMS, who have predominantly emotional and behavioural symptoms, which interfere with

SUMMARY

- ❑ Premenstrual syndrome (PMS) refers to the emotional, behavioural and physical symptoms that regularly recur during the luteal phase (i.e. second half) of the menstrual cycle. Women with severe PMS, who have predominantly emotional and behavioural symptoms, may have premenstrual dysphoric disorder (PMDD), which has specific diagnostic criteria.
- ❑ Diagnosis of PMS and PMDD should be based on clinical history and prospective charting of symptoms by the patient over two or three menstrual cycles.
- ❑ Many drug and non-drug treatments have been advocated for PMS, but few are supported by good quality, large, randomised controlled trials (RCTs).
- ❑ Since PMS is a chronic problem, with symptoms lasting possibly until the menopause, the side effects and cost of treatment are important, as well as efficacy.
- ❑ Consensus and expert opinion suggest that support, along with lifestyle and dietary treatments, should be tried initially in mild to moderate PMS. Treatment should be stepped up according to severity and/or response.
- ❑ Drug therapy, as an adjunct to support, lifestyle and dietary treatment should be considered for women with symptoms that are severe (i.e. PMDD or other severe PMS symptoms) or resistant to conservative treatment. Drug choice is based on symptoms.
- ❑ Selective serotonin-reuptake inhibitors should be considered for women with PMDD, as RCTs have shown that they can reduce symptoms.
- ❑ Bromocriptine, danazol, oestrogen patches, and gonadotrophin releasing hormone analogues are usually only used by specialists for severe or resistant PMS/PMDD, because of side effects.

Date of preparation: February 2003

their day-to-day functioning or relationships, may have **premenstrual dysphoric disorder (PMDD)**.⁵

Up to 95% of women of reproductive age suffer from PMS symptoms,³ but in the UK only a fifth of those reporting symptoms seek medical help.⁶ Severe PMS or PMDD is rare — it is thought that only about 5% of symptomatic women have symptoms that seriously interfere with their relationships or lifestyle.^{3,7} However, a survey of 300 UK women, who reported PMS symptoms, found that 13% of those who worked took time off in the previous year because of PMS.⁶

The precise cause of PMS is unknown. However, it is accepted that symptoms only occur during an ovulatory cycle.⁸ In the past, it was thought that PMS was caused by progesterone deficiency, but this theory is unproven.⁹ Women should be reassured that their symptoms are unlikely to be due to a hormone imbalance.⁵ The most probable cause is an interaction between ovarian steroids and central nervous system neurotransmitters, particularly serotonin. Women who have PMS may be especially susceptible to fluctuating levels of ovarian steroids.⁸

How is PMS diagnosed?

Although there are a variety of ways of diagnosing PMS, it is accepted that the patient should have symptoms consistent with PMS, with a symptom-free period that coincides with the onset of menses, or soon after.^{5,8} This should be assessed by asking the patient to complete a prospective symptom diary for two or three menstrual cycles.⁸ Various charts are available — a useful chart can be downloaded from the National Association for Premenstrual Syndrome website (www.pms.org.uk — for patient helpline tel: 0870 777 2177).

To meet the criteria for PMDD, women should have had at least five of the following symptoms during most months of the past year: depressed mood or dysphoria; anxiety or tension; affective

lability; irritability; decreased interest in usual activities; concentration difficulties; marked lack of energy; marked change in appetite; hypersomnia or insomnia; feeling overwhelmed; or other physical symptoms. One symptom should include irritability, tension, dysphoria or lability of mood. The symptoms must interfere with social and occupational functioning and should be present during the week before menstruation and remit a few days after the onset of menses.¹⁰

The patient's psychiatric and medical history should be considered and other disorders (e.g. hypothyroidism, anaemia and depression) excluded.^{8,10} Usually, the cyclic nature of symptoms will point to PMS or PMDD. However, some women can have an additional underlying psychiatric or medical disorder, and some conditions (e.g. asthma, epilepsy, migraine and depression⁸) are worsened in the luteal phase.¹⁰

How is PMS treated?

