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Setting standards to improve women's health

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MANAGEMENT OF PREMENSTRUAL SYNDROME

This is the first edition of this guideline.

1. Purpose and scope

The aim of this guideline is to review the diagnosis and management of premenstrual syndrome (PMS); in particular, the evidence for pharmacological and non-pharmacological treatments.

2. Introduction and background

Approximately 5% of women experience severe premenstrual symptoms which include depression, anxiety, irritability and loss of confidence, and physical symptoms including bloating and mastalgia. There is currently no consensus in the management of PMS, with a wide range of treatment options available.

2.1 Definition of PMS

A working definition of PMS is 'a condition which manifests with distressing physical, behavioural and psychological symptoms, in the absence of organic or underlying psychiatric disease, which regularly recurs during the luteal phase of each menstrual (ovarian) cycle and which disappears or significantly regresses by the end of menstruation'.[1] The degree and type of symptoms can vary significantly from woman to woman. Symptoms of PMS are distinguished from normal physiological premenstrual symptoms because they cause significant impairment to daily activity (Table 1).

Table 1. Definitions of the different types of premenstrual syndrome

Type	Definition
Premenstrual syndrome	PMS symptoms leading up to menstruation and completely relieved by the end of menstruation
Mild	Does not interfere with personal/social and professional life
Moderate	Interferes with personal/social and professional life but still able to function and interact, although may be suboptimally
Severe	Unable to interact personally/socially/professionally—withdraws from social and professional activities (treatment resistant)
Premenstrual exaggeration	Background psychopathology, physical or other condition with incomplete relief of symptoms when menstruation ends
Prementrual dysphoric disorder	This is a research criteria, not in general use outside the USA. This definition of severe PMS has been adopted by the American Psychiatric Association

2.2 Aetiology and prevalence

The precise aetiology of PMS remains unknown but cyclical ovarian activity and the effect of estradiol and progesterone on the neurotransmitters serotonin and gamma-aminobutyric acid (GABA) appear to be key factors. Absence of PMS before puberty, in pregnancy and after the menopause supports the theory that cyclical ovarian activity is important. The prevalence of severe PMS is variable between 3% to 30%.[2,3] PMS appears more prevalent in women who are obese, perform less exercise and are of lower academic achievement. There is a lower incidence of PMS in women using hormonal contraception.

3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews, DARE and EMBASE), TRIP, Medline (1966–2006), Psych INFO (1960–2006), CINHAL (1982–2006), BNI (1985–2006) were searched. The databases were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search. Search words included 'premenstrual syndrome', 'premenstrual tension', 'late luteal phase dysphoric disorder', 'premenstrual dysphoric disorder', 'PMDD', 'PMS', 'LLPDD', 'PMT' and the search was limited to humans and English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews. Enquiries for relevant information were also made to pharmaceutical industry and researchers for missing studies and discussion with patient advocacy groups e.g. NAPS (National Association for Premenstrual Syndrome).

4. How is PMS diagnosed?

When assessing women with PMS, symptoms should be recorded prospectively, over two cycles using a symptom diary, as retrospective recall of symptoms is unreliable. ✓

There are many symptom diaries available but the Daily Record of Severity of Problems (DRSP) problems is well-established and simple for patients to use (See Appendix 1).[4]

Typical psychological symptoms include mood swings, irritability, depression and feeling out of control; physical symptoms include breast tenderness, bloating and headaches; behavioural symptoms include reduced visuospatial and cognitive ability and an increase in accidents.

5. How should severe PMS be treated?

When treating women with PMS:

- **general advice about exercise, diet and stress reduction should be considered before starting treatment**
- **women with marked underlying psychopathology as well as PMS should be referred to a psychiatrist**
- **symptom diaries (DRSP) should be used to assess the effect of treatment.** ✓

Lifestyle adjustments such as improved self-care, low glycaemic index diet and stress-reduction have not been studied in depth but are good general health advice and should be considered before starting treatment. There is evidence from non-randomised trials that exercise improves PMS symptoms.[5] It is an important principle to avoid complex gynaecological and hormonal interventions at the outset.

