BJOG An International Journal of Obstetrics and Gynaecology

Royal College of Obstetricians & Gynaecologists

Management of Premenstrual Syndrome

Green-top Guideline No. 48

February 2017

Please cite this paper as: Green LJ, O'Brien PMS, Panay N, Craig M on behalf of the Royal College of Obstetricians and Gynaecologists. Management of premenstrual syndrome. BJOG 2017;124:e73–e105.

DOI: 10.1111/1471-0528.14260

Management of Premenstrual Syndrome

This is the second edition of this guideline, which was first published in 2007 under the same title.

Executive summary of recommendations

How is premenstrual syndrome (PMS) diagnosed?

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

A symptom diary should be completed by the patient prior to commencing treatment. ✓

Gonadotrophin-releasing hormone (GnRH) analogues may be used for 3 months for a definitive diagnosis if the completed symptom diary alone is inconclusive. [*New 2016*] ✓

What aspects are involved in delivering a service to women with PMS?

When should women with PMS be referred to a gynaecologist?

Referral to a gynaecologist should be considered when simple measures (e.g. combined oral contraceptives [COCs], vitamin B6, selective serotonin reuptake inhibitors [SSRIs]) have been explored and failed and when the severity of the PMS justifies gynaecological intervention. ✓

Who are the key health professionals to manage women with severe PMS?

Women with severe PMS may benefit from being managed by a multidisciplinary team comprising a general practitioner, a general gynaecologist or a gynaecologist with a special interest in PMS, a mental health professional (psychiatrist, clinical psychologist or counsellor) and a dietician. [*New 2016*] ✓

How is PMS managed?

Are complementary therapies efficacious in treating PMS?

Women with PMS should be informed that there is conflicting evidence to support the use of some complementary medicines. C

An integrated holistic approach should be used when treating women with PMS. ✓

Interactions with conventional medicines should be considered. ✓

Is there a role for cognitive behavioural therapy (CBT) and other psychological counselling techniques?

When treating women with severe PMS, CBT should be considered routinely as a treatment option. A

Hormonal medical management of PMS

Which COC has the best evidence for managing PMS, including regimens delivering ethinylestradiol?

When treating women with PMS, drospirenone-containing COCs may represent effective treatment for PMS and should be considered as a first-line pharmaceutical intervention. [*New 2016*] B

What is the optimum COC pill regimen, e.g. continuous, cyclical or flexible?

When treating women with PMS, emerging data suggest use of the contraceptive pill continuously rather than cyclically. ✓

How efficacious is percutaneous estradiol?

Percutaneous estradiol combined with cyclical progestogens 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 is used to suppress ovulation. ✓

How can the return of PMS symptoms be avoided during estrogen therapy with progestogenic protection?

When using transdermal estrogen to treat women with PMS, the lowest possible dose of progesterone or progestogen is recommended to minimise progestogenic adverse effects. [*New 2016*] A

Women should be informed that low levels of levonorgestrel released by the levonorgestrel-releasing intrauterine system (LNG-IUS) 52 mg can initially produce PMS-type adverse effects (as well as bleeding problems). [*New 2016*] ✓

Micronised progesterone is theoretically less likely to reintroduce PMS-like symptoms and should therefore be considered as first line for progestogenic opposition rather than progestogens. [*New 2016*] ✓

What is the optimum regimen for prevention of endometrial hyperplasia?

When treating women with percutaneous estradiol, a cyclical 10–12 day course of oral or vaginal progesterone or long-term progestogen with the LNG-IUS 52 mg should be used for the prevention of endometrial hyperplasia. [*New 2016*] ✓

When using a short duration of progestogen therapy, or in cases where only low doses are tolerated, there should be a low threshold for investigating unscheduled bleeding. [*New 2016*] ✓

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

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

For how long can estradiol be used safely and what is the risk of recurrence?

Due to the uncertainty of the long-term effects of opposed estradiol therapy, treatment of women with PMS should be on an individual basis, taking into account the risks and benefits. [*New 2016*] ✓

What is the evidence for efficacy and adverse effects 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 in the luteal phase for breast symptoms, it also has potential irreversible virilising effects. [*New 2016*] A

Women treated with danazol for PMS should be advised to use contraception during treatment due to its potential virilising effects on female fetuses. [*New 2016*] ✓

How effective are GnRH analogues for treating severe PMS?

GnRH analogues are highly effective in treating severe PMS. [*New 2016*] A

When treating women with PMS, GnRH analogues should usually be reserved for women with the most severe symptoms and not recommended routinely unless they are being used to aid diagnosis or treat particularly severe cases. [*New 2016*] ✓

How should women with PMS receiving add-back therapy be managed?

When treating women with severe PMS using GnRH analogues for more than 6 months, add-back hormone therapy should be used. [*New 2016*] A

When add-back hormone therapy is required, continuous combined hormone replacement therapy (HRT) or tibolone is recommended. A

Women should be provided with general advice regarding the effects of exercise, diet and smoking on bone mineral density (BMD). ✓

Women on long-term treatment should have measurement of BMD (ideally by dual-energy X-ray absorptiometry [DEXA]) every year. Treatment should be stopped if bone density declines significantly. [*New 2016*] D

Can GnRH analogues be useful in clarification of diagnostic category?

When the diagnosis of PMS is unclear from 2 months' prospective Daily Record of Severity of Problems (DRSP) charting, GnRH analogues can be used to establish and/or support a diagnosis of PMS. [*New 2016*] ✓

What is the role for progesterone and progestogen preparations in treating PMS?

There is good evidence to suggest that treating PMS with progesterone or progestogens is not appropriate. [*New 2016*] A

There is no evidence to support the use of the LNG-IUS 52 mg alone to treat PMS symptoms. Its role should be confined to opposing the action of estrogen therapy on the endometrium. ✓

Non-hormonal medical management of PMS

How do selective SSRIs work in PMS and how should they be given?

SSRIs should be considered one of the first-line pharmaceutical management options in severe PMS. [*New 2016*] A

What is the efficacy of SSRIs in treatment of PMS?

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

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

SSRIs should be discontinued gradually to avoid withdrawal symptoms, if given on a continuous basis. ✓

What are the risks and adverse effects of SSRIs?

Women with PMS treated with SSRIs should be warned of the possible adverse effects such as nausea, insomnia, somnolence, fatigue and reduction in libido. [*New 2016*] ✓

Is there evidence for improved efficacy with other SSRI regimens?

When using SSRIs to treat PMS, efficacy may be improved and adverse effects minimised by the use of luteal-phase regimens with the newer agents. [*New 2016*] A

What preconception and early pregnancy advice should be given regarding SSRIs/serotonin–noradrenaline reuptake inhibitors (SNRIs)?

Women should be provided with prepregnancy counselling at every opportunity. They should be informed that PMS symptoms will abate during pregnancy and SSRIs should therefore be discontinued prior to and during pregnancy. [*New 2016*] ✓

Women should be informed how to safely stop SSRIs. [*New 2016*] ✓

Women with PMS who become pregnant while taking an SSRI/SNRI should be aware of the possible, although unproven, association with congenital malformations. They should be reassured that if such an association does exist, it is likely to be extremely small when compared to the general population. [*New 2016*] B

Are diuretics efficacious in the treatment of PMS?

