Review Article

MANAGEMENT OF PREMENSTRUAL DISORDERS

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ABSTRACT

The impact of premenstrual disorders(PMDs) on women's lives is largely under-recognized. Inconsistent diagnostic guidelines and poor evidence base for effective treatment strategies lead to inadequate management. The diagnostic categories as per the Consensus Group of the International Society for Premenstrual Disorders (ISPD) divide PMDs to Core PMDs and Variant PMDs and can be clinically useful. Non-pharmacological methods like exercise, dietary modifications and cognitive behavioral therapy may be used for PMDs associated with mild distress, but the evidence base remains inadequate. Evidence indicates that that serotonin re-uptake inhibitors citalopram, escitalopram, fluoxetine, paroxetine and sertraline, and the serotonin and noradrenaline reuptake inhibitor venlafaxine are effective for severe PMDs.

Keywords: Premenstrual disorders, premenstrual dysphoric disorder, management.

INTRODUCTION

Although the syndrome of premenstrual tension was first described in the 1930s,[1] the diagnostic criteria of premenstrual disorders (PMDs) and their management strategies have been constantly revised. Inclusion of premenstrual dysphoric disorder (PMDD) in the Appendix B of the Diagnostic and Statistical Manual of mental disorders, fourth edition (DSM-IV) helped to enhance research on its epidemiology, aetiology, clinical features and management. Seventy-five per cent of women suffer from different forms of PMDs,[2] but consensus regarding definitions, diagnosis and treatment is still in the formative stages. Focus on evidence based diagnostic guidelines and treatment strategies have increased after the inclusion of PMDD as a separate category in Diagnostic and Statistical Manual of mental disorders, fifth edition (DSM 5).[3] The current evidence based treatment strategies for the varied spectrum of PMDs still remain largely inadequate. I attempt to review the current literature regarding the definitions, diagnostic criteria and management options available for PMDs, keeping in mind the needs of a practising clinician.

EVOLUTION OF THE DIAGNOSTIC GUIDELINES AND RECENT DEVELOPMENTS

PMDs are characterised by a cluster of somatic and psychological symptoms of varying severity that occur during the luteal phase of the menstrual cycle and resolve during menses.[4,5] The diagnostic guidelines for PMDs have been undergoing constant revision in the past fifteen years. Understanding the evolution of the different terms related to these disorders is important for effective management.

Please cite this article as: Nakulan A. Management of premenstrual disorders. Kerala Journal of Psychiatry 2017; 30(1):17-23.

According to World Health Organisation International Classification of Diseases (ICD) 10th edition (WHO 2004), at least one symptom out of a broad range of physical and emotional symptoms should be present in the premenstrual phase, without specification of severity, to diagnose 'premenstrual tension syndrome'.[6] These criteria are not helpful for defining study populations or for planning management.

Till recently, PMDs have been conceptualised as a spectrum. Isolated premenstrual symptoms without any impact on daily life are at one end of the spectrum and the severe PMDD at the other end. In between these extremes lie the clinically significant premenstrual syndrome.

There is a glaring lack of clarity in the various definitions of premenstrual syndrome (PMS) which would impair accurate diagnosis and subsequent management. A large proportion of women experience premenstrual symptoms which do not meet the criteria for PMDD but are clinically significant and require intervention. So, the American College of Obstetricians and Gynaecologists (ACOG) and the World Health Organization introduced formal diagnostic criteria for detecting clinically significant PMS. This included one physical or psychological symptom in the five days prior to menses. The symptoms must occur in three consecutive menstrual cycles and must subside within four days of menses onset. The symptom(s) must cause significant impairment and must be verified by prospective rating for diagnosis.[7]

A recent and significant development is the recognition of PMDD as a separate diagnostic category under the Diagnostic and Statistical Manual of mental disorders (5th ed.) (DSM 5).[3,8] The diagnosis is based on a peri-menstrual pattern of at least five physical, affective, and/or behavioural symptoms, with a requirement of at least one of the key affective symptoms of affective lability (mood swings, tearfulness, sensitivity to rejection); irritability or anger that is often characterized by increased interpersonal conflicts; marked depressed mood, hopelessness, or self-deprecating thoughts; or anxiety, tension or feeling on edge. The woman may also experience cognitive symptoms like difficulty concentrating or a sense of feeling overwhelmed or out of control. These can be accompanied by behavioural and physical symptoms such as anergia, loss of interest in usual activities, changes in appetite or food cravings, changes in sleep patterns, and physical symptoms such as joint or muscle pain, breast tenderness or swelling, sensation of bloating, or weight gain. These symptoms must have occurred during most menstrual cycles in the past year to meet criteria for PMDD diagnosis. Symptoms must be absent or minimal in the post-menstrual week. In addition to impairment due to PMDD symptoms, the concept of distress to the individual has also been included in DSM 5 unlike DSM-IV-TR. The symptoms should be confirmed by prospective daily ratings for at least two symptomatic cycles; this may be accomplished via tools such as the Daily Record of Severity of Problems (DRSP), the Calendar of Premenstrual Experiences, or the Premenstrual Assessment Form (PAF).[9,10,11] Till then, only a provisional diagnosis of PMDD may be made.