6. Service delivery

6.1 What is the most appropriate setting for the management of women with severe PMS?.

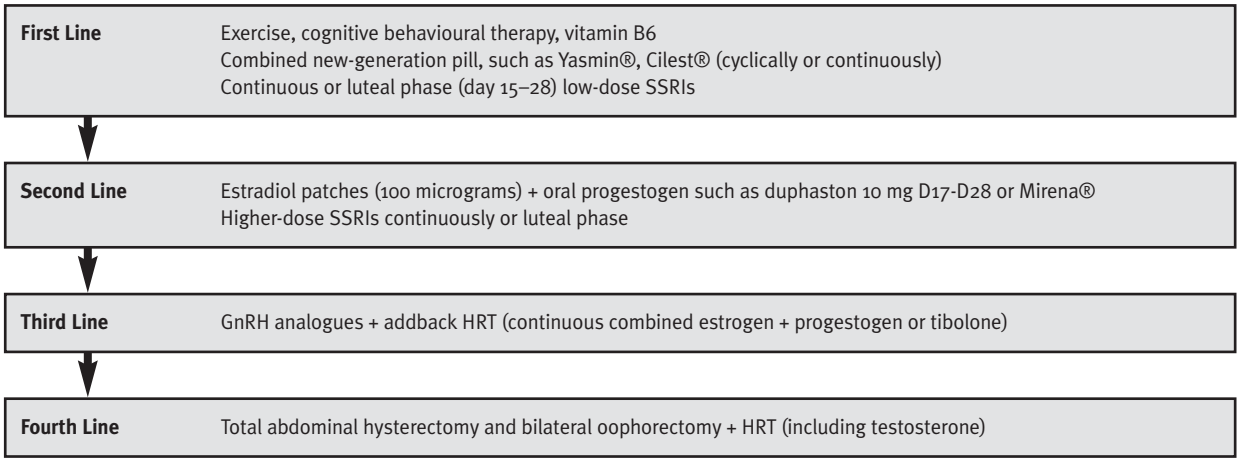
When treating women with PMS, referral to a gynaecologist should be considered when simple measures have been explored and failed and when the severity of the PMS justifies gynaecological intervention. ✓

General practitioners should deal with most cases of PMS. Awareness of the condition and training in its management is essential. Ideally, women with severe PMS should be managed by a multidisciplinary team which might comprise of a hospital or community gynaecologist, psychiatrist or psychologist, dietician and counsellor. While such services are rarely provided in any NHS setting, referral to gynaecologists should be reserved for women who have been fully evaluated as having PMS and when simpler forms of therapy have been explored. Where there is multidisciplinary provision of care, this is of benefit both from the diagnostic and therapeutic point of view, giving the ability to offer a broad range of interventions from lifestyle interventions and cognitive behavioural therapy to the rarely required gynaecological interventions.[6]

6.2 Is it important that a PMS service offers the full range of treatments (traditional and complementary)?

When treating women with PMS, an integrated approach is beneficial. This may include complementary medicines which themselves may not be evidence based. ✓

Figure 1. Possible treatment regimen for the management of severe PMS



Although many complementary therapies for PMS are not evidence based, it is generally agreed among health professionals treating women with PMS that an integrated approach is beneficial for the majority of women.[7] Figure 1 summarises the evidence-based pharmacological options for treatment of women who have moderate to severe PMS or for those in whom simple measures have failed. However, service provision for such services as complementary medicine and clinical psychology, and indeed separately identified PMS clinics, are rarely available in either the NHS or private sector.

6.3 Use of unlicensed treatments in PMS

When treating women with PMS, unlicensed treatment can be justified where evidence for efficacy and safety exists. ✓

Most efficacious treatments used in PMS are unlicensed for PMS.

7. Complementary therapies

Is there any evidence for the use of complementary therapies?