Many drug and non-drug treatments have been advocated for PMS, but few are supported by good quality, large, randomised controlled trials (RCTs).³ In addition, studies often include women who do not have a clear diagnosis of PMS, or who may not represent most patients presenting in primary care.⁸

Since PMS is a chronic problem, with symptoms lasting possibly until the menopause, the side effects and cost of treatment, as well as efficacy, are particularly important.¹¹ Consensus and expert opinion suggests that support, along with lifestyle and dietary treatments, should be tried initially in mild to moderate PMS. Treatment should be stepped up according to severity and/or response.⁸ Despite a lack of evidence, this seems a reasonable approach. Survey data suggest that about a quarter of women reporting PMS symptoms in the UK take non-prescription drugs and almost half of these women report satisfaction with such treatments.⁶

Drug therapy, as an adjunct to support, lifestyle and dietary

treatments, should be considered for women with symptoms that are severe (e.g. PMDD) or resistant to conservative treatment.⁸ However, drug interactions with some non-drug and dietary treatments (e.g. herbal remedies) are not well documented.

Non-drug treatment and dietary supplements

Most PMS studies show a high placebo response, suggesting that non-drug factors are an important part of treatment.⁸ For some patients, support and reassurance may be all that is required.⁴ It can be helpful to encourage women to identify and avoid triggers (e.g. stress) that exacerbate their symptoms.¹⁰ Despite a lack of robust evidence for most non-drug treatments and dietary supplements, some women find them helpful. The **panel** on page 11 discusses the main studies available.

Drug treatment

The Royal College of Obstetricians and Gynaecologists recommends that treatment decisions in menstrual disorders are based on symptoms,⁷ which can vary in nature and severity.^{4,11} Before starting any drug for PMS, it is worth establishing that some aspect of the woman's life has been impaired⁸ and finding out what non-prescription measures have been tried. The patient's opinion⁷ and the likelihood of pregnancy should also be considered. Drugs that suppress ovulation are unsuitable for women who are trying to conceive and many drugs are unsafe in pregnancy.

Not all drugs commonly used for PMS are licensed for this indication. Licensed drugs include progesterone and various progestogens for PMS, fluoxetine for PMDD, bromocriptine for cyclical menstrual disorders, particularly breast symptoms, and danazol for severe cyclical mastalgia.

Women who suffer from bloating and breast tenderness may try over-the-counter **diuretics**. A very small RCT (n=22) found that a US product containing

Some non-drug treatments and dietary supplements commonly used for PMS

Exercise

Fully-published RCTs showing benefit of exercise in PMS are lacking,^{3,8} but it is reasonable to recommend that all women with PMS exercise regularly because of the other health benefits.⁸

Alternative therapies

Systematic reviews have found insufficient evidence that relaxation therapy, massage, reflexology or chiropractic treatment are effective in PMS.^{3,12} RCTs have found that cognitive behavioural therapy reduces symptoms, but the size of its effect is unclear.³

Calcium

A multicentre, double-blind RCT¹³ (n=466) found that taking 1,200mg of calcium per day for three cycles significantly reduced womens' mean premenstrual symptom score compared with placebo. However, the results must be viewed cautiously because other PMS treatments were not excluded.

Magnesium

A systematic review of magnesium treatment identified three small RCTs. The first trial found an overall improvement in PMS symptoms, but the second found no effect and the third found a significant reduction in fluid retention only.¹²

Agnus castus (chasteberry) fruit

A placebo-controlled RCT in Germany evaluated 170 women and found that 20mg of agnus castus daily significantly improved PMS symptoms and was well-tolerated.¹⁴ However, it is unclear whether similar efficacy and tolerability will be seen with all preparations available in the UK.

Dietary changes

RCTs of dietary changes are lacking,¹¹ but some women find that the following are helpful:^{5,15}

- limiting caffeine, alcohol and salt intake
- eating small, frequent meals high in complex carbohydrates
- eating a healthy, low-fat, high-fibre diet with good vitamin and mineral balance.

