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ISPMD consensus on the management of premenstrual disorders

Tracy Nevatte,
Institute for Science and Technology in Medicine, Keele University, Stoke on Trent, UK

Patrick Michael Shaughn O'Brien,
Academic Unit of Obstetrics and Gynaecology, University Hospital North Staffordshire, Keele University School of Medicine, Stoke on Trent, Staffordshire, UK

Torbjorn Bäckström,
Umea Neurosteroid Research Center, Department of Clinical Sciences, Norrland University Hospital, Umea, Sweden

Candace Brown,
Department of Psychiatry, University of Tennessee Health Science Centre, Memphis, TN, USA

Department of Obstetrics, University of Tennessee Health Science Centre, Memphis, TN, USA

Department of Gynaecology, University of Tennessee Health Science Centre, Memphis, TN, USA

Lorraine Dennerstein,
Department of Psychiatry, University of Melbourne and National Ageing Research Institute, Melbourne, VIC, Australia

Jean Endicott,
Department of Psychiatry, Columbia University, New York, NY, USA

C. Neill Epperson,
Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Department of Obstetrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Department of Gynecology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Elias Eriksson,
Institute of Neuroscience and Physiology, Göteberg University, Göteberg, Sweden

Ellen W. Freeman,
Department of Obstetrics/Gynecology, University of Pennsylvania, Philadelphia, PA, USA

Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Uriel Halbreich,
State University of New York at Buffalo and WPA, New York, NY, USA

Khalid Ismail,

Correspondence to: Tracy Nevatte, t.nevatte@keele.ac.uk.

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School of Clinical and Experimental Medicine, Birmingham Women's Foundation Trust, College of Medical and Dental Sciences, University of Birmingham, Edgbaston, Birmingham, UK

Nicholas Panay,
Queen Charlotte's and Chelsea and Westminster Hospitals, Imperial College London, London, UK

Teri Pearlstein,
Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Providence, RI, USA

Andrea Rapkin,
Department of Obstetrics and Genecology, David Geffen School of Medicine at University of California, Los Angeles, CA, USA

Robert Reid,
Queen's University, Kingston, ON, Canada

David Rubinow,
University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Peter Schmidt,
Section on Behavioral Endocrinology, National Institute of Mental Health, Bethesda, MD, USA

Meir Steiner,
Department of Psychiatry, Behavioural Neurosciences, Obstetrics and Gynaecology, St Joseph's Healthcare, McMaster University, 301 James Street South, Hamilton, ON L8P3B6, Canada

John Studd,
Department of Gynaecology, Chelsea and Westminster Hospital, London, UK

Inger Sundström-Poromaa,
Department of Women's and Children's Health, Obstetrics and Gynaecology, UU, 751 85 Uppsala, Sweden

Kimberly Yonkers, and
Department of Psychiatry, New Haven, CT, USA

Department of Obstetrics, New Haven, CT, USA

Department of Gynaecology, New Haven, CT, USA

Consensus Group of the International Society for Premenstrual Disorders

Tracy Nevatte: t.nevatte@keele.ac.uk

Abstract

The second consensus meeting of the International Society for Premenstrual Disorders (ISPMD) took place in London during March 2011. The primary goal was to evaluate the published evidence and consider the expert opinions of the ISPMD members to reach a consensus on advice for the management of premenstrual disorders. Gynaecologists, psychiatrists, psychologists and pharmacologists each formally presented the evidence within their area of expertise; this was followed by an in-depth discussion leading to consensus recommendations. This article provides a comprehensive review of the outcomes from the meeting. The group discussed and agreed that careful diagnosis based on the recommendations and classification derived from the first ISPMD consensus conference is essential and should underlie the appropriate management strategy. Options for the management of premenstrual disorders fall under two broad categories, (a) those influencing central nervous activity, particularly the modulation of the neurotransmitter serotonin and (b) those that suppress ovulation. Psychotropic medication, such as selective serotonin reuptake inhibitors, probably acts by dampening the influence of sex steroids on the brain. Oral

contraceptives, gonadotropin-releasing hormone agonists, danazol and estradiol all most likely function by ovulation suppression. The role of oophorectomy was also considered in this respect. Alternative therapies are also addressed, with, e.g. cognitive behavioural therapy, calcium supplements and *Vitex agnus castus* warranting further exploration.

Keywords

Premenstrual syndrome; Premenstrual dysphoric disorder; Variant premenstrual disorder; Core premenstrual disorder; Premenstrual exacerbation; PMS; PMDD

Introduction

The definition, diagnosis and management of premenstrual disorders (PMDs) have always been challenging. These conditions affect reproductive aged women and can have a substantial impact on quality of life, with resultant impairment of education/work, interpersonal relationships and home life. It is imperative to establish the correct diagnosis using clearly defined criteria and to provide individualised, evidence-based treatment on the basis on the specific timing, severity and nature of symptoms, as well as on patient preferences.

Method

Following the first International Society for Premenstrual Disorders (ISPMD) consensus meeting (O'Brien et al. 2011), a second meeting was convened to discuss ways in which the premenstrual disorders may best be managed. The aim was to reach a consensus that would be published and easily accessible for health professionals across all disciplines likely to encounter women presenting with premenstrual disorders. The group, consisting of international experts in the fields of gynaecology, psychiatry, pharmacology and practice nursing, met at the Royal College of Obstetricians and Gynaecologists (RCOG), London in March 2011. Prior to the meeting, each expert was asked to prepare a presentation about their specific area of expertise regarding premenstrual disorders which included an evidence-based review of the literature and their own clinical experience of premenstrual disorder management. Following each presentation, the group further discussed that evidence and reached an agreement as to how to best manage premenstrual disorders using that particular treatment strategy. Subsequently, further discussions were undertaken by email in which the members of the previous consensus meeting were invited to comment. As a result, this article is a comprehensive expert review of the evidence presented with resulting recommendations for premenstrual disorder management. The main treatment sections are preceded by introductory sub-sections detailing the outcomes of the discussions at the London meeting with regards diagnosis, epidemiology and underlying biology.