When treating women with PMS, complementary medicines may be of benefit, but clinicians need to consider that:

- **data from clinical studies are limited and underpowered**
- **the referring clinician retains legal responsibility for the patient's wellbeing when they refer patients to complementary therapists**
- **Interactions with conventional medicines should be considered.**

✓

Table 2. Summary of complementary therapies

Complementary therapy	Benefit	Types of studies	Numbers in the study	Note
Lifestyle changes (reduction in alcohol, caffeine and refined high glycaemic index carbohydrates	Unknown	–	N/A	–
Reflexology[43–45]	Some benefit	Small uncontrolled studies	38	–
Vitamin B6[46,47]	No	Meta-analysis	940 (9 published trials)	Peripheral neuropathy with high doses. Department of Health and MCH restrict the daily dose to 10 mg
Magnesium[48,49]	Yes	Double-blind, placebo-controlled	70 (2 published trials)	Used in the premenstrual phase
Nutritional supplements (multivitamins)[50–53]	Unknown	–	400 (several published studies)	Unclear which are the active ingredients
Calcium/vitamin D[54–57]	Some benefit	Case–control studies	30 (double-blind placebo-controlled study)	–
Isoflavones[58]	Yes	Double-blind randomised	49	Further data before recommendation
Agnus castus[59]	Yes	Randomised placebo-controlled	170	There is no standardised quality-controlled preparation
St John's wort[60,61]	Unknown	Observational	Small	Significant interactions with conventional medicines. BNF advises avoid concomitant use with SSRIs.
Ginkgo biloba[62]	Yes	Placebo-controlled	143	Further data before recommendation
Pollen extract[63]	Yes	Double-blind, placebo-controlled	32	Further data before recommendation
Evening primrose oil[64–66]	No	Randomised double-blind, placebo-controlled	156 from 3 randomised controlled trials	Benefits cyclical mastalgia only
Light therapy[67]	Unknown	Double-blind, randomised, cross-over	14	Concern about safety [39]

Table 2 summarises available data for complementary therapies. The best data appear to exist for Vitamin D /calcium, magnesium and for Agnus castus.

It is difficult to assess the true value of most of these therapeutic interventions because they are freely available without prescription or physician recommendation, with little regulation of efficacy or safety. Most are not licensed or registered for treatment of PMS.

There has been concern about the safety of bright light therapy and the possibility of retinopathy.[8] There may be drug interactions with other medicines. St John's wort, particularly, has a long list of interactions.

8. Managing severe PMS with cognitive behavioural therapy

When treating women with severe PMS, cognitive behavioural therapy should be considered routinely as a treatment option. **A**

A clinical psychology service should be available for this patient group. ✓

A recent study examined the relative effectiveness of fluoxetine (20 mg daily) and cognitive behavioural therapy (CBT) (ten sessions), and combined therapy (fluoxetine plus CBT) in women with premenstrual dysphoric disorder (PMDD).[9] This was a randomised treatment trial lasting 6 months; follow-up was undertaken 1 year post-treatment. Significant improvement occurred in all three treatment groups after 6 months of treatment. Fluoxetine was associated with a more rapid improvement but, 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.

Evidence level Ib

9. Management of PMS with selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and noradrenaline reuptake inhibitors (SNRIs)

9.1 What is the evidence for efficacy of SSRIs in treatment of PMS?

Physical and psychological symptoms of PMS improve with SSRIs. **B**

In view of their proven efficacy and safety in adults, SSRIs/SNRIs should be considered one of the first-line pharmaceutical management options in severe PMS. **A**

Prescribing should be restricted to those health professionals (gynaecologists, psychiatrists or GPs) who have a particular expertise in this area. ✓

The Commission on Human Medicines (formerly the Committee on Safety of Medicines) endorses the view that SSRIs are effective medicines in the treatment of depression and anxiety conditions and that the balance of risks and benefits in adults remains positive in their licensed indications. ✓

There is increasing evidence that serotonin may be important in the pathogenesis of PMS. A number of SSRIs have been used to treat severe PMS/PMDD. One study consisted of two phases with an initial single-blind washout period followed by a randomised, double-blind, placebo-controlled trial lasting six menstrual cycles. Fluoxetine at 20 mg or 60 mg was found to significantly reduce symptoms of tension, irritability and dysphoria, as well as physical symptoms compared with placebo, as measured by visual analogue scales ($P < 0.001$).[10] The mean percentage improvement in the luteal-phase score from baseline was four to six times greater in the fluoxetine groups than in the placebo group. The adverse effects reported during the trial were dose related, with significantly fewer events occurring in the placebo group and the group receiving 20 mg fluoxetine/day than in the group given 60 mg fluoxetine/day ($P < 0.001$). A meta-analysis of all available randomised controlled trials involving SSRIs used in premenstrual syndrome confirmed superior efficacy compared with placebo.[11]