Spironolactone can be used in women with PMS to treat physical symptoms. [*New 2016*] C

How can PMS be managed surgically?

Can surgical management of PMS be justified and is it efficacious?

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

When treating women with PMS, hysterectomy and bilateral oophorectomy can be considered when medical management has failed, long-term GnRH analogue treatment is required or other gynaecological conditions indicate surgery. [*New 2016*] ✓

Should the efficacy of surgery 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. ✓

What is the role of HRT after surgical management?

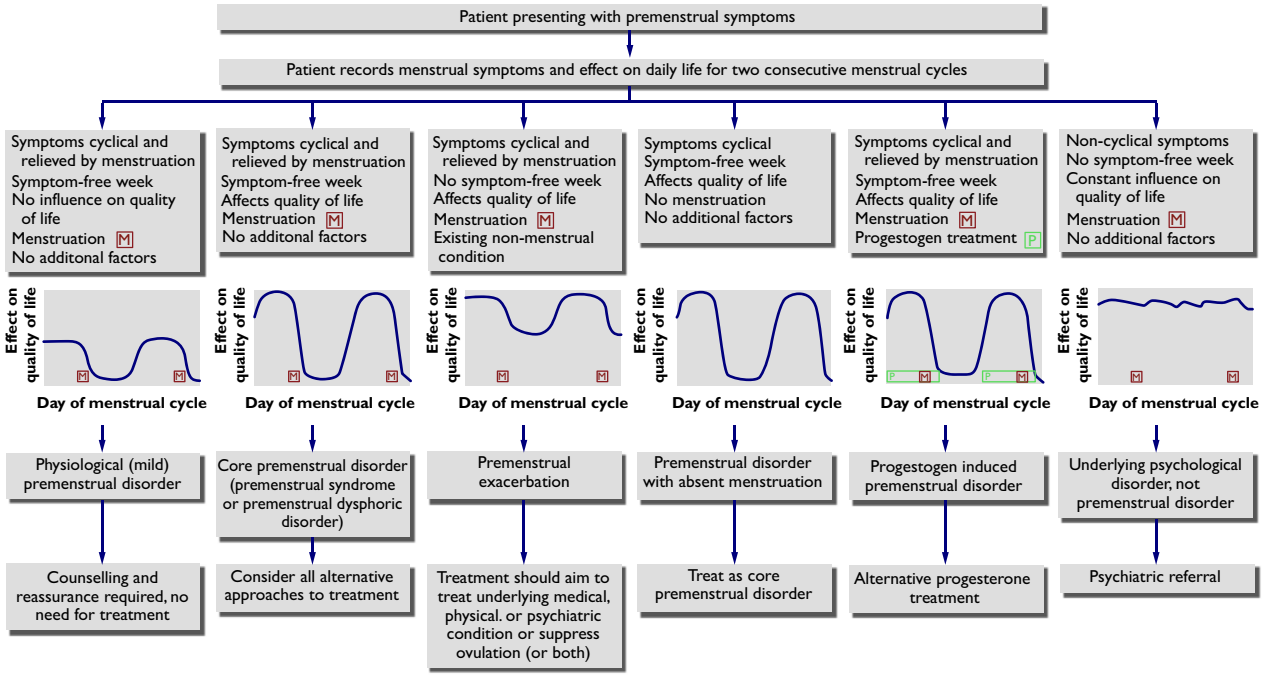
Women being surgically treated for PMS should be advised to use HRT, particularly if they are younger than 45 years of age. [*New 2016*] ✓

Is there a role for endometrial ablation, oophorectomy or hysterectomy alone?

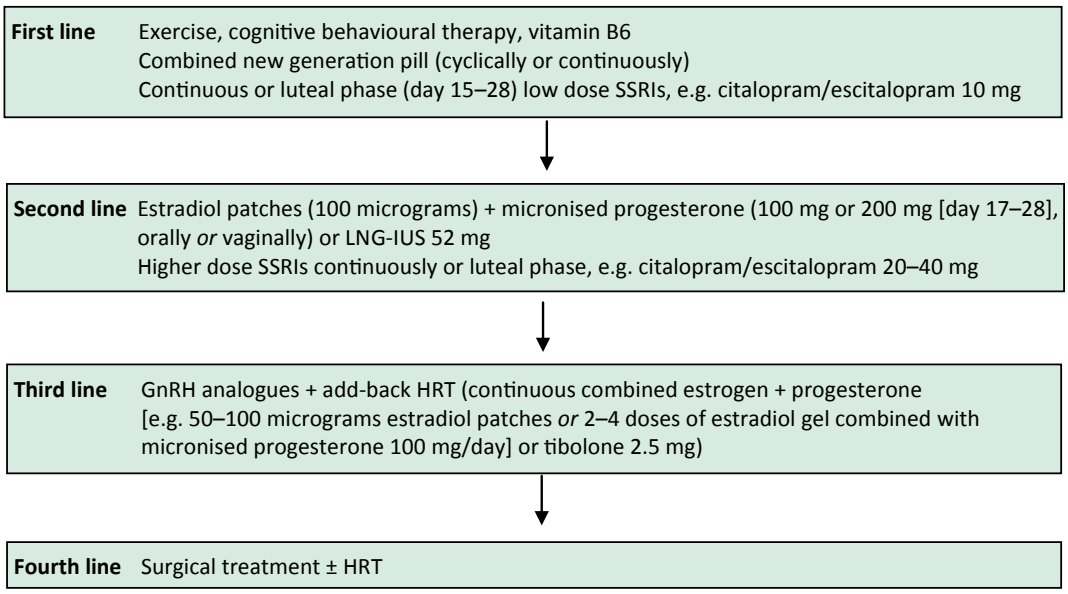
When treating women with severe PMS, endometrial ablation and hysterectomy with conservation of the ovaries are not recommended. [*New 2016*] ✓

Bilateral oophorectomy alone (without removal of the uterus) will necessitate the use of a progestogen as part of any subsequent HRT regimen and this carries a risk of reintroduction of PMS-like symptoms (progestogen-induced premenstrual disorder). [*New 2016*] ✓

Classification of PMS



How PMS is treated – a decision-making algorithm



1. Purpose and scope

The aim of this guideline is to review the diagnosis, classification and management of premenstrual syndrome (PMS). The evidence for pharmacological and nonpharmacological treatments is examined.

2. Introduction and background epidemiology

Since the 2007 guideline, there has been considerable work by the International Society for Premenstrual Disorders (ISPMD) and the National Association for Premenstrual Syndrome (NAPS) to achieve consensus on the recognition, diagnosis, classification and management of PMS. Misdiagnosis of PMS (e.g. confusion with bipolar disorder) and the use of a wide range of treatments, often with little evidence for effectiveness and safety, demand that these issues are addressed.

