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Fortnightly Review

Helping women with premenstrual syndrome

P M S O'Brien

Premenstrual syndrome has been dismissed by many doctors because their experiences have been limited to observations of their own cycles or those of their wives and female colleagues, most of whom experience only mild psychological symptoms with the ovarian endocrine cycle. Mild physiological symptoms occur in as many as 95% of women of reproductive age, only 5% being totally free from symptoms. Around 5% of symptomatic women complain of such severe symptoms that their lives are totally disrupted during the second half of the cycle. Symptoms may be so severe that they lead to suicide, parasuicide, and acts of violence against others.

The first step in helping women with premenstrual syndrome is for doctors to recognise the importance of the disorder and to distinguish true premenstrual syndrome from the milder and much commoner physiological symptoms. Women with premenstrual syndrome must also be distuinguished from women with a psychiatric disorder, whose symptoms are not related to the ovarian endocrine cycle. Failure to make these two distinctions has led to inappropriate and ineffective treatment.

Summary points

- About 5% of women suffer premenstrual symptoms severe enough to disrupt their lives in the two weeks before onset of menstruation
- Premenstrual syndrome seems to be caused by abnormal neurotransmitter response to normal ovarian function
- It is important to evaluate timing of symptoms and their severity in women presenting with the premenstrual syndrome
- The most effective treatment is abolition of the ovarian cycle by drugs or surgery but this is appropriate in only the most severely affected women
- Treatments for women with moderate symptoms have not been properly evaluated in clinical trials
- Stress management, relaxation techniques, exercise, and dietary changes often help women to cope with the symptoms and may be all that is required in mild cases

Cause of premenstrual syndrome

No medical specialty has accepted responsibility for treating or conducting research into premenstrual syndrome. Little conclusive information exists on either aetiology or treatment. The current consensus is that normal ovarian function rather than hormone imbalance is the cyclical trigger for biochemical events within the central nervous system and other target tissues. A psychoneuroendocrine mechanism triggered by the normal endocrine events of the ovarian cycle seems the most plausible explanation. Logical approaches to treatment would therefore include modulation or removal of the ovarian steroid trigger or modulation or correction of neurotransmitter metabolism.

Both bilateral oophorectomy[1] and suppression of ovaries with analogues of gonadotrophin releasing hormone[2] reliably cure premenstrual syndrome by eliminating the ovarian trigger, while serotonergic drugs treat premenstrual syndrome by modulating the neuroendocrine response to the ovary.[3] No convincing evidence exists of an excess or deficiency of either oestrogen or progesterone in the aetiology of premenstrual syndrome.[4]

Recent research shows that women with premenstrual syndrome who have had a hysterectomy and bilateral oophorectomy do not redevelop symptoms when they receive continuous oestrogen therapy. They do, however, develop well defined symptoms when given progesterone or progestogens (fig 1). The severity of symptoms is positively correlated to the progesterone concentration. This supports an ovarian endocrine basis for premenstrual syndrome and virtually excludes aetiological theories related to uterine or endometrial function such as the release of "menotoxins."

Recent research has also discounted the role of sodium and water retention.[5] Most women who develop premenstrual bloatedness and abdominal distension in the luteal phase do not show increases in weight, total body water, extracellular fluid volume, total exchangeable body sodium, or plasma volume. This finding also questions the rationale for diuretic therapy.

Recent research into the unexplained abnormal

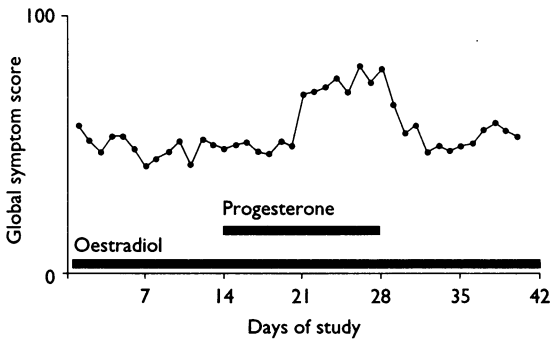

FIG 1—*Symptom scores for premenstrual syndrome in women who have had hysterectomy and bilateral oophorectomy and require hormone replacement therapy. During oestrogen only therapy they have no symptoms. When progesterone is added experimentally for two weeks symptoms recur. (C Henshaw et al, unpublished data)*