Evidence level Ia

Physical symptoms associated with PMDD, including breast tenderness, bloating and headache, were also assessed.[10,12] Daily fluoxetine treatment significantly improved physical symptoms in women with PMDD when symptoms were measured using VAS, PMTS-SR and PMTS-O. The mechanism remains unclear but the authors state that the perception of physical symptoms may have been improved by the beneficial effect of SSRIs on mood.

Evidence level Ib

9.2 Is the evidence for luteal-phase use (2–4 weeks/cycle of SSRIs) as strong as that for continuous treatment?

When treating women with PMS, either luteal phase or continuous dosing with SSRIs can be reccomended. **B**

The evidence for the efficacy of treatment in the symptomatic premenstrual phase is increasing and the data appear robust. A randomised, double-blind study compared the responses to luteal-phase or full-cycle dosing of sertraline in 31 women fulfilling criteria for severe premenstrual syndrome who completed a preceding double-blind, short-term treatment trial that lasted three menstrual cycles. The results showed that the total premenstrual daily symptom report (DSR) scores were lower in the luteal-phase dosing group in each of the three treatment months but the differences were not statistically significant from full-cycle dosing group. Further analysis of each of the 17 DSR items showed significant differences ($P < 0.05$) in favour of luteal-phase dosing for mood swings, nervous tension, feeling out of control and confusion.[13] There are also data to suggest that luteal-phase dosing improves symptoms that continue into the post-menstrual phase.[14]

Evidence level Ib

9.3 Is there any evidence on how SSRIs should be discontinued when used in PMS?

When treating women with PMS, it is recommended that SSRI therapy should be withdrawn gradually to avoid withdrawal symptoms, if given on a continuous basis. This is unnecessary if treatment is with low-dose luteal-phase. ✓

Gastrointestinal disturbances, headache, anxiety, dizziness, paraesthesia, sleep disturbances, fatigue, influenza-like symptoms, and sweating are the most common features of abrupt withdrawal of an SSRI or marked reduction of the dose; the dose should be tapered over a few weeks to avoid these effects.

9.4 Do the benefits outweigh the risks and adverse effects?

Women with PMS treated with SSRIs should be warned of possible adverse effects such as nausea, insomnia and reduction in libido. ✓

SSRIs and SNRIs should be prescribed by psychiatrists and doctors with a special interest, when treating women with PMS, as a few suicides in young people with depression have been reported. ✓

The Medicines and Healthcare products Regulatory Agency (MHRA) has recently cautioned that psychiatrists and those with a specialist interest only should be permitted to prescribe SSRIs and SNRIs because of suicide attempts in a very small number of young patients being treated for depression.[15] This has not been reported for patients being treated for PMS or PMDD.

9.5 Is there evidence for improved efficacy with other SSRI/SNRI regimens?

When treating women with PMS, efficacy and adverse effects of SSRIs may be optimised by the use of luteal-phase regimens with the newer agents. **A**

The use of newer SSRIs, such as citalopram, may produce resolution of symptoms where other SSRIs have failed.[16] Severe PMS also improves significantly with either luteal-phase or symptom-onset dosing of escitalopram with good tolerability.[17] Women with more severe PMS may respond better to luteal-phase dosing than symptom-onset dosing. There are also data supporting the use of the SNRIs for PMDD.[18]

Evidence level Ib

9.6 Are there data comparing SSRIs to ovulation suppression or for synergistic effects of SSRIs with ovulation suppression methods?

Even though there are good reasons why combined therapy may be of benefit, there are no data confirming this possibility.

10. Management of PMS with cycle-modifying hormonal agents

Is there a role for ovulation suppression regimens in the management of PMS?

A number of drugs are available that suppress ovulation but they have significant adverse effects which may influence the efficacy of the treatment or the duration for which they may be given.