2.1 Definition of PMS

PMS encompasses a vast array of psychological symptoms such as depression, anxiety, irritability, loss of confidence and mood swings. There are also physical symptoms, typically bloatedness and mastalgia. It is the timing, rather than the types of symptoms, and the degree of impact on daily activity that supports a diagnosis of PMS. The character of symptoms in an individual patient does not influence the diagnosis. In order to differentiate physiological menstrual symptoms from PMS, it must be demonstrated that symptoms cause significant impairment to the individual during the luteal phase of the menstrual cycle.[1]

2.2 Classification of PMS (ISPMD consensus)

Core premenstrual disorders (PMDs) are the most commonly encountered and widely recognised type of PMS. As with all PMDs, symptoms must be severe enough to affect daily functioning or interfere with work, school performance or interpersonal relationships. The symptoms of core PMDs are nonspecific and recur in ovulatory cycles. They must be present during the luteal phase and abate as menstruation begins, which is then followed by a symptom-free week. There is no limit on the type or number of symptoms experienced; however, some individuals will have predominantly psychological, predominantly somatic or a mixture of symptoms (Appendix II).

There are also PMDs that do not meet the criteria for core PMDs. These are called 'variant' PMDs and fall into four subtypes.

1. '**Premenstrual exacerbation of an underlying disorder**', such as diabetes, depression, epilepsy, asthma and migraine. These patients will experience symptoms relevant to their disorder throughout the menstrual cycle.
2. '**Non-ovulatory PMDs**' occur in the presence of ovarian activity without ovulation. This is poorly understood due to a lack of evidence, but it is thought that follicular activity of the ovary can instigate symptoms.
3. '**Progestogen-induced PMDs**' are caused by exogenous progestogens present in hormone replacement therapy (HRT) and the combined oral contraceptive (COC) pill. This reintroduces symptoms to women who may be particularly sensitive to progestogens. Although progestogen-only contraceptives may introduce symptoms, as they are noncyclical they are not included within variant PMDs and are considered adverse effects (probably with similar mechanisms) of continuous progestogen therapy.

4. '**PMDs with absent menstruation**' include women who still have a functioning ovarian cycle, but for reasons such as hysterectomy, endometrial ablation or the levonorgestrel-releasing intrauterine system (LNG-IUS) they do not menstruate.[2]

An additional term, premenstrual dysphoric disorder (PMDD) classified by the American Psychiatric Association in 1994[3] requires fulfilment of strict criteria. The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) demands five out of 11 stipulated symptoms, one of which must include mood.[4] The symptoms must strictly occur in the luteal phase and must be severe enough to disrupt daily functioning. However, these restrictive criteria may exclude women with a narrow range of severe symptoms who should receive treatment.

Care must be taken not to label women with underlying psychiatric or somatic disorders that do not appear to be influenced by the menstrual cycle as having PMS.

2.3 Prevalence and aetiology

Four in ten women (40%) experience symptoms of PMS and of these 5–8% suffer from severe PMS.[5] A cross-sectional survey of 929 women based in Southampton who completed a 6-week prospective symptom diary revealed a 24% prevalence of premenstrual symptoms.[6] Although the aetiology remains uncertain, it revolves around the ovarian hormone cycle, which is reinforced by the absence of PMS prior to puberty, during pregnancy and after the menopause. Currently two theories predominate and appear interlinked. The first suggests that some women are 'sensitive' to progesterone and progestogens, since the serum concentrations of estrogen or progesterone are the same in those with or without PMS. The second theory implicates the neurotransmitters serotonin and γ-aminobutyric acid (GABA). Serotonin receptors are responsive to estrogen and progesterone, and selective serotonin reuptake inhibitors (SSRIs) are proven to reduce PMS symptoms. GABA levels are modulated by the metabolite of progesterone, allopregnanolone, and in women with PMS the allopregnanolone levels appear to be reduced.[7]

3. Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews and DARE), EMBASE, Trip, MEDLINE, Psych INFO, CINAHL, the Allied and Complementary Medicine Database (AMED), and the British Nursing Index (BNI) were searched. The search was restricted to articles published between 2005 and March 2014 in the English language. The databases were searched using the relevant Medical Subject Headings (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', 'PMD', 'LLPDD', 'PMT'. The search was restricted to humans and there were no language restrictions.

Where possible, recommendations are based on available evidence. In the absence of published evidence, these have been annotated as 'good practice points'. Further information about the assessment of evidence and the grading of recommendations may be found in Appendix I.

4. How is PMS diagnosed?

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

A symptom diary should be completed by the patient prior to commencing treatment. ✓

Gonadotrophin-releasing hormone (GnRH) analogues may be used for 3 months for a definitive diagnosis if the completed symptom diary alone is inconclusive. ✓

There are many patient-rated questionnaires available. However, the Daily Record of Severity of Problems (DRSP) remains the most widely used and is simple for patients to use.[2] The DRSP has also been consistently shown to provide a reliable and reproducible record of symptoms (see Appendix III).[8] The Premenstrual Symptoms Screening Tool (PSST)[9] is another patient-rated questionnaire; however, it is retrospective and has been validated for screening but not diagnosis. Various attempts at electronic data capture have been attempted. Commercially available diagnostic apps are now available, but these require validation. Another easily accessible symptom diary exists on the NAPS website (www.pms.org.uk). This diary is not validated but is sufficient to be used in the context of clinical practice.[10]

Before any form of treatment is initiated, symptom diaries should be completed over at least two consecutive menstrual cycles. Treatment may improve symptoms, therefore masking underlying PMS, but it can also create a pattern of symptoms incompatible with a diagnosis of PMS, making the interpretation of DRSP charts confusing. These charts should be brought by the patient to any future appointments.

Symptom diaries can sometimes be confusing and inconclusive: this is most likely to occur in those patients with variant PMDs. GnRH analogues, which are widely used within gynaecology, can be useful in separating those with and those without PMS by inhibiting cyclical ovarian function. These should be used for 3 months to establish a definitive diagnosis. This is to allow a month for the agonist to generate a complete hormonal suppressive effect, as well as providing 2 months' worth of symptom diaries.

5. What aspects are involved in delivering a service to women with PMS?

5.1 When should women with PMS be referred to a gynaecologist?

Referral to a gynaecologist should be considered when simple measures (e.g. COCs, vitamin B6, SSRIs) have been explored and failed and when the severity of the PMS justifies gynaecological intervention. ✓

General practitioners will manage the majority of cases of PMS; therefore, awareness of the condition together with up-to-date information on its management is essential. Referral to secondary care should be reserved for those with confirmed PMS in whom simple measures have failed to control symptoms. In women whose symptom diaries demonstrate noncyclical symptoms, an underlying psychiatric or somatic disorder should be considered.

5.2 *Who are the key health professionals to manage women with severe PMS?*

Women with severe PMS may benefit from being managed by a multidisciplinary team comprising a general practitioner, a general gynaecologist or a gynaecologist with a special interest in PMS, a mental health professional (psychiatrist, clinical psychologist or counsellor) and a dietician. ✓

While this set-up is desirable, it is not widely available or implemented within the National Health Service (NHS). There are specialist clinics within tertiary centres to which patients can be referred. However, it is likely that the general practitioner will remain key in facilitating potential treatments. A multidisciplinary team can offer women an individualised management plan utilising a range of treatments, such as cognitive behavioural therapy (CBT) and lifestyle interventions.[11]

6. How is PMS managed?

6.1 *Are complementary therapies efficacious in treating PMS?*

Women with PMS should be informed that there is conflicting evidence to support the use of some complementary medicines. C

An integrated holistic approach should be used when treating women with PMS. ✓

Interactions with conventional medicines should be considered. ✓

Although there is limited evidence to support the use of complementary therapies, some women with PMS may benefit from a holistic approach.[12] This is particularly important for women in whom hormonal therapy is contraindicated. It is important to evaluate evidence carefully for PMS as there is a 36–43% placebo response.[13,14]

Evidence level 1–

Table 1 summarises current research into the benefits of selected complementary therapies for the treatment of PMS.