Classification

Recently, the International Society for Premenstrual Disorders published a classification consensus that is outlined in Table 1 (O'Brien et al. 2011).

Ovulation clearly underlies the pathogenesis of core premenstrual disorder with symptoms appearing during the luteal phase and resolving by the end of menstruation with a symptom-free interval in the follicular phase. There are typical premenstrual symptoms but it is the timing rather than the nature of these symptoms that is important. A key factor for consideration is the impact of premenstrual symptoms upon a woman's quality of life. The timing of symptoms can be accurately recorded using prospective daily records of symptom severity.

Quantification

The key to effective management is to achieve a precise diagnosis from prospectively administered symptom rating scales. The Daily Record of Severity of Problems (DRSP) (Endicott et al. 2006; Borenstein et al. 2007) is one easily accessible, well-validated prospective rating scale that can be used to elucidate the pattern of symptoms. The minimum length of recording is two consecutive cycles; if there is a discrepancy between the two menstrual cycles a third cycle of rating should be carried out. Symptom recording can now be achieved online via mobile phone, iPAD, laptop or desktop computer (Symptometrics, www.symptometrics.com) and the DRSP can be downloaded from the internet (RCOG 2007, Green-top guideline no. 48). Before requesting a patient to prospectively record her symptoms for at least two consecutive menstrual cycles, use of the premenstrual screening tool may be of benefit (Steiner et al. 2003, 2011).

Epidemiology

A large number of population-based studies addressing the prevalence of premenstrual complaints in Western countries has been undertaken (Woods et al. 1982; Andersch et al. 1986; Johnson et al. 1988; Rivera-Tovar and Frank, 1990; Ramacharan et al. 1992; Deuster et al. 1999; Sveindóttir and Bäckström 2000; Angst et al. 2001; Soares et al. 2001; Cohen et al. 2002a; Wittchen et al. 2002). Although these investigations have applied different inventories, and although most of them have been based on retrospective rather than prospective reporting, the outcomes have been reasonably congruent, suggesting a vast majority of women of fertile age to report at least one premenstrual symptom, and severe premenstrual complaints (including a condition meeting the criteria for PMDD) to afflict 2–10 % (Halbreich et al. 2003; Epperson et al. 2012; Hartlage et al. 2012). Similar results were also obtained from a cross-sectional population-based study of 1,202 women from three Asian countries in which nearly 90 % reported at least one cyclical premenstrual symptom and 2–3 % met PMDD criteria (though not confirmed by prospective symptom assessment) (Dennerstein et al. 2010a; Dennerstein et al. 2010b).

Analysis of data from cross-sectional community-based studies of 7,226 women from 14 countries aged 15–49 years revealed that, across all the countries studied, physical symptoms were the most prevalent (Dennerstein et al. 2011), irritability being the main mood symptom among the four most prevalent complaints (Dennerstein et al. 2011). In line with this finding, a survey of 1,488 German women aged 14 to 24 also found physical complaints to be more common than mood symptoms (Wittchen et al. 2002). While somatic symptoms are more frequently reported than mood symptoms in the general population, the relative importance of different symptoms for the reduction in life quality in women reporting severe premenstrual complaints remains to be disclosed.

Population-based epidemiological studies applying strict DSM criteria, including daily prospective symptom rating for two consecutive cycles, are difficult to undertake, given the burden imposed on the participating subjects, which may lead to the studied sample being non-representative. Nevertheless, the few studies that have been undertaken using such a design suggest the prevalence of prospectively confirmed PMDD to be 2–5 % or lower (Sveindóttir and Bäckström 2000; Dennerstein et al. 2010a, b; Hartlage et al. 2012).

Underlying mechanisms

The high prevalence of premenstrual complaints, with a majority of women of fertile age reporting at least mild premenstrual symptoms, suggests that premenstrual symptoms should not be regarded as something abnormal. Premenstrual dysphoric disorder may be considered as an extreme variant of a physiological influence of sex steroids on the brain and other organs. While the relationship between the luteal phase of the menstrual cycle and symptom

development in women with PMD/PMDD is obvious, many questions remain unanswered including: (1) the role played by the different sex steroids (or sex steroid metabolites) in eliciting the symptoms, (2) the mechanisms translating this influence into changes in, e.g. mood and behaviour and (3) how women with PMDD differ biologically from those lacking symptoms or those with only mild premenstrual complaints. To what extent physical symptoms (e.g. breast tenderness and bloating) are exclusively due to an influence of sex steroids on peripheral organs or, like the mood symptoms, partly due to the influence of these hormones on the brain remains a matter of controversy. A few current hypotheses on these issues will be briefly presented. Premenstrual symptoms may start at the time of ovulation and increase in parallel with the rise in serum progesterone and estradiol during the luteal phase but continue to increase after the hormonal levels are beginning to decline. Symptom severity reaches a peak during the last five premenstrual days and sometimes the initial days of menstruation; in many subjects the symptoms are restricted to these days (Hartlage et al. 2012). Once the steroids have returned to early follicular phase levels, the symptoms diminish and resolve by 3–4 days after the onset of menstrual bleeding. During the postmenstrual phase there is a period of well-being closely related to the rise in serum estradiol (Bäckström et al. 1983). This pattern of symptoms suggests that there is a symptom-provoking factor produced by the corpus luteum of the ovary. In line with this, in spontaneous or induced anovulatory cycles, when a corpus luteum is not formed and progesterone and estradiol are not produced, the symptom cyclicity disappears (Bäckström et al. 2011).