10.1 The combined oral contraceptive pill

When treating women with PMS, newer contraceptive pill types may represent effective treatment for PMS and should be considered as one of the first-line pharmaceutical interventions. **B**

Although able to suppress ovulation and used commonly to improve PMS symptoms, the combined pill was initially not shown to be of benefit in randomised prospective trials.[19] This is probably because the daily progestogen in the second-generation pills (i.e. levonorgestrel or norethisterone) regenerate PMS-type symptoms. A new combined contraceptive pill (Yasmin®, Schering Health) contains an anti-mineralocorticoid and anti-androgenic progestogen, drospirenone. Initial studies suggest that this is beneficial. There are data from observational and small randomised trials supporting its efficacy.[20]

A randomised controlled trial of 450 subjects has shown that a lower-dose version of Yasmin (Yaz®, with 20 micrograms ethinylestradiol and 3 mg drospirenone), is effective for treating PMDD.[21] This oral contraceptive pill, however, is not yet available in the UK and is only licensed for PMDD in USA.

10.2 Should use of combined oral contraceptive pill be continuous or cyclical?

When treating women with PMS, emerging data suggest that consideration should be given to use of the contraceptive pill continuously rather than cyclically. ✓

Logically, continuous therapy would seem to be appropriate; however, there are only limited data to support this. A recent study showed that a 168-day extended regimen of drospirenone and ethinylestradiol led to a significant decrease in premenstrual-type symptoms compared with a standard 21/7-day regimen.[22] Further efficacy and safety data are required to allow firm recommendation of this regimen.

10.3 Percutaneous estradiol (patch and implant)

What is the ideal dose and route?

Percutaneous estradiol, either as an implant or as a patch, combined with cyclical progestogen, has been shown to be effective for the management of physical and psychological symptoms of severe PMS. **A**

When treating women with PMS, alternative barrier or intrauterine methods of contraception should be used when estradiol (patches and implant) are used to suppress ovulation. ✓

Oral preparations give insufficient estradiol levels to suppress ovarian activity. A placebo-controlled trial demonstrated that implant 17β estradiol combined with cyclical progestogen is effective for the management of physical and psychological symptoms of severe PMS. Administered as a 100-microgram implant, this proved to be highly effective when compared with placebo.[23] Both implants and patches have been evaluated in controlled trials. Implants are less commonly used for PMS since patches have become available.

In a randomised, double-blind, placebo-controlled trial of 20 women with crossover at 3 months, transdermal estradiol patches (200 micrograms) was assessed and found to be highly effective.[24] Women in the active treatment group received two 100-microgram estradiol patches followed by placebo and 20 women were treated in reverse order. Significant improvements occurred after changing to active treatment in five of six negative MDQ (Menstrual Distress Questionnaire) symptom clusters and in six of ten PDQ (Premenstrual Distress Questionnaire) symptoms. There was concern that estradiol 200 micrograms twice weekly was still too high a dose to be used as long-term therapy. A subsequent randomised study[25] showed that 100-microgram estradiol patches twice weekly were as effective as 200 micrograms in reducing symptom levels in severe premenstrual syndrome and this dosage was better tolerated.

Evidence level Ib

How can progestogen intolerance be minimised to maximise efficacy?

When treating women with PMS, treatment with the lowest possible dose of progestogen is recommended to minimise adverse effects. A

Women should be informed that low systemic levels of levonorgestrel released by the levonorgestrel intrauterine system (LNG-IUS) can initially produce PMS-type adverse effects (as well as bleeding). ✓

Use of continuous estradiol normally necessitates the addition of cyclical progestogen (10–12 days) to avoid endometrial hyperplasia in women who have a uterus. A study of long-term treatment with the 100-microgram dosage using a low dose of cyclical norethisterone acetate (NETA) (1 mg) (10 days/cycle) has shown benefit over placebo over eight cycles with continued improvement in a 6-month extension.[26] Intrauterine administration of progestogen has the potential to avoid systemic absorption and hence avoid progestogenic effects. The LNG-IUS as progestogen replacement can maximise efficacy by minimising PMS-like adverse effects. Low systemic levels of levonorgestrel released by the LNG-IUS can initially produce PMS-type adverse effects (as well as bleeding) in the progestogen intolerant woman. Despite this, it might still be of advantage to use a LNG-IUS or vaginal progesterone (cyclogest pessaries or crinone gel 8% – not licensed for this indication in this age group) in the progestogen intolerant woman.[26,27]