Unsaturated fatty acids, as contained in evening primrose oil, have been shown in one prospective randomised trial[15] to improve menstrual symptoms compared with placebo at both 1 g/day and 2 g/day dosages. There was no measurable change in cholesterol levels.

Dante et al.[16] conducted a systematic review into herbal remedies for PMS. Four of the trials, including almost 600 women, supported the use of *Vitex agnus castus* L. (also known as chasteberry). However, this study concluded that there were inadequate safety data to support its use.

Whelan et al.[17] conducted a systematic review of 29 randomised controlled trials (RCTs). Two of these studies (n = 499) revealed consistent evidence for calcium in alleviating both physical and psychological symptoms of PMS. The evidence for both vitamin B6 and *Vitex* was contradictory in this review and therefore advice could not be given for either. Due to the lack of power, reliable recommendations cannot be provided.

Table 1. Summary of evidence for selected complementary therapies

Complementary therapy	Benefit	Types of studies	Numbers in the study	Note
Exercise[22–25]	Some benefit	Nonrandomised and randomised	72 (4 published studies)	High quality studies recommended.
Reflexology[26]	Some benefit	Randomised	35	
Vitamin B6[27–39]	Mixed results	Double-blind Randomised Cross-over	1067 (13 published studies)	Peripheral neuropathy with high doses (most studies performed using higher doses). Department of Health restricts the daily dose to 10 mg.
Magnesium[37,40,41]	Mixed results	Double-blind Randomised Cross-over	153 (3 published studies)	Used in premenstrual phase.
Multivitamins[42–45]	Unknown	–	400 (several published studies)	Unclear which are the active ingredients.
Calcium/ vitamin D[46,47]	Yes	Double-blind Randomised Cross-over	499 (2 published studies)	
Isoflavones[48,49]	Mixed results	Double-blind Randomised Cross-over	72 (2 published studies)	May benefit menstrual migraine.
Vitex agnus castus L.[19,39,50–54]	Yes	Double-blind Randomised	923 (7 published studies)	There is no standardised preparation.
St John's Wort[20,21,55,56]	Mixed results	Double-blind Placebo-controlled	401 (4 published studies)	May benefit physical and behavioural symptoms. Many withdrew from one study due to adverse effects. Significant interactions with conventional medicines. The British National Formulary advises avoid concomitant use with SSRIs.
Ginkgo biloba[57,58]	Some benefit	Double-blind Placebo-controlled	233 (2 published studies)	
Saffron[59]	Yes	Double-blind Placebo-controlled	47	Further data before recommendation.
Evening primrose oil[15,60–63]	Some benefit	Double-blind Placebo-controlled Cross-over	215 (4 published studies)	May benefit women with cyclical breast symptoms.

Table 1. (Continued)

Complementary therapy	Benefit	Types of studies	Numbers in the study	Note
Acupuncture[64–73]	Some benefit	Case–control	235 (10 published studies)	High risk of bias. Further data before recommendation.
Lemon balm[74]	Some benefit	Double-blind Placebo-controlled	100 (1 published study)	PMS severity quantified by PSST. Further data before recommendation.
Curcumin[75]	Some benefit	Double-blind Placebo-controlled	70 (1 published study)	PMS severity quantified by an unvalidated symptom score. Further data before recommendation.
Wheat germ[76]	Some benefit	Triple-blind Placebo-controlled	84 (1 published study)	PMS severity quantified by an unvalidated symptom score. Further data before recommendation.

A systematic review[18] focusing on the use of *Vitex* illustrated that in four out of five discrete placebo-controlled trials and two comparator trials, *Vitex* was superior to placebo, pyridoxine and magnesium in the treatment of PMS. In another study, it appeared comparable to fluoxetine for PMDD.[16] The safety of *Vitex* is described as excellent, with adverse effects being infrequent and mild.[18,19] Studies have shown a dose dependent treatment response; however, due to the variability in quality and content of preparations a dosage range to treat PMS cannot be recommended.

RCTs including St John's Wort (*Hypericum perforatum*) show conflicting results. A trial[20] including 36 women with mild PMS showed significant improvements in physical and behavioural symptoms but no improvement in mood or pain-related symptoms. Another trial[21] including 125 women found no evidence of benefit but felt that this may be attributable to low statistical power. St John's Wort interacts with other medications, in particular it should not be used concurrently with SSRIs and can render low dose COCs ineffective.

Evidence level 1–

6.2 *Is there a role for CBT and other psychological counselling techniques?*

When treating women with severe PMS, CBT should be considered routinely as a treatment option.

A

Hunter et al.[77] conducted a randomised trial comparing fluoxetine, CBT and the combination of fluoxetine and CBT for the treatment of PMDD. After a 6-month treatment period, all three treatment groups showed evidence of benefit, which was similar for each group, with fluoxetine combined with CBT no more effective than the two component therapies used separately. Fluoxetine showed quicker improvements; however at follow-up CBT was associated with better maintenance of treatment effects compared with fluoxetine.

Evidence level 1+

A meta-analysis identified five RCTs testing CBT against a control intervention. The evidence was poor due to a high risk of bias but demonstrated a significant reduction in depression, anxiety and behavioural problems. If CBT proves successful to a patient it would avoid pharmacotherapy and potential adverse effects.[78]

Evidence level 1–

6.3 *Hormonal medical management of PMS*

6.3.1 What is the role of cycle-modifying agents in managing PMS?

6.3.1.1 Which COC has the best evidence for managing PMS, including regimens delivering ethinylestradiol?

When treating women with PMS, drospirenone-containing COCs may represent effective treatment for PMS and should be considered as a first-line pharmaceutical intervention. B

Despite the combined pill's ability to suppress ovulation, studies initially illustrated no benefit in the treatment of PMS.[79] This may be attributed to the progestogens in second-generation pills (levonorgestrel or norethisterone) regenerating PMS-type symptoms. Further research has therefore been directed towards new combined contraceptives, in particular those containing the antimineralocorticoid and antiandrogenic progestogen, such as drospirenone. Evidence level 2+

A Cochrane review[80] involving five RCTs and 1920 participants looked into the effectiveness of drospirenone (3 mg) and ethinylestradiol COCs against placebo or an alternative COC, where the progestogen was substituted for desogestrel (150 micrograms) or levonorgestrel (150 micrograms). This concluded that, when compared with placebo, drospirenone-containing oral contraceptives used for 3 months did reduce the severity of symptoms for those with PMDD (mean difference −7.92; 95% CI −11.16 to −4.67). The severity of symptoms was rated using validated questionnaires and where nonvalidated tools were used the original data were analysed. Evidence level 1−

A double-blind, placebo-controlled, cross-over trial[81] of 64 subjects showed drospirenone 3 mg and ethinylestradiol 20 micrograms to be effective for treating PMDD, based upon DRSP chart scoring. The mean decrease from baseline scoring was −12.47 (95% CI −18.28 to −6.66, $P < 0.001$). Participants were allocated to their initial treatment arm for three cycles and swapped to the alternative treatment arm after one cycle treatment-free.

