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Diagnosis and management of premenstrual syndrome

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First line	● Exercise (vitamin B6, Vitex agnus castus) ● Cognitive behaviour therapy/mindfulness-based cognitive therapy ● Continuous or luteal phase (days 15-28) low-dose SSRIs (i.e. fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) or SNRIs (i.e. duloxetine and venlafaxine) ● Combined new generation pill (cyclically or continuously)
Second line	● Oestradiol patches (100-200 mcg) + micronised progesterone (100 mg or 200 mg days 17-28, orally or vaginally) or LNG-IUS 52 mg ● Continuous or luteal phase (days 15-28) high-dose SSRIs
Third line	GnRH analogues + add-back HRT (continuous combined oestrogen + progesterone (e.g. 50-100 mcg oestradiol patches or 2-4 doses of oestradiol gel combined with micronised progesterone 100 mg/day) or tibolone 2.5 mg/day
Fourth line	Surgical treatment ± HRT

FIGURE 1
Treatment algorithm for premenstrual syndrome

How do women present in primary care?

THE TERM PREMENSTRUAL SYNDROME (PMS) REFERS TO A CONSTELLATION OF MOOD AND PHYSICAL symptoms that occur during the luteal phase of the menstrual cycle. Various approaches have been taken to define the syndrome, arising predominantly from the fields of psychiatry and gynaecology (see box 1 and table 1, p16).

The main factor that separates these definitions is the severity of the symptoms required for a diagnosis. However, the National Association for Premenstrual Syndrome suggests that: 'If PMS symptoms affect personal and/or social and/or professional quality of life then this should be regarded as being clinically significant PMS, warranting prompt diagnosis, appropriate recognition, psychological support and evidence-based medical care. Some cases of PMS will also qualify for a premenstrual dysphoric disorder (PMDD) diagnosis, but in non-PMDD cases of severe PMS, symptoms may have an equally, or even more, serious impact on the sufferer'.

How should diagnosis be confirmed?

PRESENTATION

Women can present to primary care with any of the mood and physical symptoms that occur within the spectrum of PMS. Some women give a clear history of onset during the luteal phase of the menstrual cycle, with improvement taking place within a few days after the onset of menses.

However, other women present with fluctuating symptoms without making a connection with their menstrual cycle, and some make a connection where this does not exist. There are no tests for PMS (e.g. blood tests) and diagnosis is dependent on the history.

DIAGNOSIS

Diagnosis of PMS is complicated by a number of conditions with overlapping symptoms. These include generalised anxiety disorder, mood disorders (e.g. bipolar disorder, major depressive disorder, dysthymia), dysmenorrhoea, iatrogenic use of hormonal treatments (e.g. the contraceptive pill), substance misuse, borderline personality disorder, chronic fatigue syndrome, irritable bowel syndrome, and thyroid disease (e.g. hypothyroidism or hyperthyroidism).

The most common conditions that overlap are anxiety and mood disorders, where the symptoms are present all month long. However, differentiation of these, and other, conditions can be very difficult if the physician relies solely on retrospective symptoms, as recall can be unreliable. Therefore, it is considered best practice for PMS symptoms to be prospectively recorded by patients using a symptom diary, e.g. the Daily Record of Severity of Problems (DRSP),[1] see figure 2, p17, for a period of not less than two months. From a practical perspective, some women may find it easier to use app diaries such as Clue and PreMentricS.

What are the evidence-based treatments?

MANAGEMENT

PMS treatment should be considered within a biopsychosocial model. Adopting healthy lifestyle choices, such as regular exercise, is likely to have a beneficial effect on many core PMS symptoms and should be a first-line treatment, see figure 1, above. »

Box 1

Definitions of premenstrual syndrome

The criteria specified by the American Psychiatric Association focus mainly on psychological symptoms. These are defined within DSM-V under the category of premenstrual dysphoric disorder (PMDD).[2] This definition requires that five out of 11 stipulated symptoms (one of which must be from a list of four specific mood symptoms) are present during the luteal phase of the menstrual cycle. The diagnosis excludes exacerbation of another psychiatric disorder (e.g. depression or panic disorder) and requires symptoms to be severe enough to disrupt daily functioning.

