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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