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organ response to normal ovarian endocrine function has been directed towards neurotransmitter function. There are several possible mediators of ovarian steroid action within the brain. These include the catecholamines, monoamines, endogenous opioid peptides and encephalins, γ-aminobutyric acid, serotonin, and prostaglandins.[6] Concentrations of β endorphin seem to be lower during the luteal phase in women with premenstrual syndrome, and modulation of β endorphin concentration by naltrexone or clonidine reduces symptoms.[6]

Serotonin has also been a focus of research.[3] Decreased serotonergic activity seems to be important in endogenous depression, and studies of platelet and whole blood serotonin concentration suggest serotonin deficiency in patients with premenstrual syndrome. Drugs which increase serotonin concentration either by stimulating release or by inhibiting reuptake seem to improve the psychological symptoms associated with premenstrual syndrome.[3]

Definition and diagnosis

Women with premenstrual syndrome commonly present to their doctor with a self diagnosis and the doctor has to confirm this or exclude other causes for their symptoms. Women may present with four categories of symptoms.[4]

Physiological premenstrual symptoms—Physiological symptoms are not severe enough to disrupt normal lives and do not require specific treatment. These women may need counselling and reassurance, particularly if they have been led to believe they have a syndrome through media publicity about the disorder.

Psychiatric disorders wrongly attributed to premenstrual syndrome—Because many of the symptoms found in depression resemble those of premenstrual syndrome, women (and doctors) often confuse the two.

Primary premenstrual syndrome is usually defined as the recurrence of psychological, behavioural, or physical symptoms during the luteal phase of the menstrual cycle. The symptoms should resolve completely by the end of menstruation and women should be free of symptoms for a time between menstruation and ovulation. The symptoms must be sufficiently severe to interfere appreciably with normal functioning or interpersonal relationships.

Secondary premenstrual syndrome—The definition is similar to that of primary premenstrual syndrome. They are differentiated by the partial rather than complete resolution of symptoms after menstruation. Women often have underlying psychological problems as well as a cyclical disorder.

The nature of the symptoms of premenstrual syndrome is less important than the timing. The box lists some of the most characteristic symptoms. When evaluating patients it is important to determine the impact of menstruation on the symptoms and the effect the symptoms have on the patients' lives. Women should be asked to complete symptom charts daily for two months. Recording symptoms retrospectively is inaccurate and should not be used as a basis for treatment.[7]

The advisory committee to the workshop group to revise the third edition of *Diagnostic and Statistical Manual of Mental Disorders (DSM-III)*, proposed the term late luteal phase dysphoric disorder, which refers only to the mood disturbance of premenstrual syndrome and excludes women who have symptoms throughout the luteal phase of the cycle. Premenstrual syndrome and luteal phase dysphoric disorder have wrongly been used interchangeably.

Characteristic symptoms of premenstrual syndrome

Physical
- Abdominal distension or bloatedness
- Severe mastalgia
- Headache or migraine

Psychological
- Aggression
- Depression
- Tension
- Loss of control

DIAGNOSTIC TESTS

It is sometimes difficult to distinguish which category a patient fits into. A formal psychiatric evaluation, including detailed analysis, structured interviews, and objective questionnaires may help to clarify the diagnosis in more difficult cases.

A gonadotrophin releasing hormone analogue test is often useful in women with severe symptoms in whom the diagnosis remains in doubt. Goserelin, a gonadotrophin releasing hormone agonist analogue, is given monthly for three months to eliminate cyclical ovarian function completely; the effect on symptoms is determined. Complete elimination of symptoms implies that the symptoms are solely dependent on ovarian activity, and the diagnosis is primary premenstrual syndrome. If symptoms continue into the third month an underlying psychiatric problem is present.