The American College of Obstetricians and Gynecologists has focused more equally on psychological and physical symptoms in its definition of premenstrual syndrome (PMS). This specifies that only one out of six specified mood symptoms, and one of four specified physical symptoms, are present. Further, it does not exclude exacerbation of another psychiatric disorder. However, it requires that there must be associated subjective reports of dysfunction.

The World Health Organization focuses predominantly on psychological symptoms. These are defined, under the term premenstrual tension syndrome (PMTS) within the ICD-10. It requires that only one out of nine stipulated mood, or one out of a list of other physical symptoms are present. Further, it does not exclude symptoms caused by the exacerbation of another psychiatric disorder or require subjective reports of dysfunction.

The International Society for Premenstrual Disorders (ISPMD) has defined a core premenstrual disorder (PMD)[3] that does not specify the nature or number of psychological or somatic symptoms required. Instead it focuses on the timing of symptoms (i.e. presenting during the luteal phase, resolving by the end of menstruation, with a symptom-free interval in the follicular phase) with the primary requisite being that premenstrual symptoms cause significant impairment.

Most treatments for PMS are not licensed for this purpose. However, the Royal College of Obstetricians and Gynaecologists has published evidence-based guidelines for the management of PMS (Green-top Guideline No. 48).[4] The options available are summarised below:

Psychological therapy

There is evidence from randomised controlled trials to support the use of mindfulness-based cognitive therapy[5] and cognitive behaviour therapy (CBT)[6] in the treatment of PMS. Where possible women with severe PMS should be routinely considered for psychological therapy. While resources mean this is often not possible, recent studies have supported delivery of CBT in groups, and remotely using internet-based CBT[7] which may increase availability in the longer term.

Pharmacological therapy

Studies support the use of continuous and luteal phase dosing of selective serotonin reuptake inhibitors (SSRIs)[8] and suggest that they should be considered as one of the first-line pharmacological interventions. There is also evidence to support the use of serotonin-noradrenaline reuptake inhibitors (SNRIs).

As with many medications prescribed to women of reproductive age, it is best to discuss the possible, although

Table 1

Diagnostic criteria for premenstrual syndromes

Organisation	Criteria	Diagnostic term	Number of mood and physical symptoms required	Can include the exacerbation of another psychiatric disorder?	Requires significant functional dysfunction?	Prevalence in women of reproductive age
American Psychiatric Association	DSM-V	Premenstrual dysphoric disorder (PMDD)	5/11 symptoms, (one of which must be from a list of four specific mood symptoms)	No	Yes	5%
American College of Obstetricians and Gynecologists	N/A	Premenstrual syndrome (PMS)	1/6 mood symptoms and 1/4 physical symptoms	Yes	Yes	30%
World Health Organization	ICD-10	Premenstrual tension syndrome (PMTS)	1/9 mood symptoms or one physical symptom	Yes	No	80%
International Society for Premenstrual Disorders	N/A	Prementrual disorders (PMD)	Unspecified (may be physical or mood symptoms)	Unspecified	Yes	Unclear

FIGURE 2
Daily Record of Severity of Problems symptom diary[1]

DAILY RECORD OF SEVERITY OF PROBLEMS

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

Name or Initials _____

Month/Year _____

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

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

key points

SELECTED BY

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The term premenstrual syndrome (PMS) refers to a constellation of mood and physical symptoms that occur during the luteal phase of the menstrual cycle. The National Association for Premenstrual Syndrome suggests that: 'If PMS symptoms affect personal and/or social and/or professional quality of life then this should be regarded as being clinically significant PMS.'

Some women give a clear history of onset during the luteal phase of the menstrual cycle, with improvement taking place within a few days after the onset of menses. However, other women present with fluctuating symptoms without making a connection with their menstrual cycle. There are no diagnostic tests for PMS and diagnosis is dependent on the history.