DIAGNOSTIC CRITERIA AS PER THE CONSENSUS GROUP OF THE INTERNATIONAL SOCIETY FOR PREMENSTRUAL DISORDERS(ISPD)

To address the ongoing difficulty in diagnosis, the Consensus Group of the ISPD in 2011 has published diagnostic criteria for PMDs.[12] Symptoms associated with PMDs can vary from being somatic, psychological, or a mixture of both. They proposed that PMDs are to be divided into two categories: Core PMDs which are the typical PMDs associated with spontaneous ovulatory menstrual cycles, and Variant PMDs which are separate from Core PMD and comprises of PMDs with more complex characteristics.

The key component of Core PMDs is the timing of symptoms with relation to ovulation. The symptoms must appear during the luteal phase and subside with menstruation. There should be a

symptom-free period in the follicular phase. The symptoms should be present in most menstrual cycles (two out of three). Importantly, the severity or impact of symptoms must affect normal daily functioning; interfere with work, school performance or interpersonal relationships; or cause significant distress.

The Core PMDs comprises of Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD). PMS is distinguished from the normal psychological and somatic premenstrual symptoms experienced by many women because of its negative influence on daily functioning and level of distress. Both the current ACOG definition of PMS mentioned earlier and the current DSM 5 definition of PMDD meet the criteria of a Core PMD. The diagnosis of PMDD represents a type of PMD in which the psychological symptoms are severe. There are strict criteria for the diagnosis of PMDD that aim to differentiate it from other types of core PMD. These are reflected in the DSM 5 diagnostic criteria for PMDD mentioned earlier.

The Variant PMDs comprise of four categories. Premenstrual exacerbation occurs when there is magnification of an underlying somatic, medical or psychiatric disorder during the luteal phase of the ovarian cycle. Conditions that exhibit premenstrual exacerbation are diabetes, migraine, epilepsy, asthma and depression.[13] PMD due to non-ovulatory ovarian activity occurs when symptoms arise from continuous ovarian activity which does not lead to ovulation. It may result from cyclical follicular activity that fails to culminate in normal ovulation.[14] Progestogen induced PMD is an iatrogenic form of PMD where women receiving exogenous progestogen may develop symptoms which are similar to premenstrual symptoms. PMD without menstruation occurs in women who experience premenstrual symptoms despite surgical or drug-induced amenorrhoea.

These revised diagnostic criteria can help enhance evidence based research by introducing more homogeneity of study populations. The clinical categorization will also aid in effective management.[15]

EPIDEMIOLOGY

The disparity in the diagnostic concepts regarding PMDs has led to significant heterogeneity in study populations in the past. Studies show that 20-40% of women have symptoms satisfying criteria for PMS and at least 8% of women in the reproductive age group have symptoms meeting criteria for a diagnosis of PMDD.[4,16,17]

Prospective symptom rating scales used for a definitive diagnosis of PMDs require daily monitoring by the individual. This affects compliance and can delay diagnosis. It is of interest to note that the prevalence of PMDs according to recent studies done using prospective symptom ratings are similar to most of the prevalence studies done in the past which used retrospective questionnaires.[18] Hence, the significance of prospective symptom rating for the diagnosis of these disorders needs re-evaluation.

NEED FOR DIAGNOSIS OF PREMENSTRUAL DISORDERS

PMDD leads to significant economic burden and also impact the quality of life of the affected individuals. Decreased work productivity and increased work absenteeism have been documented.[19] It has also been reported that the mental health related quality of life burden was higher in women with PMDD than the general population.[20]

Detecting PMDs in women of the reproductive age group has implications in the early diagnosis of other mood disorders affecting this category of women. Lifetime comorbidity between PMS and other mood disorders in women have been estimated to be around 30-70%.[18] The risk of developing peri-menopausal depression and postnatal depression has been reported to be higher in women who have PMS.[21-23] Hence, screening of women affected by PMS during these risk periods could enable early detection and better prognosis of depression.