Various biochemical markers have been claimed to identify premenstrual syndrome. These include assays for thyroid hormones, cortisol, melatonin, platelet serotonin, progesterone, gonadotrophins, and sex hormone binding globulin. There is no evidence to support the use of any of these as a diagnostic test.[4]

Treating patients

Some women can be helped very simply. Women with physiological premenstrual changes will benefit from counselling and reassurance and those with non-cyclical psychiatric problems should be helped by early identification of their problem, with appropriate referral and therapy.

Treatment of women with very severe premenstrual syndrome is also relatively easy as it is easier to justify medical or surgical elimination of the menstrual cycle.

Patients with serious but less severe symptoms remain the most difficult to manage. Treatments that do not eliminate ovulation or ovarian fuction are unreliable. The response of patients is inconsistent and treatments are generally based on little credible scientific data.

Numerous treatments have been proposed over the past 60 years. This suggests that they are either ineffective or that the high placebo effect in premenstrual syndrome leads to overoptimistic conclusions being drawn.

Non-pharmacological methods

The pathogenesis of premenstrual syndrome is almost certainly more complex than the combination of ovarian activity and the resulting neurotransmitter changes. Many other factors may have a role, including environmental, psychosocial, and personal factors such as stress, interpersonal relationship problems, underlying psychopathology, personality, self esteem, general health, and wellbeing. It is not surprising that women respond to seemingly non-specific measures like vitamin therapy, dietary change, self help, exercise, psychotherapy, stress managment, and relaxation techniques (box).[8] Indeed, such approaches are more

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appropriate for many women than are hormones, surgery, and psychiatric consultation. Gynaecologists, endocrinologists, and psychiatrists should be consulted only when such measures have failed.

Non-pharmacological treatment

Counselling
Stress management
Complementary approaches (hypnosis, acupuncture, yoga)
Cognitive therapy
Dietary manipulation

Relaxation and stress management can be included in formalised psychotherapy or taught through acupuncture, hypnosis, or yoga to suit the patient.[9] Such methods are difficult to evaluate precisely.

Exercise, vitamin therapy, and dietary change improve general health and self esteem and may increase women's tolerance to premenstrual change and thus reduce the impact of premenstrual syndrome.[8] Although having regular carbohydrate meals to combat hypoglycaemia has been advocated enthusiastically, there is evidence that premenstrual "hypoglycaemia" is not related to low blood sugar levels and thus there is no justification for this approach.[10]

Many specific dietary interventions have been suggested and include vitamins B-6 and A, magnesium, calcium, and evening primrose oil. The use of vitamin B-6, calcium, and magnesium has some logic as they are cofactors in neurotransmitter synthesis—for example, in the conversion of tryptophan to serotonin. There are studies to support and refute their efficacy.[8 10]

Evening primrose oil has been strongly promoted in recent years. Although there is good evidence that it relieves breast symptoms, studies on general premenstrual syndrome show only trends in favour of its use compared with placebo.[11 12] The studies were not large enough to achieve sufficient power to conclude that the treatment is ineffective. Since evening primrose oil has few side effects women should be allowed to self medicate, but it is expensive.

Non-hormonal drugs

Many non-hormonal drugs are used for the premenstrual syndrome, though few seem effective. Psychotropic drugs, particularly serotonin uptake inhibitors, have recently been shown to be helpful in women with exclusively premenstrual psychological disturbance and those with secondary premenstrual syndrome: fluoxetine and clomipramine have both been found effective in double blind trials.[3 13 14]

Diuretics are useful only in women who have appreciable weight gain in the luteal phase of the cycle. Women with bloatedness and even severe abdominal distention without weight gain cannot be retaining fluid and will not be helped by diuretics. When diuretics are necessary, the use of an aldosterone antagonist such as spironolactone should reduce the chances of developing idiopathic oedema.[15]

Progesterone and progestogens

The widespread use of progesterone probably results from the enthusiasm of its advocacy rather than its pharmacotherapeutic efficacy.[16] Extensive anecdotal evidence has led to claims for efficacy by a few authors but randomised double blind placebo controlled trials do not support this view.[17]

Only one study has shown that dydrogesterone is better than placebo in premenstrual syndrome, although it has been widely used since the 1970s. Cyclical medroxyprogesterone acetate and the depot preparation have reduced symptoms but only in limited trials.

