Premenstrual Syndrome-A Minireview on Update of Recent Guidelines of Management

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Abstract

Premenstrual Syndrome (PMS) comprises a range of physical, psychological and behavioral symptoms experienced by many premenopausal women during the luteal phase of the menstrual cycle. They experience symptoms like irritability, depression, sleep disorders, breast discomfort, headache, weight gain, changes in appetite, feeling of bloatedness etc. While premenstrual dysphoric disorders is a severe subtype of PMS when a woman is suffering from atleast 5 distinct psychological premenstrual symptoms.

Based on the RCOG guideline, exercise, cognitive behavioral therapy (CBT), vitamin B6, new generation combination oral contraceptives having drospirenone (cyclically or continuously) and or low dose selective serotonin reuptake inhibitors (SSRI’s) used continuously during the luteal phase are recommended 2nd line treatment. Gonadotropin analogues with add back hormonal therapy are recommended as 3rd line treatment, with TAH (total abdominal hysterectomy) with BSO (bilateral salpingooophorectomy) as 4th line treatment. Although progestogens were the most common prescribed treatment earlier it is no longer found desirable, as has the prescription of vitamin B6 decreased, although SSRI prescribing has increased. It is suggested to classify the PMS subtype based on sertraline response for individualized treatment.

Keywords: PMS; CBT; OC with Drospirenone; SSRI; Progestogen; Vitamin B6; Gonadotropin Analogue; TAH with BSO

Introduction

The simplest definition of the premenstrual syndrome (PMS) is a common sense one: the cyclic appearance of one or more of a large constellation of symptoms just prior to menses, occurring to such a degree that lifestyle or work is affected, followed by a period of time entirely free of symptoms. The most frequently encountered symptoms include the following: abdominal bloating, anxiety or tension, breast tenderness, crying spells, depression, fatigue, lack of energy, unprovoked anger or irritability, difficulty concentrating, thirst and appetite changes and variable degrees of oedema of the extremities-usually occurring in the last 7 - 10 days of the cycle. The exact collection of symptom in an individual is irrelevant, the diagnosis is made by prospectively and accurately charting the cyclic nature of symptoms. However the symptoms are not to be underrated: the various symptoms of PMS have been recounted time and again in clinicians offices in poignant details, often noting a feeling of being overwhelmed or out of control. The most common symptoms are the various manifestations of mood disorders, recurring in a stable pattern from menstrual cycle to menstrual cycle [1]. When women's daily moods are prospectively charted a subgroup of women emerges in which mood changes demonstrated a cyclic pattern with increasing symptoms during the luteal phase and an elimination of symptoms at or soon after menses. Fewer than 50% of women who complain of PMS can be demonstrated to have a pattern of mood changes with cyclic pattern [2].

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There are 2 established guidelines for the diagnosis of PMS. The first is from the American Psychiatric Association (APA) and consists of criteria for what APA has designated as the premenstrual dysphoric disorders. According to the APA, this disorder should be differentiated as more severe than PMS; however most assuredly there is a broad spectrum of severity and thus differentiation is not helpful or useful. The APA criteria for diagnosis which corresponds to the previously mentioned simple definition are as follows:

1. Symptoms are temporally related to the menstrual cycle, beginning during the last week of the luteal phase and remitting after the onset of menses
2. The diagnosis requires at least 5 of the following and 1 of the symptoms must be one of the first 4
   - Markedly depressed mood, feeling of hopelessness
   - Marked anxiety or tension
   - Marked affective lability e.g. sudden onset of being sad, tearful, irritable, or angry
   - Persistent and marked anger or irritability, or increased interpersonal conflicts
   - Decreased interests in usual activities
   - Easy fatigability or marked lack of energy
   - Changes in appetite, overeating or food craving
   - Hypersomnia and insomnia
   - Feeling of being overwhelmed or out of control
   - Physical symptoms such as breast tenderness, headache, edema, joint or muscle pain, weight gain
3. The symptoms interfere with work or usual activities or relationships
4. The symptoms are not an exacerbation of another psychiatric disorder. This is in part, a diagnosis of exclusion.

The guidelines from the National Institute of Mental Health (NIMH) state that the diagnosis requires the documentation of at least 30% increase in severity of symptoms, 5 days prior to menses compared with the 5 days following menses [3]. Using the NIMH and APA criteria it is estimated that about 5% of women of reproductive age can be diagnosed with disruptive PMS [4-6].

Approximately 40% of women report problems related to their cycles, and from 2 - 10% report a degree of impact on work or lifestyle [7,8]. The exact prevalence, however is difficult to ascertain. The symptoms are difficult to quantitate. A further problem which complicates evaluation of published studies is, along with evaluation of individual cases, is that behavior is usually related to menstruation in a retrospective fashion. This is prone to marked subjective bias [9]. For e.g. studies in the literature point out that some women do not actually experience problems in relation to menstruation but believe that they do [9]. It is argued convincingly, that most women in culture have been conditioned to expect fluid retention, pain and emotional reactions. These stereotypic expectations are precisely what are reported when retrospectively charting is utilized. Most important, carefully constructed studies (prospective) with appropriate statistical analysis show no significant variation associated with the cycle for cognitive, motor or social behavior and functioning even in women diagnosed in PMS [10-12].

