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. ✓