Diagnosis of PMS is complicated by a number of conditions with overlapping symptoms. These include generalised anxiety disorder, mood disorders (e.g. bipolar disorder, major depressive disorder, dysthymia), dysmenorrhoea, iatrogenic use of hormonal treatments (e.g. the contraceptive pill), substance misuse, borderline personality disorder, chronic fatigue syndrome, irritable bowel syndrome, and thyroid disease. The most common conditions that overlap are anxiety and mood disorders, where the symptoms are present all month long. However, differentiation of these, and other, conditions can be very difficult if the physician relies solely on retrospective symptoms, as recall can be unreliable. Therefore, it is considered best practice to use a symptom diary.

PMS treatment should be considered within a biopsychosocial model. Adopting healthy lifestyle choices, such as regular exercise, is likely to have a beneficial effect on many core PMS symptoms and should be a first-line treatment. There is evidence from RCTs for mindfulness-based cognitive therapy and cognitive behaviour therapy in the treatment of PMS. Where possible women with severe PMS should be routinely considered for psychological therapy.

Studies support the use of continuous and luteal phase dosing of SSRIs and suggest that they should be considered as one of the first-line pharmacological interventions. There is also evidence to support the use of SNRIs. The COCP should be considered as a first-line pharmacological intervention when treating some women with PMS. This can be prescribed cyclically, but some women benefit from continuous (i.e. back-to-back) regimens. Currently, the strongest evidence supports the use of new (third) generation COCP preparations.

Women with confirmed PMS who fail to respond to first-line treatments should be referred to secondary care. The ideal multidisciplinary service includes gynaecologists and psychiatrists with a special interest in PMS, and access to other professionals including clinical psychologists/counsellors, dietitians and neurologists.

unproven, association between SSRI/SNRI use and congenital malformations if taken during pregnancy. However, a recent study suggests that SSRI/SNRI exposure during the first trimester is driven by yet to be determined confounding factors.[9] Further, regardless of causation, the absolute risk for septal heart defects is extremely low.[10] 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 any putative risk may be further diminished. However, women on continuous or higher-dose treatment should be advised of the risk of discontinuation symptoms if they abruptly stop their treatment.

Hormonal therapies

Progesterone: Treating PMS with progesterone or progestogens is not supported by current evidenced-based studies.[11,12] However, progesterone pessaries or suppositories (e.g. Cyclogest 200-800 mg days 12–14 until the onset of menstruation) remain a licensed treatment for PMS.

The combined oral contraceptive pill (COCP): Studies suggest that the COCP should be considered as a first-line pharmacological intervention when treating some women with PMS. This can be prescribed cyclically, but some women benefit from continuous (i.e. back-to-back) regimens.

Currently, the strongest evidence supports the use of new (third) generation COCP preparations. While it has been suggested that drospirenone-containing COCPs with a shortened hormone-free interval may be particularly effective, the evidence to support this is limited.[13]

It is also important for clinicians to be aware of the reported association between hormonal contraceptives and increased risk of depression in some women[14] and to remain mindful of the risk of venous thrombotic events associated with the COCP in certain women.

Percutaneous oestradiol: Continuous percutaneous bioidentical oestradiol in the form of implants (e.g. 50 mg implant) or transdermal preparations (e.g. 100 mcg patch twice each week or 1 mg gel twice each day) have been reported to be effective in the treatment of physical and psychological symptoms of severe PMS. The dose of oestrogen prescribed is usually enough to suppress ovulation but the contraceptive efficacy is unclear and additional contraceptive measures should be taken.

In women with a uterus it is important to combine continuous oestradiol with cyclical progesterone or progestogens to avoid endometrial hyperplasia. Progestogenic opposition with oral micronised bioidentical progesterone (e.g. Utrogestan 200 mg days 17-28) is recommended as first line as it is probably less likely to cause PMS-like symptoms than other progestogens (e.g. norethisterone acetate).

Vaginal administration of progestogens can be used in women with a poor tolerance of oral treatment (e.g. Utrogestan 200 mg or Cyclogest 200 mg pessaries on days 17-28). Intrauterine administration using a levonorgestrel intrauterine system (LNG-IUS) can also be considered (e.g. Mirena 52 mg). An advantage of this approach is that it provides contraception where needed.