Suppression of the endogenous cycle

If women do not respond to the less invasive treatments, the next step is to eliminate the ovarian trigger. There are several medical methods by which the endogenous ovarian or menstrual cycle could, in theory, be suppressed. These include combined oral contraceptives (cyclically or continuously), danazol, continuous progestogen, oestradiol patches, oestradiol implants, and gonadotrophin releasing hormone analogues (table). Surgical methods will be discussed later.

ORAL CONTRACEPTIVE PILL

Cyclical combined oral contraceptives suppress ovulation but endocrine cyclicity remains.[18] This probably accounts for the unpredictable response to treatment with monophasic and triphasic pills.[19] Some side effects of oral contraceptives are similar to symptoms of premenstrual syndrome and women may develop these for the first time. It would be more logical to give oral contraceptives continuously. In clinical practice this has been disappointing, and no research supports their use.

DANAZOL

If danazol is given continuously in doses which suppress ovulation and menstruation the symptoms of premenstrual syndrome are abolished.[20 21] It has also been shown to reduce symptoms at lower doses.[22] Trials are currently under way to determine its value when given only during only the luteal phase. The use

Pharmacological treatment for premenstrual syndrome

	Suggested use	Regimen	Comment
Pyridoxine	Initial stages of treatment	100 mg daily orally	Limited evidence
Gamolenic acid	Initial stages of treatment Breast symptoms	3-4 capsules twice daily orally	Good evidence in mastalgia, limited evidence for premenstrual syndrome
Fluoxetine	When psychological symptoms predominate Secondary premenstrual syndrome	20 mg daily orally	Early results encouraging
Bromocriptine	Mastalgia	2·5 mg at night orally	No effect on general premenstrual syndrome
Spironolactone	For proved premenstrual weight gain only	100 mg daily in second half of cycle	Reasonable evidence for relief of bloatedness
Dydrogesterone	General premenstrual syndrome	10 mg twice daily on 12th-26th day of cycle orally	Limited evidence Useful progestogen during oestrogen therapy
Progesterone	General premenstrual syndrome	Pessaries/suppositories 400-800 mg up to twice daily	No supportive research evidence but widely used
Danazol	Severe general premenstrual syndrome	100, 200, 400 mg daily	Watch for side effects Monitor lipids with long term therapy
Oestradiol patch	General premenstrual syndrome	200 μg with cyclical progestogen	Progestogen may restimulate premenstrual syndrome
Oral contraception	General premenstrual syndrome	Continuous combined should be most effective	Results of research confusing
Oestradiol implant	Severe premenstrual syndrome	50, 100 mg implant with cyclical progestagen ± testosterone	Progestogen may restimulate premenstrual syndrome
Gonadotrophin releasing hormone analogues	Severe premenstrual syndrome	3·6 mg subcutaneously every 28 days for up to six months	Completely eliminates symptoms Hypo-oestrogenic side effects limit duration of therapy

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of this drug is limited by its perceived side effects, which have probably been overstated. Reversible masculinising side effects are a risk but these are rare. Masculinisation of a female fetus is also a risk if pregnancy should occur. If long term treatment is contemplated lipid levels should be monitored.

OESTROGEN PATCHES AND IMPLANTS

Initial reports of oestradiol implants showed sustained improvement when compared with placebo implants. These early studies also found no evidence of restimulation of the premenstrual syndrome symptoms during treatment with the cyclical progestogen. Although oestradiol implants have an important role in certain patients, long term use can cause problems. In a study of 50 women over two to eight years, new premenstrual syndrome symptoms developed in 58%.[23] These symptoms can be managed by adjusting the type and dose of progestogen. Several patients (16%) had a hysterectomy, mainly because of progestogenic side effects and bleeding. There were no cases of thrombosis, pulmonary embolus, breast disease, or atypical endometrial hyperplasia. Sixty four per cent of the women also received a testosterone implant and it is not known what proportion of the improvement in symptoms was due to testosterone.

The effect of oestradiol patches has also been investigated in 40 women who received two 100 μg patches every third day.[24] They also received cyclical norethisterone. Significant improvement in symptoms was shown compared with placebo.