Vitamin B₆

A systematic review of nine RCTs found that vitamin B₆ reduced overall and depressive symptoms of PMS.¹⁶ However, there was no dose-response relationship and trials were poor quality. Women should limit the dose to 50 or 100mg per day, as higher doses can cause peripheral neuropathy.^{8,16}

Vitamin E

Vitamin E has been recommended for mastalgia,⁸ but evidence to support its use in PMS is minimal. One RCT (n=75) has shown that vitamin E 300 IU per day significantly reduced some psychological and physical symptoms, but not breast tenderness, weight gain, bloating and swollen extremities.¹⁷ A subsequent RCT did not find significant benefits with 400 IU of vitamin E per day.¹²

Evening primrose oil

A systematic review¹⁸ of seven RCTs (n=329) found that there was not enough evidence to determine the efficacy of evening primrose oil in PMS. It may have a small effect but large trials are needed to confirm this. *Efamast* recently lost its product licence for mastalgia because it no longer met current regulatory requirements for efficacy.¹⁹

ammonium chloride and caffeine produced more weight loss than placebo in the luteal phase.³ However, there is little evidence that most women with PMS have water retention. Most evidence of benefit from diuretics in PMS comes from small studies with spironolactone.³

We are not aware of any RCTs of **paracetamol** used specifically in PMS. However, it is a logical first choice analgesic for premenstrual headache or general aches and pains.

Non-steroidal anti-inflammatory drugs (NSAIDs) are worth considering if PMS is associated with dysmenorrhoea, headaches or musculoskeletal symptoms.¹¹ Only mefenamic acid and naproxen have been studied in small RCTs, which found that they improved symptoms, including headache, fatigue, aches and pains, and mood.^{3,10} Other NSAIDs (e.g. ibuprofen) may also be effective. However, NSAIDs can cause fluid retention.²⁰

Selective serotonin-reuptake inhibitors (SSRIs) are the drugs of choice for women with PMDD. A systematic review²¹ of 15 RCTs

of SSRIs in 994 women with severe premenstrual dysphoric symptoms found that SSRIs improved physical and psychological symptoms. The most frequently studied drugs were fluoxetine and sertraline. However, **fluoxetine** (at a dose of 20mg daily) is the only SSRI currently licensed in the UK for PMDD.

The largest trial of fluoxetine in such patients was a six-month, double-blind RCT²² that compared fluoxetine 60mg daily, fluoxetine 20mg daily and placebo in 313 women with late luteal-phase dysphoric disorder (an older term with similar criteria to PMDD). For the 277 women who completed the first cycle, the luteal-phase score (based on tension, irritability and dysphoria) improved from baseline by 52% with fluoxetine 60mg, 44% with fluoxetine 20mg and 7% with placebo. However, the analysis of this study has been criticised,²³ and more people withdrew because of side effects on the 60mg dose, which is not licensed for PMDD.²²

Symptoms of PMDD recur soon after stopping SSRIs, but RCTs have not evaluated SSRIs' long-term effects in this condition.²³

Intermittent fluoxetine dosing during the luteal phase only, has been suggested as a safer and cheaper option to continuous treatment.⁸ However, fluoxetine is not currently licensed for such use, and more evidence is required.²³

Anxiolytics are not routinely recommended for PMS or PMDD. A few small RCTs suggest that alprazolam and buspirone can improve some symptoms.³ However, alprazolam is sedative and carries a risk of dependence.⁴ Both anxiolytics are licensed for short-term treatment of anxiety only, and there is stronger evidence for SSRIs in PMDD.