Evidence level Ib

10.4 What is the effect of estradiol on the premenopausal endometrium and breast tissue?

When treating women with PMS with estradiol, women should be informed that there are insufficient data to advise on the long-term effects on breast and endometrial tissue. C

There is insufficient evidence to determine whether there is an increased risk of endometrial or breast carcinoma in premenopausal women using percutaneous patches and cyclical progestogen or LNG-IUS. Randomised placebo-controlled trial data in large populations looking at major outcome measures over a long period of time are lacking.

Evidence level IV

10.5 Danazol

What is the evidence for efficacy of danazol in the treatment of PMS?

Women with PMS should be advised that, although treatment with low-dose danazol (200 mg twice daily) is effective, its use should be considered in light of its potential irreversible virilising effects. **A**

Women treated with danazol for PMS should be advised to use contraception during treatment. ✓

Cycle suppression may be achieved using danazol, an androgenic steroid. Mansel *et al.* first assessed the effect of danazol on PMS symptoms in a study randomised on the basis of the complaint breast tenderness.[28] It demonstrated benefit for breast but not PMS symptoms. Other studies have shown greater benefit.[29,30] A randomised, double-blind, crossover study compared three successive cycles of danazol at a dose of 200 mg twice daily with three cycles of placebo.[30] Twenty-eight of 31 women completed at least one cycle of treatment while recording symptoms. From this study, the authors demonstrated that danazol at a dose of 200 mg twice daily was superior to placebo for the relief of severe PMS during the premenstrual period. However, this superiority is muted or even reversed when the entire cycle is considered. This may be explained by the fact that danazol therapy does have some nuisance effects which may interfere with the usual symptom-free late follicular phase of women with PMS. One solution suggested for this problem might be to limit danazol treatment to the luteal phase only. One study of danazol given only in the luteal phase demonstrated improvement in breast symptoms only but with minimal adverse effects.[31]

Evidence level Ib

10.6 Gonadotrophin-releasing analogues

How effective are GnRH analogues for treating severe PMS?

Early resort to GnRH therapy is not recommended and prolonged use should be retained for women with the most severe symptoms. ✓

GnRH analogue therapy results in profound cycle suppression and elimination of premenstrual symptoms. Lack of efficacy suggests a questionable diagnosis rather than a limitation of therapy. **A**

When treating women with severe PMS with GnRH analogues:

- **therapy should be recommended as second- or even third-line treatment**
- **therapy should not be used as a first-line treatment, except for women with the most severe PMS, due to its hypoestrogenic effects**
- **add-back hormone therapy is recommended**
- **low-dose therapy is not recommended.** **A**

GnRH analogues have been successfully employed to suppress ovarian steroid production. A recent meta-analysis of GnRH analogues has confirmed their efficacy compared with placebo.[32] Seventy-one women on active treatment were identified in seven trials. The overall standardised mean difference (SMD) for all trials was –1.19 (CI –1.88 to –0.51) (Cohen criteria: 0.3 small, 0.5 medium, 1.0 large effect) The odds ratio for benefit was 8.66 (95% CI 2.52–30.26). The SMD was –1.43 and OR 13.38 (CI 3.9–46.0) if data were taken only from anovulation trials. Efficacy of symptom relief was greater for physical than for behavioural symptoms: physical SMD –1.16 (CI –1.53 to –0.79); behavioural SMD –0.68 (CI –1.11 to –0.25) but difference was not significant $P = 0.484$.

Evidence level Ia

Is there any evidence for low-dose GnRH analogue therapy?

One trial used low-dose GnRH to eliminate symptoms without ovulation suppression; however, it showed no benefit over placebo.[33]

Evidence level Ib

What is the best type of add-back therapy and does add-back hormone therapy limit efficacy?

When treating women with PMS where add-back hormone therapy is required, continuous combined HRT or tibolone should be recommended, as it reduces menopausal symptoms without reappearance of PMS-like progestogenic effects.