Another double-blind RCT[82] of 450 participants comparing the same contraceptive pill with placebo also supported its use in PMDD. Evidence level 1+

This oral contraceptive is now available on the NHS in the UK; it is licensed in Europe and the USA for PMDD but only in women requiring oral contraception.

6.3.1.2 What is the optimum COC pill regimen, e.g. continuous, cyclical or flexible?

When treating women with PMS, emerging data suggest use of the contraceptive pill continuously rather than cyclically. ✓

Continuous therapy would seem appropriate; there are some data to support this. Phase I of a study[83] showed that a 168-day extended regimen of drospirenone 3 mg and ethinylestradiol 30 micrograms led to a significant decrease in premenstrual-type symptoms compared with a standard 21/7-day regimen. Phase II of this trial extended the continuous use of this COC for a total of 364 days. Menstrual symptoms were recorded using DRSP charts. The results concluded that mood, headache and pelvic pain scores improved Evidence level 2−

when compared with a 21/7-day regimen. There was a high level of satisfaction, with most women continuing on this regimen 6 months on from the 364-day trial.[84] This trial used a preparation that is currently available in the UK as a 24/4-day regimen containing ethinylestradiol 20 micrograms and drospirenone 3 mg; however, phase II of the study supports continuous use and this may be considered for off-label usage.

Evidence level 2–

6.3.2 How efficacious is percutaneous estradiol?

Percutaneous estradiol combined with cyclical progestogens 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 is used to suppress ovulation.

✓

Percutaneous preparations give sufficient estradiol levels to suppress ovarian activity. A placebo-controlled trial demonstrated that implants of 17β-estradiol combined with cyclical progestogens are effective for the management of severe PMS symptoms. Administered as a 100-mg implant, this proved to be highly effective when compared with placebo.[85] Both implants and patches have been evaluated in controlled trials but gels have not. Implants are available in the UK but are unlicensed for use in PMS.

In a randomised, double-blind, placebo-controlled trial of 20 women with cross-over at 3 months, transdermal estradiol patches (200 micrograms) were assessed and found to be highly effective.[86] Significant improvements occurred after changing to active treatment, proven by the use of symptom questionnaires. 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[87] showed that 100-microgram estradiol patches twice weekly were as effective as 200 micrograms in reducing symptom levels in severe PMS and this dosage was better tolerated.[88]

Evidence level 1+

Although doses are usually sufficient to suppress ovulation, contraceptive efficacy has not been demonstrated and so should not be relied upon; additional contraceptive measures should be adopted. It is also important to ensure appropriate endometrial protection (see section 6.3.4).

6.3.3 How can the return of PMS symptoms be avoided during estrogen therapy with progestogenic protection?

When using transdermal estrogen to treat women with PMS, the lowest possible dose of progesterone or progestogen is recommended to minimise progestogenic adverse effects.

A

Women should be informed that low levels of levonorgestrel released by the LNG-IUS 52 mg can initially produce PMS-type adverse effects (as well as bleeding problems).

✓

Micronised progesterone is theoretically less likely to reintroduce PMS-like symptoms and should therefore be considered as first line for progestogenic opposition rather than progestogens.

✓

Use of continuous estradiol necessitates the addition of cyclical progesterone or progestogens (10–12 days/cycle) to avoid endometrial hyperplasia in women who have a uterus. A study of long-term treatment over eight cycles using a 100 mg estradiol patch with a low dose of cyclical norethisterone acetate (1 mg; 10 days/cycle) has shown benefit compared with placebo, with continued improvement in a 6-month extension.[89]

Evidence level 1+

Intrauterine administration of progestogen has the potential to avoid systemic absorption and hence minimise progestogenic effects. The LNG-IUS 52 mg 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 progestogen-intolerant women and on rare occasions it will need to be removed due to the persisting adverse effects.[90–92]

Micronised oral progesterone (100 or 200 mg) has fewer androgenic and unwanted adverse effects compared with progestogens such as norethisterone and levonorgestrel. Progesterone may act as a diuretic and a central nervous system anxiolytic and so in theory could also alleviate PMS symptoms, although there is currently little evidence to demonstrate this.[90] Micronised progesterone can also be administered vaginally, which may be better tolerated by avoiding first-pass hepatic metabolism.[93,94] Vaginally administered progesterone avoids the formation of psychoactive metabolites such as allopregnanolone.

Evidence level 2–

6.3.4 What is the optimum regimen for prevention of endometrial hyperplasia?

When treating women with percutaneous estradiol, a cyclical 10–12 day course of oral or vaginal progesterone or long-term progestogen with the LNG-IUS 52 mg should be used for the prevention of endometrial hyperplasia. ✓

When using a short duration of progestogen therapy, or in cases where only low doses are tolerated, there should be a low threshold for investigating unscheduled bleeding. ✓

The lowest dose for the shortest time should limit unwanted progestogenic effects, and therefore an oral dose (micronised progesterone 100 mg or norethisterone 2.5 mg) for days 17–28 of each calendar month should be sufficient.[88]

Due to the lack of evidence regarding endometrial hyperplasia and neoplasia in this cohort, any suspicious symptoms should be investigated.

Evidence level 4

6.3.5 What is the safety of estradiol on the premenopausal endometrium and breast tissue?

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

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 progestogens or the LNG-IUS. Randomised placebo-controlled trial data in large populations looking at major outcome measures over a long period of time are lacking.

6.3.6 For how long can estradiol be used safely and what is the risk of recurrence?

Due to the uncertainty of the long-term effects of opposed estradiol therapy, treatment of women with PMS should be on an individual basis, taking into account the risks and benefits. ✓

Treatment of PMS is required as long as the woman's ovarian cycle continues to function. Discontinuation of treatment could allow a return of premenstrual symptoms. A reliable long-term treatment is therefore essential and should be seriously considered when evaluating treatment options.

Unlike premature ovarian failure, women with PMS still have a functioning endogenous hormone cycle. With this in mind, there are no long-term data among this specific cohort of patients.

6.3.7 What is the evidence for efficacy and adverse effects 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 in the luteal phase for breast symptoms, it also has potential irreversible virilising effects. A

Women treated with danazol for PMS should be advised to use contraception during treatment due to its potential virilising effects on female fetuses. ✓

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 of breast tenderness.[95] It demonstrated benefit for breast but no other PMS symptoms. Other studies have shown greater benefit.[96,97] A randomised, double-blind, cross-over study compared three successive cycles of danazol at a dose of 200 mg twice daily with three cycles of placebo.[97] 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 adverse effects, which may interfere with the usual symptom-free late follicular phase of women with PMS. These symptoms include acne, weight gain, hirsutism and deepening of the voice. One solution suggested for this problem might be to limit danazol treatment to the luteal phase only. One study of danazol given in the luteal phase demonstrated improvement in breast symptoms only, but with minimal adverse effects.[98]

Evidence level 1+

Danazol taken during pregnancy is known to cause cliteromegaly, labial fusion and urogenital sinus abnormalities in female fetuses. These abnormalities occur more frequently with higher doses, however cases have been reported at 200 mg daily.[99]