Several studies have shown that exogenous progesterone and progestogens may induce negative mood symptoms similar to those seen in PMD/PMDD. For example, post-menopausal women who received estrogen/progesterone hormone replacement therapy (Andréen et al. 2009) and PMS patients with induced anovulation followed by hormonal add-back (Schmidt et al. 1998; Segebladh et al. 2009) reported negative mood symptoms. Several types of progestogens have been investigated in this context and all seem to induce negative mood in sensitive individuals in a dose-dependent fashion (Andréen et al. 2009). Progesterone seems more critical than estradiol for eliciting premenstrual complaints but it cannot be excluded that estradiol may augment progesterone-induced dysphoria (Björn et al. 2003; Segebladh et al. 2009) or elicit similar symptoms per se (Schmidt et al. 1998). Notably, the fact that PMD/PMDD-like symptoms may be elicited by exogenous sex steroids in women with PMD/PMDD suggests that the difference between women with symptoms and those without is not due to differences in the ovarian production of sex steroids but to an enhanced responsiveness to the fluctuations of such hormones in those with symptoms. In the same vein, comparisons of women with PMS /PMDD and controls have not revealed any consistent findings with respect to differences in serum levels of sex steroids (Bäckström et al. 1983; Epperson et al. 2002).

The classical cytoplasmic progesterone receptor is expressed in the brain and may mediate some of the behavioural effects of progesterone. The exploration of the possible effects of selective progesterone modulators may lead to further understanding of the role of these receptors in PMD and, tentatively such substances may prove useful for the treatment of the condition. However, treatment with mifepristone (RU486) does not reduce symptoms if administered after ovulation (Schmidt et al., 1991; Chan et al. 1994).

Of possible importance for the pathogenesis of PMS/PMDD is the fact that progesterone is rapidly metabolised to allopregnanolone and pregnanolone in the ovary, liver, brain and other parts of the body (Mellon 1994) and act as positive allosteric modulators of the γ-aminobutyric acid (GABA)-A receptor complex (Majewska et al. 1986). The GABA transmitter system is the major inhibitory system in the central nervous system, and both

allopregnanolone and pregnanolone, similar to ethanol, barbiturates and benzodiazepines, increase GABA-induced chloride ion influx (Olsen and Sieghart 2009).

The monoamine serotonin is another brain transmitter that has been implicated in the pathophysiology of PMD/PMDD. This theory gains indirect support from preclinical studies showing that serotonin dampens anger and aggression in many different species is an important modulator of sex steroid-driven behaviour and also by the robust reduction in the dysphoric symptoms of PMDD/PMDs achieved by administration of serotonergic agonists such as serotonin reuptake inhibitors (SRIs). The observations that premenstrual dysphoria can be elicited or aggravated by inhibition of serotonin synthesis, obtained by depletion of the serotonin precursor tryptophan from the diet, and that serotonin-facilitating compounds other than SRIs, such as tryptophan, meta-chlorophenylpiperazine, fenfluramine and buspiron, may exert symptom-reducing effects, lend further support for an involvement of this transmitter in the mechanisms underlying PMD/PMDD. In addition, numerous reports suggest that biological markers tentatively indirectly reflecting brain serotonin transmission, such as whole blood serotonin, platelet uptake of serotonin and neuroendocrine response to tryptophan loading, differ between patients and controls (for references see Yonkers et al. 2008).

A theory implicating serotonin in the biology of PMD/PMDD is potentially compatible with one involving GABA, since these transmitters display extensive interactions with each other. However, due to the complexity of the brain, there are as yet no techniques available (with the possible exception of the use of magnetic resonance spectroscopy) to reliably quantitate levels or activity of brain transmitters, such as serotonin or GABA (Epperson et al. 2002). For this reason, theories regarding the biology underlying the mood symptoms of PMDD, like those regarding the pathophysiology of various psychiatric disorders, remain preliminary and based mainly on indirect evidence.

Treatment

In cases with severe symptoms, treatment is aimed at modifying serotonin transmission or suppressing ovulation. There is a large body of evidence supporting the use of selective serotonin reuptake inhibitors (SSRIs) administered continuously or in the luteal phase only. There may also be a role for SSRIs taken as required, although there is only limited evidence currently available regarding this strategy. In addition, ovulation suppression, as obtained by gonadotropin releasing hormone agonists, high doses of transdermal estrogen, danazol, certain oral contraceptives or bilateral oophorectomy (performed only rarely), has been found to be successful for symptom management in PMD.

Symptom-based treatment strategy

Although the consensus group rejected symptom-based classification of PMD sub-types due to lack of empirical evidence, a symptom-based treatment strategy can be useful in cases where one symptom is dominant. For example, double-blind, placebo-controlled studies suggest that spironolactone may exert a specific effect on physical symptoms without being effective for the entire syndrome and the same seem to be the case with respect to the effects of luteal phase danazol on mastalgia (O'Brien and Abukhalil 1999) and of low and intermittent dosing of the SSRI fluoxetine on mood symptoms (Steiner and Pearlstein 2000).