Both oestradiol implants and patches have an important role in severely affected young patients and in many women who are approaching the menopause.

GONADOTROPHIN RELEASING HORMONE AGONIST ANALOGUES

These drugs can be given as nasal sprays, subcutaneous injections, and long acting depot preparations. They act by creating a reversible pseudomenopause (more correctly a pseudohypophysectomy). Nasal preparations give less precise suppression of the cycle and symptoms may flare up intermittently, but depot goserelin reliably and predictably eradicates symptoms.[2] Some exacerbation of symptoms usually occurs during the initial stimulation of the pituitary receptors.

The removal of the hormonal trigger is parallelled by a hypo-oestrogenic state. The associated hot flushes are better tolerated than the symptoms of the premenstrual syndrome but long term treatment cannot be justified because of risks of osteoporosis and atherosclerotic cardiovascular disease. The symptoms usually return with the menstrual cycles (fig 2).[25] Limited courses of gonadotrophin releasing hormone agonist analogues have several important indications. Firstly, in women whose psychological health and interpersonal relationships are deteriorating greatly six months free of symptoms can be invaluable, saving marriages and jobs. Secondly, the freedom from symptoms in the absence of the ovarian endocrine cycle shows the woman and her family that her problem has a biological basis. This is especially important when those around have considered this due to psychiatric or personality problems. Finally, in severely affected women who are to undergo hysterectomy for another gynaecological disorder the potential benefit of performing bilateral oophorectomy at the same time can be shown.

Attempts have been made to protect the cardiovascular system and bone during long term treatment with gonadotrophin releasing hormone analogues by adding conventional hormone replacement therapy.[26,27] The protogestogens cause symptoms to recur in some women, but others experience continued relief. Tibolone may avoid such symptoms, but this has not been formally assessed.

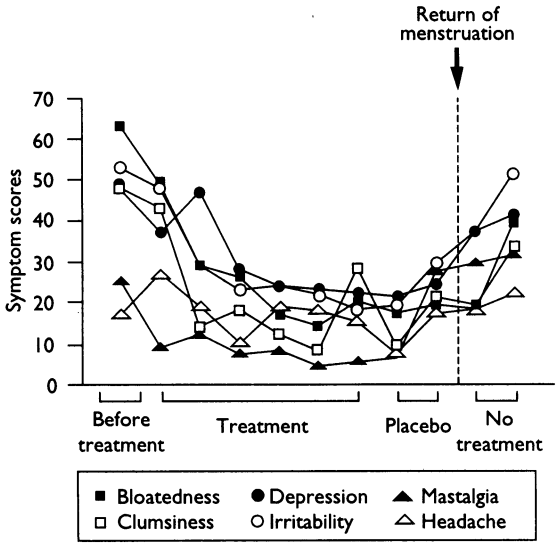

FIG 2—*Gonadotrophin releasing hormone analogues such as goserelin and buserelin virtually eliminate symptoms by the third month of treatment. Symptoms recur during placebo therapy immediately before menstruation. (Adapted from Hussain et al[25])*

Surgical approach

Surgery is rarely used to manage premenstrual syndrome (box). Symptoms persist after hysterectomy, though one study showed that symptoms were reduced without bilateral oophorectomy.[29] This may be the result of the steroid changes which occur even when the ovaries are conserved. Total hysterectomy with bilateral salpingo-oophorectomy eliminates the symptoms of premenstrual syndrome.[1] Hypo-oestrogenic side effects can be prevented by unopposed oestrogen, without the need for cyclical progestogen. This is probably the only permanent cure for premenstrual syndrome but is appropriate for only a few severely affected women. The new popularity of endoscopic surgery has led to suggestions that premenstrual syndrome may be treated by laparoscopic oophorectomy. This is not feasible as oestrogen replacement will be required and the uterus will require cyclical progestogen therapy.

Surgical approaches under investigation

Endometrial resection
Laparoscopic oophorectomy
Hysterectomy
Hysterectomy and bilateral salpingo-oophorectomy

Although the results of one uncontrolled study support the use of endometrial ablation,[30] logically this should not be effective because ovarian activity persists.