6.3.8 How effective are GnRH analogues for treating severe PMS?

GnRH analogues are highly effective in treating severe PMS. A

When treating women with PMS, GnRH analogues should usually be reserved for women with the most severe symptoms and not recommended routinely unless they are being used to aid diagnosis or treat particularly severe cases. ✓

GnRH analogues suppress ovarian steroid production and therefore cause a drastic improvement or complete cessation of symptoms in patients with core PMDs, but their effects on bone mineral density (BMD) mean that they should only be considered for severe cases. A meta-analysis identified 71 women on active treatment in seven trials.[100] The overall standardised mean difference (SMD) for all trials was −1.19 (95% CI −1.88 to −0.51). The OR for benefit was 8.66 (95% CI 2.52–30.26). The SMD was −1.43 and OR 13.38 (95% 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, 95% CI −1.53 to −0.79; behavioural SMD −0.68, 95% CI −1.11 to −0.25) but the difference was not significant ($P = 0.484$). If GnRH analogue therapy does not result in elimination of premenstrual symptoms, a lack of efficacy suggests a questionable diagnosis rather than a limitation of the therapy. Evidence level 1++

6.3.9 How should women with PMS receiving add-back therapy be managed?

When treating women with severe PMS using GnRH analogues for more than 6 months, add-back hormone therapy should be used. A

When add-back hormone therapy is required, continuous combined HRT or tibolone is recommended. A

Women should be provided with general advice regarding the effects of exercise, diet and smoking on BMD. ✓

Women on long-term treatment should have measurement of BMD (ideally by dual-energy X-ray absorptiometry [DEXA]) every year. Treatment should be stopped if bone density declines significantly. D

As symptoms return with the onset of ovarian function, therapy may (rarely) have to be continued indefinitely; GnRH alone is precluded by significant trabecular bone loss, which can occur with only 6 months of treatment. 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.[101]

Continuous combined therapy or tibolone is preferable to sequential combined therapy in order to minimise the risk of reappearance of PMS-like progestogenic adverse effects.[102,103] Both of these methods of add-back HRT combat the hypoestrogenic symptoms apparent with GnRH analogues but also maintain BMD. The overall SMD favoured neither GnRH alone nor GnRH with add-back (SMD 0.12, 95% CI −0.34 to 0.59), demonstrating there is no reversal of the beneficial effect of GnRH when using add-back.[100] Evidence level 1++

Meta-analyses[104,105] have shown smoking and high/low body mass index (BMI) to be risk factors for fractures. A high BMI in particular is associated with an increased likelihood of osteoporotic fractures and upper arm fractures. A low BMI is linked with hip fractures. A meta-analysis[106] involving six RCTs showed that activity in the form of brief, high impact exercise (less than 30 minutes) improved BMD.

Evidence level 2++

DEXA is accepted as the gold standard investigation for assessing BMD.[107] DEXA scans every year are considered useful as less frequent scans would delay diagnosis of significant bone loss and subsequent review of GnRH analogue treatment, and more frequent scans may not perceive small changes. National Institute of Health and Care Excellence guidance[108] recommends a DEXA scan frequency of every 2 years, however, this is largely based on monitoring the natural menopause and may not apply in this unique situation. Focused research in this area is required.

Evidence level 2+

6.3.10 Can GnRH analogues be useful in clarification of diagnostic category?

When the diagnosis of PMS is unclear from 2 months' prospective DRSP charting, GnRH analogues can be used to establish and/or support a diagnosis of PMS. ✓

Although not licensed for this indication, GnRH analogues are widely used as a diagnostic tool. There is currently no evidence to support their use in PMS diagnostically but extrapolating from the evidence available for treatment of PMS with GnRH analogues it seems a logical option.

6.3.11 What is the role for progesterone and progestogen preparations in treating PMS?

There is good evidence to suggest that treating PMS with progesterone or progestogens is not appropriate. A

There is no evidence to support the use of the LNG-IUS 52 mg alone to treat PMS symptoms. Its role should be confined to opposing the action of estrogen therapy on the endometrium. ✓

A systematic review[109] to evaluate the efficacy of progesterone and progestogens in the management of PMS concluded, after meta-analyses, that neither treatment demonstrated benefit, despite the fact they exhibit markedly different physiological and pharmacological effects. Ten trials of progesterone therapy (531 women) and four trials of progestogen therapy (378 women) were reviewed. All the trials of progesterone and progestogen (by both routes of administration) showed no clinically significant difference between progesterone/progestogen and placebo in symptom reduction.

Evidence level 1++

A Cochrane review[110] has also shown that the evidence for or against the use of progesterone or progestogens in PMS is equivocal. Seventeen studies were identified but only two were eligible; however, they could not be combined in a meta-analysis due to differences in study design, participants and progesterone dose. Overall, these studies were of poor quality.

Evidence level 1−

There is no evidence to support the use of the LNG-IUS 52 mg alone to treat PMS symptoms, and it is possible that its use may prolong PMS symptomatology. The intrauterine device's main function in PMS management is to oppose the action of estrogen therapy on the endometrium, ideally without provoking systemic symptoms.

Evidence level 4

6.4 *Non-hormonal medical management of PMS*

6.4.1 How do selective SSRIs work in PMS and how should they be given?

SSRIs should be considered one of the first-line pharmaceutical management options in severe PMS. A

6.4.1.1 What is the efficacy of SSRIs in treatment of PMS?

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

Women with PMS have been shown to have low concentrations of serotonin within their platelets and this varies throughout the menstrual cycle.[111] Evidence level 2+

The exact mode of action of SSRIs is unknown in PMS; however, both estrogen and progesterone have the ability to regulate the number of serotonin receptors, as shown in rat studies and human positron emission tomography (PET) studies.[112–114]

A Cochrane review[115] analysed data from 31 RCTs comparing SSRIs with placebo. SSRIs compared included fluoxetine, paroxetine, sertraline, escitalopram and citalopram. Nine studies involving 1276 women with PMS used a moderate dose SSRI and this showed that symptoms improved when compared with placebo (SMD −0.65, 95% CI −0.46 to −0.84).

When evaluating continuous dosing versus luteal dosing there was no significant difference between the SSRI regimens.[115] SSRIs appear to be effective for both physical and psychological symptoms. There are also data supporting the use of serotonin–noradrenaline reuptake inhibitors (SNRIs) for PMDD.[116] Evidence level 1−

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

SSRIs should be discontinued gradually to avoid withdrawal symptoms, if given on a continuous basis. ✓

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 (see section 6.4.1.5).

6.4.1.3 What are the risks and adverse effects of SSRIs?

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

In the Cochrane review,[115] women with PMS were more likely to discontinue treatment due to adverse effects when compared with placebo (OR 2.55, 95% CI 1.84–3.53). The most common symptoms were nausea, asthenia, somnolence, fatigue, decreased libido and sweating. All of these adverse effects are dose-dependent.