Psychotropic agents

Serotonergic antidepressants—Controlled clinical trials have provided consistent evidence of the efficacy of serotonergic antidepressants for the treatment of symptoms of PMS and PMDD (Brown et al. 2009). Selective serotonin reuptake inhibitors are effective

first-line therapy for PMS and PMDD (Shah et al. 2008), and this approach is supported by the evidence generated from numerous individual trials and by a meta-analysis of 29 randomised, placebo-controlled clinical trials (Dimmock et al. 2000; Brown et al. 2009). Efficacy has been shown for fluoxetine, sertraline, paroxetine and escitalopram (Yonkers et al. 2008; Freeman et al. 2011) as well as for the serotonin-norepinephrine reuptake inhibitor, venlafaxine.

The short onset of action of SSRIs in women with PMD/PMDD, manifesting within the first days of treatment, enables limiting the use of SSRIs to the symptomatic luteal phase of the menstrual cycle in women with core premenstrual disorder. A meta-analysis of clinical trials comparing intermittent and continuous dosing thus showed no significant difference in the efficacy of these two regimens (Dimmock et al. 2000; see review Brown et al. 2009). However, many studies suggest that intermittent treatment is equally effective as continuous treatment in reducing irritability and certain other mood symptoms, but less effective in reducing somatic symptoms (Sundblad et al. 1993; Cohen et al. 2002b; Halbreich et al. 2002; Miner et al. 2002; Länden et al. 2007; Eriksson et al. 2008). Luteal phase dosing is typically initiated 14 days before the expected onset of menstrual bleeding and concluded with the onset of menstrual bleeding or a few days later. Discontinuation symptoms with this dosing regimen have not been observed in clinical trials. There is FDA approval for the use of fluoxetine, sertraline and paroxetine with both continuous and luteal phase dosing. The European Medicines Agency has stated that these drugs seem to work and therefore certain SSRIs are approved in some countries but neither intermittent nor continuous treatment is licensed in the UK or continental Europe.

Few dose–response studies of the effect of SSRIs in PMD have been undertaken, but the weight of evidence suggests that the dose should be at least the same as in depression (Eriksson et al. 2008). Given the short onset of action, a beneficial effect should be expected at the first menstrual cycle of treatment. If there is insufficient response in the first treatment cycle, the dose might be increased in the next cycle unless precluded by side effects.

Side effects are common with the initiation of SSRIs but many of them are transient and may abate within a few days of treatment. The most common side effects include nausea, insomnia, headache, fatigue, diarrhea, dizziness and decreased libido or delayed orgasm. Nausea, which is the most common side effect, usually resolves within 4–5 days, and does not return each cycle when the treatment is given intermittently (Eriksson et al. 2008). In contrast, sexual dysfunction, including diminishing libido and anorgasmia, is usually persistent, and may, with long-term treatment, have negative consequences on relationships (Howland 2007; Moret et al. 2009) or result in non-compliance (Nurnberg 2008). However, sexual functioning recovers rapidly after discontinuation of treatment with SSRIs, which means that it is not influenced during symptom-free intervals in patients given intermittent treatment.

The overall response of PMD patients to SSRIs in clinical trials ranges from 50–90 %. No strong predictors of response have been consistently identified. However, since most studies suggest that these compounds have larger effects on mood symptoms than on somatic symptoms, it is likely that the response rate is higher in patients with mostly mood symptoms than in those in which the somatic symptoms are dominating. When there is insufficient response or unacceptable side effects with the initial SSRI, a common clinical practice is to shift to another SSRI. Failure to achieve a clinical response may also be due to the presence of other comorbid disorders, which are common in women with PMD or PMDD. A thorough review of the diagnosis and adjustments of medication for the primary comorbidity may be considered before returning to treatment specifically aimed for PMD.

Other antidepressants—The antidepressant response in PMS appears to be associated with strong serotonergic activity and is not a general antidepressant effect. Other antidepressants, which are effective for depressive disorders, such as desipramine (a tricyclic antidepressant predominantly acting on noradrenaline), buproprion (an inhibitor of dopamine and norepinephrine reuptake) and maprotiline (a selective noradrenaline reuptake inhibitor) are hence less effective than SSRIs and no more effective than placebo in PMS (Eriksson et al. 1995; Pearlstein et al. 1997; Freeman et al. 1999). Clomipramine, a tricyclic antidepressant that has strong serotonergic activity, is effective for PMS at low dosage but is somewhat less well tolerated than SSRIs.

Benzodiazepines and buspirone—If anxiety/tension and irritability are the patient's predominant symptoms of PMD, treatment with anxiolytics, such as benzodiazepines, may seem appropriate. However, anxiolytics have been less well studied in PMD/PMDD, and their use is controversial because of the risk for drug dependence. The benzodiazepine alprazolam showed a modest efficacy for PMD in some studies, while others have found it to be ineffective (Schmidt et al. 1993). If at all used for PMD, alprazolam (or other benzodiazepines) should be strictly limited to the symptomatic luteal phase, and avoided in patients at heightened risk for dependence. They cannot be regarded as evidenced-based treatment for PMD.

Buspirone is a 5HT1A partial agonist which is used for the treatment of generalised anxiety disorder, and which has been found more effective than placebo for PMD in small studies. Buspirone does *not* confer the risk of dependency that occurs with benzodiazepines. Sexual side effects that may be a problem with antidepressants appear to be low with this medication, but the efficacy in PMD is in all likelihood less than for the SSRIs.