Progesterone and progestogens (e.g. norethisterone) have been commonly used for PMS. However, a meta-analysis⁹ of 14 double-blind RCTs (n=909) found statistically but not clinically significant differences between progesterone/progestogens and placebo in their effect on overall PMS symptoms. Progestogens can even induce PMS-like symptoms.²⁰

Despite a lack of studies, **oral contraceptives (OCs)** are commonly prescribed for PMS.⁶

One three-month RCT²⁴ (n=82) found that a triphasic OC significantly reduced premenstrual breast pain and bloating, but not mood symptoms. Another short-term RCT²⁵ in PMDD (n=82) reported that drospirenone with ethinylestradiol (*Yasmin*™) significantly improved appetite, acne and food cravings, but not other symptoms. However, it was not powered to show a difference from placebo. OCs may be a reasonable choice for women requiring contraception, who have only physical PMS symptoms,^{8,11} bearing in mind that their side effects can mimic PMS.^{3,5}

Patients should be encouraged to chart their symptoms to determine response to treatment. An alternative treatment may be needed if there is no response after two or three menstrual cycles.¹⁰ Women with severe or resistant PMS/PMDD may require referral to a specialist, who might use drugs such as bromocriptine or those that suppress ovulation (e.g. danazol, oestrogen patches or gonadotrophin releasing hormone [GnRH] analogues).

Bromocriptine taken in the luteal phase (titrated to 2.5 mg twice daily) may be considered for women with severe cyclical mastalgia.^{11,26} A review of 14 small RCTs found no good evidence that it relieved other PMS symptoms, but there was limited evidence that premenstrual mastalgia improved.²⁶ Side effects (e.g. nausea, dizziness, headache, weight gain and swelling) are common.³

RCTs have shown that **danazol** significantly reduces premenstrual symptoms,³ but its androgenic side effects (e.g. weight gain, acne, hirsutism and voice changes) are unacceptable to many women.^{3,5} Taking danazol 200mg daily, in the luteal phase only, for three months is well-tolerated and reduces mastalgia but not general PMS symptoms.²⁷ However, long-term use is a concern because it reduces high density lipoprotein cholesterol levels.^{11,27}

Oestrogen patches (100 micrograms applied twice weekly) given with a progestogen for 12 days in each cycle to prevent endometrial hyperplasia, may help with PMS. However, some women find that the progestogen causes PMS symptoms and there are few published RCTs assessing this treatment.³

GnRH analogues (e.g. buserelin, goserelin or leuprorelin) relieved PMS symptoms in several small RCTs.³ Unfortunately, long-term use is limited by their hypoestrogenic side effects (e.g. hot flushes and osteoporosis) and their high cost.⁸ 'Add-back' hormone replacement therapy with oestrogen and a progestogen is used to prevent side effects,¹¹ but with some regimens this can be at the expense of lower efficacy.³

Conclusion

Unless symptoms are severe (as in PMDD), consensus suggests that management should usually begin with support, lifestyle and dietary treatments. OCs may be worth trying in women who require contraception. Women with PMDD should be identified, so that they can be considered for treatment with an SSRI.

For severe or resistant PMS, specialists or GPs with a specialist interest could try second-line drugs, such as bromocriptine or drugs that suppress ovulation (e.g. danazol, oestrogen patches and GnRH analogues). Women with cyclical mastalgia may be happy to take evening primrose oil, but there is little evidence that it is effective; bromocriptine and danazol are alternatives for severe breast symptoms, but side effects can be a problem.

References

- 1 Stolberg M. The monthly malady: a history of premenstrual suffering. *Med Hist* 2000;44:301-22.
- 2 Greene R, Dalton K. The premenstrual syndrome. *BMJ* 1953;i:1007-14.
- 3 Wyatt K. Premenstrual syndrome. In: Barton S, editor. *Clinical Evidence*, Issue 8. London: BMJ Publishing Group; 2002. p.1972-91.
- 4 Managing the premenstrual syndrome. *Drug*