Lower doses/duration of progesterone or the smaller Jaydess 13.5 mg LNG-IUS are being used off label in some specialist centres for women with severe progestogen/progesterone intolerance with ultrasound monitoring of the endometrium. While vaginal and intrauterine approaches can mitigate the reintroduction of PMS-like symptoms, they can still lead to adverse effects in some progestogen-intolerant women, requiring them to be stopped.

Gonadotropin-releasing hormone agonists (GnRHa): In women with severe PMS symptoms GnRHa can be used as a diagnostic tool (e.g. when diagnosis remains unclear after two months of DRSP charting) and/or to treat symptoms when other approaches have failed.

The mechanism of action of GnRHa is to suppress all ovarian steroid production. This approach can lead to a profound improvement of symptoms in some patients with PMS. However, other women are unable to tolerate the effects of 'medical menopause'. Further, due to their effects on bone mineral density (BMD) women, need to be given advice about conservative methods that reduce BMD loss (e.g. exercise, diet and stopping smoking).

Add-back hormone therapy (i.e. continuous combined HRT or tibolone) should also be considered either from the outset or certainly when treatment extends beyond six months and an annual DEXA scan is recommended for women receiving long-term treatment.

Hysterectomy and oophorectomy

In women with gynaecological comorbidities that require hysterectomy, and/or severe PMS where the above approaches have been unsuccessful, hysterectomy with bilateral oophorectomy offers an effective and permanent method of ovulation suppression.

This approach is particularly beneficial for women with progesterone intolerance, as it permits oestrogen replacement without the need for progestogenic opposition. Prior to this approach a preoperative trial of GnRHa is recommended to test the likelihood of success and tolerance to hormonal (i.e. oestrogen ± testosterone) add-back.

Exercise and complementary therapies

There have been studies into various therapies including: physical (exercise, reflexology and acupuncture); vitamins (e.g. B6 and D); minerals (e.g. magnesium and calcium); and herbs (Vitex agnus castus, St John's wort, Ginkgo biloba, saffron, evening primrose oil, and curcumin). Support for these treatment options is limited by small sample sizes, variability in the definition of PMS applied and the high placebo response reported in PMS.

The evidence currently available lends greatest support for exercise and Vitex agnus castus but variability in quality and content of Vitex preparations means that no specific product can be recommended.

REFERRAL

Women with confirmed PMS who fail to respond to first-line treatments should be referred to secondary care.

The ideal multidisciplinary service includes gynaecologists and psychiatrists with a special interest in PMS, and access to other professionals including clinical psychologists/counsellors, dietitians and neurologists.

At present there is only one specialist NHS tertiary referral service that has this complement of professionals, see Useful information box, right. While it is hoped that this type of multidisciplinary clinic will eventually increase in number, in the meantime, it is likely that GPs will continue to coordinate treatment through referral to specific professionals depending on the individual needs of the patient. This may, for example, involve referral to a gynaecologist with a special interest in PMS in cases where consideration of more complex hormonal manipulation is needed (e.g. GnRHa), and to a psychiatrist/clinical psychologist in more severe cases where comorbid mental health symptoms dominate the clinical picture.

Competing interests

Dr Michael Craig has no competing interests. Dr Carrie Sadler has acted in an advisory capacity for Pfizer, Consilient, Gedeon Richter and HFA Healthcare Products, has given talks organised by Bayer, Astellas and Consilient and is a coil trainer for Bayer. Mr Nick Panay has lectured and acted in an advisory capacity for Abbott, Bayer, Besins, Consilient, Fotona, Meda, Mithra, MSD, Mylan, Novo Nordisk, Pfizer, Secur, Shionogi and Theramex.

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Useful information

RCOG guideline
Premenstrual syndrome, management (Green-top Guideline No.48)
https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg48/

National Association for Premenstrual Syndrome
http://www.pms.org.uk

National Female Hormone Clinic
https://www.national.slam.nhs.uk/services/adult-services/femalehormoneclinic

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