Suppression of ovulation

Suppression of ovulation using gonadotropin-releasing hormone agonists

Treatment with gonadotropin-releasing hormone (GnRH) agonists down-regulates gonadotropin release and ultimately suppresses ovarian functioning, hence reducing estradiol and progesterone concentrations to postmenopausal levels. For these reasons, GnRH agonists have been used for the treatment of PMD and PMDD since the late 1980s. However, the usefulness of GnRH agonists long-term is limited by their cost and hypo-estrogenic side effects. In the short-term this is experienced by the women as vasomotor symptoms (flushes/flashes), and in the longer-term this may lead to vaginal atrophy, cardiovascular risks, bone demineralization, and osteoporosis. In order to eliminate these side-effects and long-term risks, estradiol and progestogen add-back is usually employed, but may trigger PMD-like symptoms.

The usefulness of GnRH agonists with or without add-back hormone replacement therapy (HRT) for treatment of premenstrual disorders has been evaluated in a meta-analysis, which included seven randomised, placebo-controlled, double-blind clinical trials with altogether 71 women (Wyatt et al. 2004). Compared to placebo, GnRH agonist treatment on its own resulted in significant symptom relief in behavioural as well as physical premenstrual symptoms. The result of the meta-analysis is also corroborated by additional randomised, placebo-controlled studies that were not included because data could not be extracted (Hammarbäck and Bäckström 1988; Mezrow et al. 1994; Schmidt et al. 1998; Hussain et al. 1992; West and Hillier 1994; Muse et al. 1984). Response rate to GnRH agonist treatment is reportedly between 60 and 75 % in these trials (Hammarbäck and Bäckström 1988; Schmidt et al. 1998; Brown et al. 1994; Freeman et al. 1997), although no uniform definition of treatment response has been employed. Furthermore, the meta-analysis also concluded that

doses sufficient for inhibiting ovulation are needed for optimal symptom relief (Sundstrom et al. 1999).

GnRH analogues are usually accompanied by “add back” of standard HRT preparations of estrogen and progestogen to avoid menopausal symptoms and morbidity. Progestogen is necessary to protect the endometrium, but may produce PMS-type side effects. However, lowering the dose of add-back HRT may help to avoid these side effects hence not reducing efficacy of GnRH agonist treatment (Wyatt et al. 2004) and is likely sufficient for protection of bone mineral density (Mitwally et al. 2002). Various types of HRT add-back have been tested but no treatment seems to be better than another. According to a randomised, placebo-controlled trial on different add-back therapies to GnRH agonist in women with premenstrual dysphoric disorder, estradiol-only replacement was associated with the lowest degree of symptom recurrence (Segebladh et al. 2009). When combined with progesterone, a low dose of estradiol was more beneficial than a higher dose, which is why a low-dose estradiol, with the addition of progesterone more intermittently, appears to be the best treatment option (Segebladh et al. 2009; Björn et al. 2003). Another way to avoid symptoms may be the use of continuous combined HRT or tibolone, which do not produce a cycle or a withdrawal bleed or additionally, the use of a progesterone-releasing intrauterine system may be considered (see later).

Gonadotropin-releasing hormone agonists are beneficial for women with PMD and PMDD but, as one would expect, not for women with premenstrual exacerbation of ongoing major depression (Freeman et al. 1997). Analyses of non-responders to GnRH with alleged PMD have suggested that these women display an altered symptom profile with more rapid symptom fluctuation and a greater degree of symptoms across the entire cycle, possibly suggesting underlying psychiatric disorders (Pincus et al. 2011). These results may imply that treatment with GnRH agonist could be used as a diagnostic test for PMD and PMDD, although systematic studies are needed to clarify this issue. The analogue is also useful as a possible pharmacological test to determine the potential efficacy of hysterectomy and bilateral oophorectomy for women with severe PMD who may wish to definitively treat their symptoms (Leather et al. 1999).

Suppression of ovulation using danazol

Danazol, an androgen analogue and in high doses an inhibitor of gonadotropin, has been used to reduce PMD. Whilst continuous danazol significantly reduced premenstrual symptoms when compared to a placebo, (Deeny et al. 1991; Hahn et al. 1995; O’Brien and Abukhalil, 1999), danazol given in the luteal phase reduced only premenstrual breast pain and none of the other associated symptoms, when compared with placebo. Long-term use of danazol can lead to masculinisation and other adverse effects. Danazol is rarely used now, but if it is, low doses are advised, and careful counselling should be undertaken regarding contraception as danazol can cause virilisation of a developing female fetus.

Suppression of ovulation using oral contraceptives

Combined oral contraceptives inhibit ovulation, hence, by definition, eliminate the luteal phase. As premenstrual disorders are triggered by ovulation and are linked to the luteal phase of the menstrual cycle, oral contraceptives should therefore be effective for the treatment of premenstrual disorders. However, in an early study, women with PMS were found to be susceptible to negative mood while using oral contraceptives (Hammarbäck and Bäckström 1989), suggesting that PMS-like symptoms may be triggered by the hormonal ingredients of the pill in sensitive women. In this vein, traditional oral contraceptives have usually not been regarded as an effective treatment for PMD, although they may exert some beneficial effects on somatic symptoms.

There is a notable lack of knowledge about the central nervous system effects of the various constituents of different hormonal contraceptives. Negative effects on mood may be related to factors such as type and dose of progestogen, schedule of administration (i.e. monophasic vs triphasic), length of pill-free intervals and dose and formulation of the estrogen (Kurshan and Epperson 2006). In this section, the focus is on blind, randomised, placebo-controlled trials and randomised comparative studies evaluating the effectiveness of various oral contraceptives for the treatment of significant premenstrual symptoms will be discussed.