A

Data show that symptoms due to the hypoestrogenic state can be virtually eliminated and bone mineral density can be maintained by the use of HRT. Continuous combined therapy or tibolone is preferable to sequential combined therapy in order to minimise the risks of symptom reappearance of PMS-like progestogenic effects.[34,35] Overall SMD favoured neither GnRH alone or GnRH with add back (CI –0.34 to 0.59) demonstrating there is no reversal of the beneficial effect of GnRH when using add-back.[34]

Evidence level Ia

How long can treatment be safely continued with/without add-back therapy?

When treating women with PMS, with GnRHa therapy:

- **Treatment should only be continued for 6 months when used alone.**
- **Treatment should be combined with HRT to reduce trabecular bone density loss. Women on long-term treatment should have annual measurement of bone mineral density (ideally by dual energy X-ray absorptiometry). Treatment should be stopped if bone density declines significantly in scans performed 1 year apart.**
- **General advice about how exercise, diet and smoking affect bone mineral density should be given.**

✓

A

B

Because symptoms return with the return of ovarian function, therapy may (rarely) have to be continued indefinitely; this is precluded by significant trabecular bone loss which can occur with only 6 months of therapy. It should be noted that GnRH analogues are only licensed for use for 6 months when used alone and are not licensed to treat PMS at all.The use of GnRH analogues with add-back estrogen or tibolone reduces trabecular bone loss. However, bone density should be monitored in women using analogues for more than 6 months, as bone loss may still occur in some individuals.[36]

Evidence level Ia

11. Progesterone and progestogens

11.1 Are progestogens and progesterone effective in treating PMS?

There is insufficient evidence to recommend the routine use of progesterone or progestogens for women with PMS.

A

A recent meta-analysis of all published studies for progestogen and progesterone treatment of PMS demonstrated no benefit for treatment.[37] The objective of this systematic review was to evaluate the efficacy of progesterone and progestogens in the management of premenstrual syndrome.Ten trials of progesterone therapy (531 women) and four trials of progestogen therapy (378 women) were reviewed. The main outcome measure was a reduction in overall symptoms of premenstrual syndrome. All the trials of progesterone (by both routes of administration) showed no clinically significant difference between progesterone and placebo. For progestogens, the overall SMD for reduction in symptoms showed a slight nonsignificant difference in favour of progestogen, with the

Evidence level Ia

mean difference being –0.036 (95% CI –0.059 to –0.014). The meta-analysis of this systematic review suggested that there was no published evidence to support the use of either exogenous progesterone or progestogens in the management of premenstrual syndrome.[38]

Evidence level Ia

Progestogens such as norethisterone and levonorgestrel can produce PMS-like effects owing to competition for the mineralocorticoid, androgen and CNS receptors. It is therefore not surprising that the data for their efficacy are poor. Even though the higher-dose progestogenic preparations such as depot medroxyprogesterone acetate are capable of suppressing the ovarian cycle, they often replace cyclical PMS with low-grade background symptoms. Natural progesterone such as micronised oral progesterone, on the other hand, is a natural diuretic and a CNS anxiolytic. As such, there is some logic in using this preparation for treatment of severe PMS but larger studies are required.[26]

Evidence level IIa

11.2 Is there any evidence for the efficacy of progesterone in PMS?

Only one of many studies of progesterone has suggested benefit.[39] Women were randomised to use progesterone pessaries (400 mg twice daily) or matching placebo, by vaginal or rectal administration, from 14 days before the expected onset of menstruation until onset of vaginal bleeding for four consecutive cycles; 45 general practitioners identified a total of 281 women. The main outcome variables were changes in the severity of each woman's most severe symptoms and in the average score of all the women's symptoms. The response to progesterone was greater than to placebo during each cycle; the difference was clinically and statistically significant.

Evidence level Ib

12. Surgical approach (hysterectomy and bilateral salpingo-oophorectomy)

12.1 Can surgical management of PMS ever be justified?

When treating women with severe PMS, hysterectomy and bilateral salpingo-oophorectomy has been shown to be of benefit.