Evidence level 1–

6.4.1.4 Is there evidence for improved efficacy with other SSRI regimens?

When using SSRIs to treat PMS, efficacy may be improved and adverse effects minimised 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.[117] Severe PMS also improves significantly with either luteal-phase or symptom-onset dosing of escitalopram with good tolerability.[118] A randomised, double-blind, placebo-controlled study[119] involving 314 women with moderate to severe PMS were randomised to sertraline 25 or 50 mg or placebo. Participants took the medication in the luteal phase for two cycles followed by one cycle of continuous dosing and ending with symptom-onset dosing for the final cycle. This showed a significant difference in favour of luteal dosing of sertraline (25 mg and 50 mg) when compared with placebo. Another double-blind, placebo-controlled trial, involving 118 women with severe PMS or PMDD, compared continuous versus luteal phase sertraline versus placebo for three cycles. There was no difference between continuous and luteal dosing and both regimens were superior to placebo.[120] Continuous and symptom-onset dosing have also been shown to be advantageous.[119,121]

Evidence level 1+

Currently, most SSRIs are licensed in the USA for PMDD, but not in the UK.

6.4.1.5 What preconception and early pregnancy advice should be given regarding SSRIs/SNRIs?

Women should be provided with prepregnancy counselling at every opportunity. They should be informed that PMS symptoms will abate during pregnancy and SSRIs should therefore be discontinued prior to and during pregnancy.

✓

Women should be informed how to safely stop SSRIs.

✓

Women with PMS who become pregnant while taking an SSRI/SNRI should be aware of the possible, although unproven, association with congenital malformations. They should be reassured that if such an association does exist, it is likely to be extremely small when compared to the general population.

B

Women taking luteal phase SSRIs can discontinue the medication safely at any time, whereas women using a continuous regimen should taper the dose over a period of time, as advised by their doctor.

Previous studies[122] assessing the risk of birth defects after use of SSRIs or SNRIs (e.g. venlafaxine) in pregnancy have been conflicting. However, many have reported cardiovascular birth defects and other major congenital defects (e.g. anal atresia, cystic kidneys, clubfoot, gastroschisis, hypospadias, limb reduction and omphalocele). The difficulty with interpretation of these studies is that they have been limited by a number of factors including a failure to control for confounding variables (e.g. socioeconomic status and substance misuse) and low statistical power.

A multinational population-based study of over 2.3 million births from five Nordic countries,[123] compared 36 772 infants exposed to SSRIs or venlafaxine during the first trimester with 2 266 875 non-exposed infants. Consistent with many of the earlier studies, it found significant small increases in the prevalence of cardiac defects (1.5% versus 1.2%; OR 1.15, 95% CI 1.05–1.26) and other major congenital defects (3.7% versus 3.2%; OR 1.13, 95% CI 1.06–1.20) in those infants exposed to SSRIs or venlafaxine. Crucially, however, this study also compared data from 2288 infants exposed to SSRIs or venlafaxine with data from their unexposed siblings. This analysis failed to find significant increases in prevalence of any cardiac birth defects (OR 0.92, 95% CI 0.72–1.17) or other major congenital defects (OR 1.06, 95% CI 0.91–1.24). The absence of an association in the sibling controlled analyses points against teratogenic effects caused by SSRIs or SNRIs and suggests that the increased risks found in the initial analysis, and many previous studies, are attributable to the confounding effect of unspecified familial and/or other lifestyle-related factors.

Evidence level 2++

In summary, published data are conflicting and it is still possible that SSRI or SNRI use in very early pregnancy may be associated with a small increased risk of congenital malformations. However, the study by Furu et al.[123] points against a substantial teratogenic risk associated with exposure to these drugs during the first trimester, and suggests that the reported risk is driven by yet to be determined confounding factors. In addition, women with PMS are likely to discontinue treatment soon after the first missed period rather than later in the first trimester and therefore the risk may be further diminished.

Evidence level 2+

6.4.2 Are diuretics efficacious in the treatment of PMS?

Spironolactone can be used in women with PMS to treat physical symptoms.

C

Two double-blind, placebo-controlled, cross-over trials[124,125] have shown improvement in both mood and physical symptoms. One study[124] included 35 women who were given spironolactone 100 mg and placebo for three cycles each. Women taking spironolactone showed improvement in mood and somatic symptoms when compared with placebo. The other study[125] involving 28 women highlighted the benefit for physical symptoms, in particular reduced weight gain.

Evidence level 1–

6.5 How can PMS be managed surgically?

6.5.1 Can surgical management of PMS be justified and is it efficacious?

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

D

When treating women with PMS, hysterectomy and bilateral oophorectomy can be considered when medical management has failed, long-term GnRH analogue treatment is required or other gynaecological conditions indicate surgery.

✓

Hysterectomy and bilateral oophorectomy is a permanent form of ovulation suppression, as this removes the ovarian cycle completely; it also removes the endometrium, allowing the use of estrogen replacement without the need for progestogen. Blinded randomised studies cannot be conducted for this intervention. Observational questionnaire data[126] suggest a highly beneficial effect in the selected women undergoing hysterectomy and bilateral oophorectomy, the majority of whom were highly satisfied following this procedure.

Evidence level 3

Severe PMS is in most cases treated successfully with medical management, but hysterectomy with bilateral oophorectomy can be justified in women in whom medical management has proven unsuccessful, where long-term GnRH analogue treatment would be required, or if gynaecological comorbidities indicate hysterectomy.

6.5.2 Should the efficacy of surgery 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. ✓

Preoperative GnRH analogues appear to be of value in predicting the effects of oophorectomy; although such a strategy has never been tested scientifically, it would seem important, particularly when surgery is being contemplated in women younger than 45 years of age and for PMS alone.[100]

Evidence level 1++

6.5.3 What is the role of HRT after surgical management?

Women being surgically treated for PMS should be advised to use HRT, particularly if they are younger than 45 years of age. ✓

Following hysterectomy, estrogen-only replacement can be used. The avoidance of progestogen prevents reintroduction of PMS-type adverse effects. 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).[127]

6.5.4 Is there a role for endometrial ablation, oophorectomy or hysterectomy alone?

When treating women with severe PMS, endometrial ablation and hysterectomy with conservation of the ovaries are not recommended. ✓

Bilateral oophorectomy alone (without removal of the uterus) will necessitate the use of a progestogen as part of any subsequent HRT regimen and this carries a risk of reintroduction of PMS-like symptoms (progestogen-induced PMD). ✓

There have been no published studies of bilateral oophorectomy with uterine conservation in PMS. Although it may be a successful option in selected patients it is not possible to predict in which patients success will be achieved, and in whom there will be a risk of the reintroduction of PMS-like symptoms during the necessary combined HRT treatment. If such a strategy is employed then women should be counselled regarding the lack of research evidence and this potential return of symptoms.

Conservation of the ovaries will lead to persistence of PMS (ISPMD classification: PMDs with absent menstruation).[128]

An RCT[129] comparing hysterectomy with the LNG-IUS 52 mg in alleviating PMS symptoms as a secondary analysis showed benefit. However, the women presented with menorrhagia and diagnosis was not prospectively confirmed using a validated tool.

Evidence level 2–

There is no reliable evidence to support endometrial ablation; however, a cohort study[130] of 36 women with menorrhagia and PMS symptoms as rated on DRSP charts showed benefit at 4–6 months' follow-up (mean difference −5.75; $P < 0.05$). Patients were not randomised on the basis of their PMS and prospective diagnosis was not established using validated tools.