TREATMENT APPROACHES TO PREMENSTRUAL DISORDERS

Obtaining a complete psychiatric and medical history is important prior to initiating management. Medical conditions like anaemia, hypothyroidism and autoimmune disorders need to be ruled out. Psychiatric comorbidities like dysthymia, anxiety disorders, depression, bipolar affective disorder and substance use disorders should be looked for.

Effective management requires precise diagnosis of the condition. Administration of prospective symptom rating scales is mandatory prior to a final diagnosis. The DRSP[9,24] is easily accessible and well validated. A minimum of two consecutive cycles should be rated, and if there is a discrepancy a third cycle has to be rated before confirming diagnosis. Symptom recording can now be achieved online via mobile phone or computer, and the DRSP can be downloaded from the internet.[25]

Many treatment strategies have been claimed to be effective for the management of PMDs, but only a few are supported by clinical evidence. Treatment should be customized in a stepwise manner, with the least invasive treatments as the first strategy followed by more invasive ones. In severe cases with dysfunctional affective symptoms, treatment is aimed at modifying serotonin transmission or suppressing ovulation.

PHARMACOLOGICAL INTERVENTIONS FOR CORE PMDS: SEROTONIN RE-UPTAKE INHIBITORS (SRIS)

The ACOG recommends pharmacotherapy as the first line treatment for PMDD.[26] Numerous clinical trials have proven efficacy of the SRIs over placebo in the management of PMDD and severe mood-related PMS.[27] The response rate for SRIs has been in the range of 60-90% compared to placebo response rate of 30-40%.[28] SRIs have been shown to reduce mood and physical symptoms as well as to improve the quality of life and social functioning. The serotonergic tricyclic antidepressant clomipramine, selective serotonin reuptake inhibitors (SSRIs) like citalopram, escitalopram, fluoxetine, paroxetine and sertraline, and the serotonin and noradrenaline reuptake inhibitor venlafaxine have shown effectiveness.[18]

SSRIs have been shown to have a faster onset of therapeutic action in PMDD than in major depression. This short onset of action makes intermittent dosing (administering the medication only during the luteal phase) possible.[29] Intermittent dosing maybe preferred in women who are concerned with adverse effects and cost associated with long term use of SSRIs. For intermittent dosing to be successful, women should have regular menstrual cycles and should adhere to the timing of dosage. Women with coexisting mood and anxiety disorders who develop mood symptoms outside of the luteal phase, have irregular menstrual cycles, or experience intolerable adverse effects upon SSRI discontinuation should be considered candidates for a continuous daily SSRI dosing regimen throughout the menstrual cycle. Meta-analyses of randomized clinical trials (RCTs) reveal a moderate to large effect size for continuous and luteal phase SSRI treatment, with no clear difference between the two dosing regimens.[29] 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.

Symptom onset therapy is a method that has been examined with fluoxetine, citalopram, paroxetine, sertraline and escitalopram. In this method, women take the SRI as soon as symptoms of PMDD appear, till menstruation.[18,29] *Semi-intermittent dosing* is suitable for women with premenstrual exacerbation of an underlying mood or anxiety disorder. This regime involves a combination of continuous daily dosing of SSRI with increased doses during the luteal phase.[30]

Available evidence regarding the doses required for management of PMDs suggests that the dose should be at least the same as in depression.[27,30,31] If there is insufficient change in symptoms in the first cycle of treatment, the dose might be increased in the next menstrual cycle. Lack of response is considered after

no effect has been documented over several menstrual cycles. In some cases, a second SSRI maybe tried. Women who do not respond to intermittent dosing regimen may respond to continuous dosing regimen.[27,30,31] Failure to achieve any clinical response warrants review of diagnosis and management of other comorbid psychiatric conditions.[32]

Transient side effects like nausea, insomnia, headache, fatigue, diarrhoea, and sexual dysfunction (decreased libido and delayed orgasm) maybe seen after initiation of SSRI.[29] Long-term use of SSRI in a continuous dosing regimen can cause persistent sexual dysfunction which may result in relationship difficulties and poor drug compliance.