- 5 Ther Bull 1992;30:69-72.
- 6 Ling FW. Recognizing and treating premenstrual dysphoric disorder in the obstetric, gynecologic, and primary care practices. *J Clin Psychiatry* 2000;61(suppl 12):9-16.
- 7 Hylan TR, Sundell K, Judge R. The impact of premenstrual symptomatology on functioning and treatment-seeking behaviour: Experience from the United States, United Kingdom, and France. *J Women's Health Gend Based Med* 1999;8:1043-52.
- 8 Royal College of Obstetricians and Gynaecologists. Disorders of the menstrual cycle: Study group recommendations; 2000. Available from: URL: <http://www.rcog.org.uk/mainpages.asp?PageID=442>
- 9 The American College of Obstetrics and Gynecology (ACOG) Committee on Practice Bulletins. Clinical management guidelines for obstetrician-gynecologists: Premenstrual syndrome. *ACOG Pract Bull* 2000;(15):1-8.
- 10 Wyatt K, Dimmock P, Jones P, et al. Efficacy of progesterone and progestogens in the management of premenstrual syndrome: systematic review. *BMJ* 2001;323:776-83.
- 11 Steiner M. Premenstrual syndrome and premenstrual dysphoric disorder: guidelines for management. *J Psychiatry Neurosci* 2000;25:459-68.
- 12 Johnson SR. Premenstrual syndrome therapy. *Clin Obstet Gynecol* 1998;41:405-21.
- 13 Stevinson C, Ernst E. Complementary/alternative therapies for premenstrual syndrome: a systematic review of randomized controlled trials. *Am J Obstet Gynecol* 2001;185:227-35.
- 14 Thys-Jacobs S, Starkey P, Bernstein D, et al. Calcium carbonate and the premenstrual syndrome: Effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol* 1998;179:444-52.
- 15 Schellenberg R for the study group. Treatment for the premenstrual syndrome with agnus castus fruit extract: prospective, randomised, placebo controlled study. *BMJ* 2001;322:134-7.
- 16 National Association for Premenstrual Syndrome. Premenstrual syndrome — a clinical review, 1999 (Available from NAPS tel: 01732 760011).
- 17 Wyatt KM, Dimmock PW, Jones PW, et al. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. *BMJ* 1999;318:1375-81.
- 18 London RS, Sundaram GS, Murphy L, et al. The effect of α -tocopherol on premenstrual symptomatology: a double-blind study. *J Am Coll Nutr* 1983;2:115-22.
- 19 Budeiri D, Li Wan Po A, Dorman JC. Is evening primrose oil of value in the treatment of premenstrual syndrome? *Control Clin Trials* 1996;17:60-8.
- 20 Medicines Control Agency. What's new: Epogam and Efamast (gamolenic acid) — withdrawal of marketing authorisations, October 2002. Available from: URL: <http://www.mca.gov.uk>
- 21 British National Formulary. No. 44. London: British Medical Association/Royal Pharmaceutical Society of Great Britain; 2002.
- 22 Dimmock PW, Wyatt KM, Jones PW, et al. Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review. *Lancet* 2000;358:1131-6.
- 23 Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. *N Engl J Med* 1995;332:1529-34.
- 24 SSRIs for premenstrual dysphoric disorder. *Drug Ther Bull* 2002;40:70-1.
- 25 Graham CA, Sherwin BB. A prospective treatment study of premenstrual symptoms using a triphasic oral contraceptive. *J Psychosom Res* 1992;36:257-66.
- 26 Freeman EW, Kroll R, Rapkin A, et al. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *J Womens Health Gend Based Med* 2001;10:561-9.
- 27 Andersch B. Bromocriptine and premenstrual symptoms: a survey of double blind trials. *Obstet Gynecol Surv* 1983;38:643-6.
- 28 O'Brien PM, Abukhalil IEH. Randomized controlled trial of the management of premenstrual syndrome and premenstrual mastalgia using luteal phase only danazol. *Am J Obstet Gynecol* 1999;180:18-23.

The National Institute for Clinical Excellence (NICE) is associated with MeReC Publications published by the NPC through a funding contract. This arrangement provides NICE with the ability to secure value for money in the use of NHS funds invested in its work and enables it to influence topic selection, methodology and dissemination practice. NICE considers the work of this organisation to be of value to the NHS in England and Wales and recommends that it be used to inform decisions on service organisation and delivery. This publication represents the views of the authors and not necessarily those of the Institute.