7. Recommendations for future research

- Blinded RCTs comparing complementary therapies (in particular *Vitex agnus castus*, vitamin B6 and calcium) with placebo.
- More evidence to support the use of CBT for PMS. The difficulty remains where studies cannot be double-blinded.
- Blinded RCTs comparing different regimens of drospirenone-containing oral contraceptives and long-term data regarding the risk of continuous use.
- Evidence to support/refute the use of estradiol gel and vaginal rings in the treatment of PMS.
- Evidence to support/refute the use of LNG-IUS 13.5 mg as endometrial protection in PMS.
- Long-term safety data regarding opposed estradiol therapy on breast and endometrial tissue within a PMS cohort.
- Blinded RCTs comparing tolerance of micronised progesterone versus progestogens when used as estrogenic opposition in women with PMS.
- Safety data for SSRIs in the early first trimester of pregnancy.

8. Auditable topics

The auditable topics are based on the current ISPMD consensus[131] and are as follows:

- 100% of women referred with PMS should have this diagnosis formally confirmed by completion of at least 2 consecutive months of a prospective symptom diary, usually the DRSP.
- 100% of women with PMS should not be offered progestogen therapy alone.
- 100% of women being considered for surgical treatment should have a trial of GnRH analogue therapy.

9. Useful links and support groups

- National Association for Premenstrual Syndrome [http://www.pms.org.uk/].
- NHS Choices. *Premenstrual syndrome (PMS)* [http://www.nhs.uk/conditions/premenstrual-syndrome/Pages/Introduction.aspx].
- Royal College of Obstetricians and Gynaecologists. *Information for you. Managing premenstrual syndrome (PMS).* London: RCOG; 2009 [https://www.rcog.org.uk/en/patients/patient-leaflets/managing-premenstrual-syndrome-pms/].

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Appendix I: Explanation of guidelines and evidence levels

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 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). 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

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1−	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

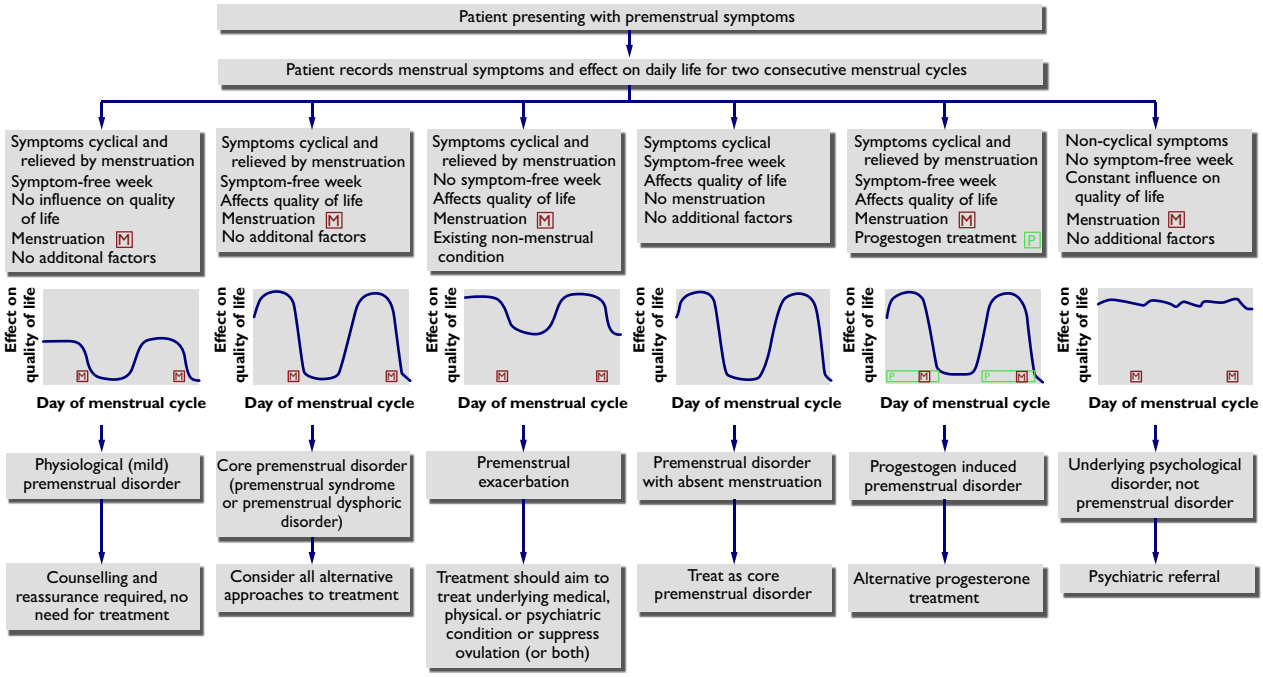
Grades of recommendations

A	At least one meta-analysis, systematic reviews or randomised controlled trials rated as 1++, and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

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

Appendix II: Classification of PMS[1]



Appendix III: Daily Recording of Severity of Problems (DRSP) symptom diary

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																															
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	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																															
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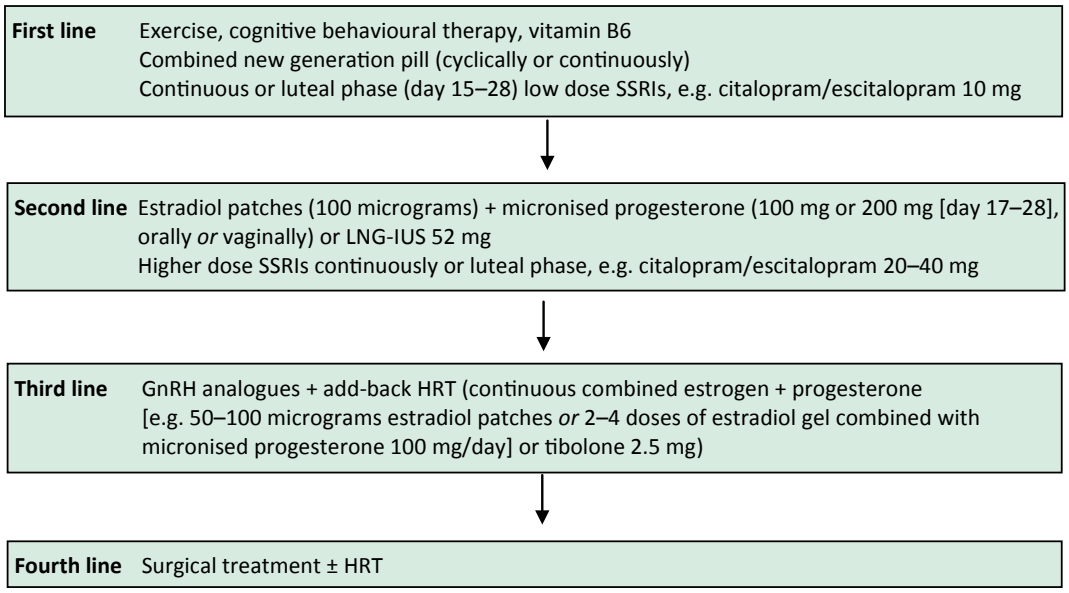
	3																															
	2																															
	1																															

Appendix IV: How PMS is treated – a decision-making algorithm[132]



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All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this guideline is available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg48/.

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

The review process will commence in 2019, unless otherwise indicated.