PHARMACOLOGICAL AGENTS OTHER THAN SRIS

Alprazolam in the luteal phase has shown modest efficacy for clinically significant premenstrual syndrome in some studies where the predominant symptoms are anxiety/tension and irritability, while others have found it ineffective.[33] It should be avoided in patients with heightened risk for substance dependence and should not be considered as evidence based therapy. Buspirone at a dose of 20 mg has been found more effective than placebo for premenstrual symptoms in small studies but efficacy in PMDs is most likely to be less than that of SSRIs.[33] Non-steroidal anti-inflammatory agents like naproxen sodium are found effective for physical symptoms. Spironolactone at a dose of 25–200 mg/day significantly improved symptoms of breast tenderness, bloating and weight gain in the premenstrual phase compared with placebo in a few studies.[30]

OVULATION SUPPRESSION STRATEGIES

There is minimal evidence for the use of various ovulation suppression strategies in the management of PMDD.[33] Their use is limited by the significant long term side effects. Ovulation can be suppressed by using oral contraceptive pills (OCPs), gonadotropin releasing hormone (GnRH) agonists, and danazol (an androgen analogue). A meta-analysis of combined OCPs containing the synthetic progestin drospirenone found that drospirenone (3 mg) plus ethinylestradiol (20 μg) somewhat reduced severe PMDD symptoms, but there was also a large placebo effect. A series of randomized, double-blind, placebo-controlled trials and one open-label sub-study on continuous dosing of levonorgestrel (90 μg) and ethynylestradiol (20 μg) showed some improvement of symptoms, but a high placebo response rate was there. Leuprolide acetate, a GnRH agonist, produced improvement in women with PMDD who had more of physical symptoms. Synthetic steroid danazol reduced emotional and physical symptoms of the premenstrual phase. Long-term use of danazol can lead to masculinisation and other adverse effects. Careful counselling should be undertaken regarding contraception as danazol can cause virilisation of a developing female fetus. The most invasive strategy for severely dysfunctional women would be a bilateral ovariectomy with hysterectomy. Careful selection of patients is mandatory, with a probable trial of chemical oophorectomy (using GnRH analogues) prior to the procedure, to evaluate the effects of permanent ovulation suppression. After the surgery, replacement levels of oestrogen have to be provided (without progesterone) till the age of menopause.[19,30,33]

ALTERNATIVE TREATMENT STRATEGIES

Very few dietary recommendations have been systematically evaluated for treating PMDs. Most of the clinical trials have used self-reported symptom questionnaires as final outcomes. Also, most studies have sample size less than hundred and only three to six menstrual cycles have been evaluated.

Two small randomised controlled trials (RCTs) reported that a beverage containing simple and complex carbohydrates was superior to iso-caloric placebo beverages in reducing premenstrual symptoms. Increased serotonin levels secondary to increased availability of tryptophan from complex carbohydrates is theorised to be the reason for this effect. Trials have found that supplementation of 1200 mg of calcium daily reduced the emotional and physical symptoms of PMDs by the second or third

treatment cycles. Meta-analyses indicate that 100 mg of vitamin B6 (pyridoxine) have weak superiority over placebo. However, peripheral neuropathy should be monitored and medication should be stopped if paraesthesia or tingling sensations occur. 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. Other recommended dietary supplements like use of magnesium and vitamin E have very minimal evidence.[19,30]

Amongst the other complementary strategies, the strongest evidence is for the herb chasteberry/Vitex agnus castus for reducing the emotional and physical symptoms of PMD compared to placebo. Herbs that require further studies in this context are Hypericum perforatum (St. John's Wort), ginkgo biloba and Crocus sativus/saffron.[19,30]

Reviews of RCTs of cognitive behavioral therapy (CBT) studies suggest weak superiority compared to placebo. CBT for PMDs addresses the irrational thoughts and focuses on improving coping strategies.[34,35] Exercise, by enhancing the beta-endorphin levels, has been reported to improve the premenstrual dysphoria, fatigue and bloating. However, there are no RCTs to confirm this.[36] Modalities with positive initial reports that may deserve further study for women with PMDs include sleep deprivation, bright light therapy, acupuncture, Qi therapy, relaxation, reflexology, massage, krill oil, lavender oil, Chinese herbs and trans-magnetic stimulation. Well-designed clinical trials with these modalities are needed before they can be implemented.

SUMMARY

The diagnostic approach towards PMDs have undergone significant changes. The evidence base of the treatment strategies is still in rudimentary stages. More studies regarding effective dosing regimens is also crucial as severe PMDs have to be treated over a long time and the long-term efficacy, safety and tolerability of these medications need evaluation. Non-pharmacologic interventions for milder forms of PMDs need to be studied systematically. Future studies need to reflect the updated diagnostic categories and need to build on current evidence.

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Source of support: None
Conflict of interest: None declared
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First submitted: 3rd March 2016
Published online: 28th February 2017