The effect on mood of oral contraceptives has long been a subject of debate. Since the initial wide spread usage of oral contraceptives, reports of depression and other emotional side-effects have been cited as the primary reason for oral contraceptive pill discontinuation (Sanders et al. 2001). In contrast, a review of 13 prospective studies of women taking oral contraceptives found no differences in negative affect between users and non-users, but the findings were not consistent. A bias could be introduced with such a study because the non-user comparator may well include patients who have discontinued oral contraception due to side effects. Some of these studies (e.g. Oinonen and Mazmanian 2002) were strengthened by the inclusion of daily mood ratings, although the women were not specifically evaluated for defined PMDs criteria prior to or during treatment. The first randomised placebo-controlled trial of oral contraceptives for premenstrual disorders studied 80 women with premenstrual symptoms who were randomised to a triphasic oral contraceptive containing ethinyl estradiol 35 mcg for days 1–21 and norethindrone 0.5 mg for days 1–7, 1 mg days 8–16 and 0.5 mg for days 17–21 (Graham and Sherwin 1992). Of the 45 women who received either the oral contraceptive or placebo for three cycles, there was a significant improvement from baseline on every symptom, except headache, but the cyclic mood changes improved equally with oral contraceptives and placebo. Significant group differences favouring the oral contraceptive were noted only for oedema and breast tenderness.

In a randomised comparison of a triphasic and monophasic preparation, 32 women with either “pure” PMS or premenstrual aggravation of mood symptoms were prospectively evaluated for one pre-treatment cycle, followed by four treatment cycles in a crossover design (Bäckström et al. 1992). All subjects received two cycles of ethinyl estradiol 30 mcg/desogestrel 150 mg (EE/DSG) and two cycles of either ethinyl estradiol 30 mcg/levonorgestrel 150 mg (EE/LNG) or the triphasic pill with ethinyl estradiol (30/40/30 mcg)/ and levonorgestrel (50/75/125 mcg). All three oral contraceptives significantly improved mood and physical symptoms. However, a placebo effect could not be excluded as none of the subjects received a placebo. In the “pure” PMS group, there were significantly lower tension, irritability and depression scores and greater well-being in the monophasic EE/DSG group compared with the mono- or triphasic LNG group. The triphasic LNG group had less breast tenderness.

Four double-blind placebo-controlled trials included newer oral contraceptives containing drospirenone, a progestin derived from 17-α-spironolactone. Drospirenone differs from 19-nortestosterone-derived progestins in that it competitively blocks free testosterone from binding to the androgen receptors and similarly blocks aldosterone from binding to the aldosterone receptor.

A study of 82 women receiving drospirenone 3 mg and ethinyl estradiol 30 mg in a traditional 21/7 regimen for the treatment of PMDD (Freeman 2001) found significant improvement compared with baseline only for symptoms of acne and appetite.

A relatively newer oral contraceptive pill formulation containing 3 mg of drospirenone and a lower dose of ethinyl estradiol (EE; 20 mcg) in regimen with a shortened hormonal-free interval of 4 days (24/4 regimen) was then studied for the treatment of PMDD in two

randomised placebo-controlled trials. In the parallel group trial, the reduction in total and individual symptom scores was significantly greater with the active compound compared with placebo in each of the three cycles (Yonkers et al., 2005).

The second published study investigated the therapeutic effectiveness of drosperinone (3 mg), EE (20 mcg) in a double-blind placebo-controlled crossover trial (Pearlstein et al. 2005). The response rate was significantly greater during the oral contraceptive intervention as assessed by DRSP and the Clinical Global Improvement Scales (CGI); the response rate was defined as >50 % decrease in either DRSP or CGI scores.

These two pivotal trials of the oral contraceptive containing drospirenone 3 mg and ethinyl estradiol 20 mcg in the 24/4 regimen resulted in the approval of this pill by the United States Food and Drug Administration for the treatment of PMDD in women who desire contraception but it was not approved in UK and continental Europe.

Based on data pooling from five trials involving 1,600 women, the Cochrane authors concluded that although the “lost to follow-up” rate was high in drug and placebo groups, oral contraceptives containing drospirenone 3 mg/EE 20 mcg in the 24/4 regimen “may be effective for PMDD”. However, the sustainability of this effect beyond three treatment cycles, efficacy in cases of less severe premenstrual symptoms, and their possible superiority over other oral contraceptives were regarded unclear (Lopez et al. 2009; Freeman et al. 2012; Halbreich et al. 2012).

Suppression of ovulation with estrogen

Although none of the studies are recent, transdermal estrogens have been shown to be effective methods of therapy for severe PMD by suppressing ovulation. In practice, this can be achieved by estrogen gel (daily), estrogen patch (changed twice per week) or an estradiol implant (inserted every 6 months). There is no randomised trial of gels but clinical trials using patches of 100 mcg (Watson et al. 1989), 200 mcg (Smith et al. 1995) and subcutaneous estradiol implants (Magos et al. 1986) showed superior efficacy compared to placebo. Without research to refute these quite old studies or reports of untoward outcomes, clinicians (gynaecologists) have continued to use this evidence over many years to successfully manage the more severe patients. A substantial amount of clinical experience accumulated in that intervening time has reinforced the findings of these original studies. Oral estrogens are normally replacement doses and insufficient to suppress ovulation. They may be effective but there are no published studies to support this.