Choice of treatment

The aim should be to provide the simplest and most effective treatment (fig 3). Patients' characteristics will influence the choice of therapy. Age and proximity to the menopause favour the use of oestrogen. The type of premenstrual syndrome, its symptoms, and their severity are important. When symptoms are predominantly psychological or the patient has secondary premenstrual syndrome serotonergic drugs may provide the most benefit. If the woman wishes to become pregnant ovulation cannot be suppressed and the risk of teratogenesis (for example, masculinisation of the female fetus with danzol) should be taken into account. Those wishing to avoid pregnancy may opt for a trial of combined oral contraception. Additionally,

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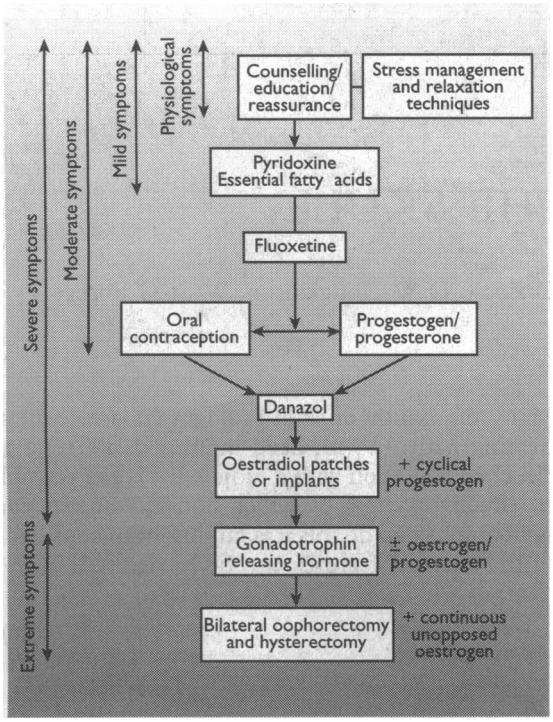

FIG 3—*Commonly used approach to mangement of premenstrual syndrome*

women should be made aware that many of the techniques used are not effective as contraception.

Severe premenstrual syndrome will, in practical terms, be defined as failure to respond to non-invasive methods. More aggressive methods will be needed for women who do not respond to the non-hormonal and non-surgical techniques.

Conclusions

Women with premenstrual syndrome can be helped. Our understanding of the problem has advanced greatly in the past few years but the final pathway in the aetiology still eludes us and there is no single, simple universal cure.

Mildly and moderately affected women can be managed with non-invasive techniques, and for severely affected patients elimination of the ovarian cycle by hormones or surgery can be justified. For women who fall between these extremes treatment is difficult and based on inadequate research.

In the long term if we are really to help women with premenstrual syndrome all doctors must be convinced of the importance of this problem. Only then will resources meet the current clinical needs. Research into premenstrual syndrome has been led almost entirely by the pharmaceutical industry. Virtually no funding has been provided for critical scientific research. And it is this, more than anything else, that will eventually enable us to treat premenstrual syndrome simply and effectively.

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THE CHALLENGE OF AIDS

By September 1992 there were 6500 patients with AIDS but anything up to 60 000 infected with HIV. Many of those with the virus are well, asymptomatic, and even unaware that they are infected, but others, although they have not yet developed AIDS, have physical, psychological, social, and occupational problems and require as much care as those with AIDS. We therefore need to be concerned not with "a few cases" but with a large number of people infected with a virus who will be making demands on every part of the health and social services. Not only are the numbers large but they will undoubtedly increase. New infections will occur, and the public health education campaign will need to continue. The best we can hope for is a slowing down of the epidemic. None of us should feel that the problem of HIV infection and AIDS is unimportant and that it will go away because of the campaign and the possible magic bullet of a cure or vaccine.

We can all hope for these things but it would be a mistake to be lulled into a state of inertia and complacency. HIV and AIDS represent the most major public health problem faced by the United Kingdom, and even possibly the world, this century. All of us will be concerned with AIDS for the rest of our professional lives.

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