C

Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) is a permanent form of ovulation suppression, as this removes the ovarian cycle completely. The procedure is only rarely performed for this indication as a lesser alternative can usually be found. However, observational questionnaire data suggest a highly beneficial effect in the selected women undergoing TAH-BSO, the majority of whom are highly satisfied following this procedure.[40]

Evidence level III

12.2 Should the efficacy of this treatment always be predicted by the prior use of GnRH analogues?

When treating women with PMS, surgery should not be contemplated without preoperative use of GnRH analogues as a test of cure and to ensure that HRT is tolerated. Such therapy should be reserved for extremely severe PMS sufferers in whom other treatment has failed.

✓

Preoperative GnRH analogues appear of value in predicting the effects of oophorectomy, although such a strategy has never been tested scientifically. It is not mandatory but would seem important, particularly when surgery is being contemplated in women of a younger age group (below 45 years).[32]

12.3 How vital is the role of continuing hormone therapy?

When treating women with PMS, HRT should be considered in women undergoing surgical oophorectomy before the age of 50 years.

✓

Without adequate hormone therapy, PMS symptoms are replaced by those of the menopause. Consideration should also be given to replacing testosterone, as the ovaries are a major production source (50%) and

deficiency could result in distressing low libido (hypoactive sexual desire disorder).[41] Women who have had a hysterectomy with ovarian conservation would be expected to continue to have cyclical symptoms even in the absence of menstruation (ovarian cycle syndrome).[42]

13. Summary

The aetiology and management of premenstrual syndrome continues to be poorly understood and in many cases inadequately managed. It is the cause of considerable morbidity and the health burden has been consistently underestimated. It is imperative that properly conducted research continues to be funded. It is only through this work that clinicians will be able to practice in a truly evidence-based way to treat this condition effectively. It is important that appropriate multidisciplinary services are provided in an appropriate setting throughout the country.

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APPENDIX 1

DAILY RECORD OF SEVERITY OF PROBLEMS

Please print and use as many sheets as you need for at least two FULL months of ratings.

Name or Initials _____

Month/Year _____

Each evening note the degree to which you experienced each of the problems listed below. Put an "x" in the box which corresponds to the severity: 1 - not at all, 2 - minimal, 3 - mild, 4 - moderate, 5 - severe, 6 - extreme.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
	Enter day (Monday="M", Thursday="R", etc) >																															
	Note spotting by entering "S" >																															
	Note menses by entering "M" >																															
	Begin rating on correct calendar day >																															
1	Felt depressed, sad, "down,", or "blue" or felt hopeless; or felt worthless or guilty	6 5 4 3 2 1																														
2	Felt anxious, tense, "keyed up" or "on edge"	6 5 4 3 2 1																														
3	Had mood swings (i.e., suddenly feeling sad or tearful) or was sensitive to rejection or feelings were easily hurt	6 5 4 3 2 1																														
4	Felt angry, or irritable	6 5 4 3 2 1																														
5	Had less interest in usual activities (work, school, friends, hobbies)	6 5 4 3 2 1																														
6	Had difficulty concentrating	6 5 4 3 2 1																														
7	Felt lethargic, tired, or fatigued; or had lack of energy	6 5 4 3 2 1																														
8	Had increased appetite or overate; or had cravings for specific foods	6 5 4 3 2 1																														
9	Slept more, took naps, found it hard to get up when intended; or had trouble getting to sleep or staying asleep	6 5 4 3 2 1																														
10	Felt overwhelmed or unable to cope; or felt out of control	6 5 4 3 2 1																														
11	Had breast tenderness, breast swelling, bloated sensation, weight gain, headache, joint or muscle pain, or other physical symptoms	6 5 4 3 2 1																														
	At work, school, home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency	6 5 4 3 2 1																														
	At least one of the problems noted above caused avoidance of or less participation in hobbies or social activities	6 5 4 3 2 1																														
	At least one of the problems noted above interfered with relationships with others	6 5 4 3 2 1																														

APPENDIX 2

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

This guideline was produced on behalf of the Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists by **Dr N Panay MRCOG, London.**

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

The Guidelines review process will commence in December 2010
unless otherwise indicated