Women receiving unopposed estrogen will require progestogen to prevent endometrial hyperplasia and irregular bleeding, but because of the progestogen intolerance found in these women, a smaller dose of shorter duration is required, usually in the form of 2.5 mg of norethisterone or 100 mg of oral micronised progesterone for the first 7–10 days of each calendar month; this will produce a regular withdrawal bleed on about days 10 to 13 of each calendar month. Resetting the periods in this way prevents abnormal bleeding; instead normal, usually scanty bleeding occurs at a predictable time of the month. Another minor advantage of this regimen is that periods now occur 12 times a year rather than 13 (Studd 2011). This is based on clinical experience rather than clinical trial and it is likely that the symptom benefits of reduced progestogen dose are offset by an unquantified risk of endometrial hyperplasia.

Administration of progestogen directly to the endometrium using the levonorgestrel-containing intrauterine system may be an effective option because after the first few months, minimal systemic progestogen levels occur and excellent endometrial protection is afforded. It is also a highly effective contraceptive. Some systemic absorption does occur, with

highest levels in the first 3–4 months, and can produce symptoms of depression, tiredness and bloating in about 10 % of women with progestogen intolerance (Elovainio et al. 2007). These symptoms disappear but if the device ultimately requires removal, then they do so within 24 h of removal of the IUS. This combination is widely practiced; there are published studies showing effective treatment with estrogen and there is compelling published evidence that the levonorgestrel prevents endometrial hyperplasia. Even so there is no study published confirming the efficacy of estrogen/IUS combined treatment.

Eliminating ovulation by surgery

Removal of the uterus whilst conserving the ovaries is not effective in treating any premenstrual disorder (Bäckström et al. 1981). Similarly endometrial ablation would not be expected to be beneficial. This is not surprising as in both of these approaches ovarian endocrine cyclicity is maintained resulting in persisting symptoms following the surgery.

Successful surgical treatment of severe PMD hence requires hysterectomy and bilateral salpingo-oophrectomy (BSO) (Casper and Hearn 1990; Casson et al. 1990). Hysterectomy with BSO has been shown to have a beneficial effect on both the mood and physical symptoms. Success rates are high and long-lasting (Cronje et al. 2004) but only as long as estrogen (unopposed) is administered long-term to prevent the symptoms and complications of estrogen deficiency. Since the original papers were published the surgery can now be performed laparoscopically with a one-two day hospital stay. When such a patients request hysterectomy and BSO, careful selection is required which probably includes testing the potential effect of the elimination of ovulation using GnRH analogues, with or without estrogen, (which has yet to be formally evaluated). After surgery, estrogen given at replacement levels should be administered to the age of the menopause and, of course, without progestogen. Removal of just the ovaries would be effective but the persistence of the uterus (and hence endometrium) would require the administration of progestogen with the likelihood of reintroduction of PMS symptoms.

Alternative therapies

Although multiple dietary recommendations, including frequent meals containing complex carbohydrates or protein (“slow burning fuels”), decreased refined sugar, reduced salt and elimination of caffeine have been proposed for treating PMDs, few have been systematically evaluated. Increased complex carbohydrate intake during the luteal phase is theorised to increase tryptophan availability leading to increased central serotonin levels. Two small randomised controlled trials reported that a beverage containing simple and complex carbohydrates was superior to isocaloric placebo beverages in reducing premenstrual symptoms (Freeman et al. 2002; Sayegh et al. 1995).

Calcium is the dietary supplement with the strongest empirical support in PMDs (Whelan et al. 2009). Increasing calcium levels is theorised to regulate periovulatory calcium homeostasis. A large RCT demonstrated that calcium 600 mg twice a day was superior to placebo in improving premenstrual emotional and physical symptoms in 466 women with prospectively confirmed PMS (Thys-Jacobs et al. 1998). Additional support for calcium was reported in a smaller study (Khajehei et al. 2009).

Vitamin B6 100 mg daily has demonstrated weak superiority compared to placebo in meta-analyses of nine RCTs (Wyatt et al. 1999) and 13 RCTs (Whelan et al. 2009). Patients should be cautioned that if the vitamin B6 is not effective, increasing the dose of in an effort to achieve complete relief of symptoms may lead to peripheral neuropathy, even with 200 mg per day. Pyridoxine should be discontinued if there is evidence of tingling or numbness of the extremities.

Mixed results have been reported for magnesium and vitamin E and one study reported negative results with soy isoflavones (see review, Whelan et al. 2009). A recent RCT reported superior efficacy for an essential fatty acid preparation containing linoleic acid, gamma-linolenic acid, oleic acid and vitamin E in improving PMS compared to placebo (Rocha Filho et al. 2011). Increasing prostaglandin E1 levels is theorised to regulate tissue sensitivity to prolactin (Rocha Filho et al. 2011). However, previous RCTs with evening primrose oil (containing linoleic acid and gamma-linolenic acid) have failed to demonstrate superiority compared to placebo (see review, Whelan et al. 2009).

Encouraging results exist for chasteberry/*Vitex agnus castus* for decreasing premenstrual emotional and physical symptoms of PMDs compared to placebo (see reviews, Whelan et al. 2009; Dante and Facchinetti 2011). Chasteberry has dopaminergic effects but its potential mechanism of action in PMDs is unknown. Hypericum perforatum/St. John's Wort may be superior to placebo, particularly for premenstrual physical symptoms (see review, Dante and Facchinetti 2011). Herbs that deserve further study include ginkgo biloba and *Crocus sativus*/saffron (see reviews, Whelan et al. 2009; Dante and Facchinetti 2011).

Several studies have been conducted with cognitive-behaviour therapy (CBT) for women with PMDs. The efficacy of cognitive therapy may include modification of irrational thinking and increasing coping strategies. Reviews of randomised controlled trials (RCTs) of CBT studies suggest weak superiority compared to placebo or wait-list controls (see reviews, Busse et al. 2009; Lustyk et al. 2009). One study that compared CBT with fluoxetine reported that both treatments were effective but fluoxetine was superior for anxiety while CBT had superior long-term efficacy (Hunter et al. 2002). Other psychological interventions for PMDs have undergone only limited study.

Although no RCTs of exercise have been conducted in women with prospectively confirmed PMDs, exercise has been reported to improve premenstrual dysphoria, fatigue and bloating (Daley 2009). It is commonly considered that exercise improves premenstrual symptoms through elevation of beta-endorphin levels and improved well-being however there is no evidence to confirm this. Small RCTs have suggested efficacy of sleep deprivation and light therapy (Parry et al. 2008, see review Shechter and Boivin 2010). These treatments are theorised to regulate circadian rhythms; however the duration of any therapeutic effects, if any, is unclear. Modalities with positive initial reports that may deserve further study for women with PMDs include acupuncture, Qi therapy, relaxation, reflexology, massage, krill oil, lavender oil, Chinese herbs and transmagnetic stimulation. Members of the consensus group commented that these should only be offered in the context of well-designed clinical trials.

The strongest evidence for efficacy of non-pharmacological treatments for PMDs exists for calcium, chasteberry and cognitive-behaviour therapy.

Conclusion

A management strategy for a patient with a premenstrual disorder can only be developed following accurate symptom quantification and diagnosis.

If a symptom-free week following menstruation is lacking, it is important to question the diagnosis of a premenstrual disorder and proceed with further investigation as a continuous psychiatric or physical condition unrelated to the menstrual cycle will require an alternative management strategy.

Mild premenstrual symptoms that by definition have minimal impact on the woman's quality of life do not require treatment but reassurance and support may be required.

The diagnosis of a premenstrual disorder when menstruation is absent (e.g. after an endometrial ablation or hysterectomy with ovarian conservation) follows the same general guidelines as if the diagnosis was of core premenstrual disorder. Measurement of basal body temperature, progesterone or use of urinary ovulation kits to identify the timing of ovulation in relation to the peak of symptoms, during the prospective rating of daily symptoms, may be useful as the index menstrual period is lost or these women

If the diagnosis is of a progesterone-induced premenstrual disorder then the possibilities for management are many. They are mainly theoretical and based on clinical experience and there is little true evidence for their support. These include change in type of progestogen or route of administration (intrauterine); reduced dose, duration and frequency; avoiding progestogen and monitor endometrium; continuous combined estrogen and low-dose progestogen; perform a hysterectomy or use a concomitant SSRI. For full recent review see Baker and O'Brien 2012.

Premenstrual exacerbation of an underlying physical or psychiatric disorder may be treated either by managing the symptoms of the underlying condition, so that the additional premenstrual impact is bearable or by ovulation suppression using the methods mentioned in this article.

If core premenstrual disorder is diagnosed, the treatment approaches outlined above in detail should be used. It is important to take into account

- the severity of the symptoms
- the woman's plans to conceive or contraception needs
- the response to previous treatment approaches

Treatment approaches may be one of the non-drug approaches, a serotonin reuptake inhibitor or via ovulation suppression (estrogen, specific COC, GnRH with or without add back, estrogen, with progestogenic endometrial protection) or surgery. A patient's willingness to accept a particular treatment modality must be ascertained as her choice—she may not be willing to try hormonal therapy or SSRIs for example. Surgical intervention (meaning almost exclusively hysterectomy and bilateral oophorectomy), though the only permanent cure, should be the last resort and then only after detailed counselling and a trial period of a GnRH agonist.

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Table 1

The classification of premenstrual disorders (adapted from O'Brien, 2011—note, this classification was misaligned in the table of the first publication)

Premenstrual disorder category	Characteristics
Core premenstrual disorder[a] (PMD)	Symptoms occur in ovulatory cycles
	Symptoms are not specified—they may be somatic and/or psychological
	Symptoms are absent after menstruation and before ovulation
	Symptoms recur in luteal phase
	Symptoms must be prospectively rated (two cycles minimum)
	Symptoms must cause significant impairment (work, school, social activities, hobbies, interpersonal relationships, distress)
Variants PMDs	
Premenstrual exacerbation	Symptoms of an underlying psychological, somatic or medical disorder significantly worsen premenstrually
PMD due to non-ovulatory ovarian activity (rare)	Symptoms result from ovarian activity other than those of ovulation
Progestogen-induced PMD[b]	Symptoms result from exogenous progestogen administration
PMD with absent menstruation	Symptoms arise from continued ovarian activity even though menstruation has been suppressed

[a] Core premenstrual disorder can subdivided into (1) predominantly somatic symptoms, (2) predominantly psychological symptoms or (3) mixed somatic and psychological symptoms. A sub-group of women with predominantly psychological symptoms, with or without somatic symptoms, may also fulfil DSM-IV criteria for premenstrual dysphoric disorder (PMDD) and the proposed DSM-5 criteria (American Psychiatric Association, 2000). This represents consensus reached at the second meeting

[b] Onset of symptoms after initiation of progestogen treatment