Etiologies and Treatment

There is an impressive list of biological theories

1. Low progesterone (P) levels
2. High estrogen (E2) levels
3. Falling E2 levels
4. Changing E2/P ratio

5. Increased aldosterone activity
6. Increased renin angiotensin activity
7. Increased adrenal activity
8. Endogenous endorphin withdrawal
9. Subsequent hypoglycemia
10. Central changes in catecholamines
11. Vitamin deficiencies
12. Excess prolactin secretion

Studies before 1983 did not incorporate appropriate diagnostic criteria and therefore suffers from inaccuracy and heterogeneity. Since 1983, efforts to isolate a specific pathophysiologic mechanism have failed to demonstrate differences between women with and without symptoms for all hormone levels throughout the menstrual cycle (including E2, P, T, FSH, LH, Prl and SHBG) on weight gain and measurements of substances involved in fluid regulation like aldosterone [13]. This further includes connection could be demonstrated both in the circulating levels and the pattern of secretion over the menstrual cycle. Additionally no connection could be demonstrated between PMS and 2 endogenous metabolites of P, allopregnanolone and pregnanolone [14]. Dynamic testing has shown no abnormalities in the hypothalamo-pituitary axis and its relationship with the adrenal glands, the thyroid glands, the ovaries. No differences can be found in magnesium, zinc, vitamin A, Vitamin E, Thiamine or vitamin B6 [15]. Some have argued for a greater changes in endorphins, proposing that the luteal phase symptom complex is due to a withdrawal from endogenous opioids (in effect an autoaddiction and withdrawal) but others have been unable to detect a difference in circulating endorphins in symptomatic patients [16-18]. Differences have been reported in various biological factors, but these differences are not always confined to the luteal phases. Some of the factors besides endorphins, include response to TRH, melatonin secretion, red blood cell magnesium levels, growth hormone and cortisol response to tryptophan, cortisol response to CRH, free cortisol secretion and cortisol secretion patterns. The strongest argument against a luteal phase hormonal change is derived from experiments utilizing the P antagonist mifepristone (RU-486), in combination with hcg or placebo to induce bleeding at various times during the cycle. Altering the menstrual cycle has no effect on the timing or severity of the PMS response, thus the neuroendocrine and endocrine events during the luteal phase should not be involved.

In general, thyroid function is normal in patients with PMS [19]. About 10% of women with PMS have abnormal thyroid function but this is consistent with the prevalence rate of subclinical hypothyroidism. Although there are no differences in TSH responses, TRH, pts with PMS do demonstrate more abnormal responses, both exaggerated and blunted (which would balance out in group comparisons) [20]. However these abnormal responses occur just as often in the follicular phase, as in the luteal phase. Furthermore, there is no evidence of a therapeutic response to thyroxine compared to placebo even in pts with abnormal response to TRH.

Role of Vitamin D-Not much role has been found [21].

Treatment

Various methods of treatment have been proposed each championing a presumed etiology. All of the following have failed to demonstrate any clear cut benefits over placebo: oral contraceptives; vitamin B6; Bromocriptine; monoamine oxidase inhibitors and synthetic prostegastational agents [22]. The use of spironolactone has many advocates, especially for women with a major complaint of bloating, however appropriate double blind placebo controlled trials have failed to show a clinical impact (other than in bloatedness) greater than placebo. It has been argued that pts with PMS have a deficiency in linoleic acid metabolism and evening primrose oil has been advocated for therapy. Evening primrose oil is extracted from the seeds of the evening primrose, because it provides linoleic acid, gamma linolenic acid (precursors of prostaglandins). Approximately blinded and controlled studies failed to find to find a difference while comparing primrose oil with a placebo. The one present study used retrospective assessment of systems, a method known to be inaccurate [23]. Significant improvement has been noted with the use of prostaglandin synthesis inhibitors but it is difficult to know, if this is influenced by a positive impact on dysmenorrheal [24].

In the past an enormous publicity was given to the use of P treatment by injection or vaginal suppository, long proposed and promoted by Dalton [25]. In early studies that failed to detect a positive effect of P, were criticized for study size and P dose [26-29].

A very well documented study attempted to remove a placebo effect by providing no contact with the investigators or any health care providers during the course of the study, both P and placebo failed to achieve an improvement in symptoms [30]. The criticisms of study size and P dose were effectively removed in a randomized placebo controlled, double blind clinical cross over trial of 168 women [32]. P in doses of 400 mg and 800 mg did not differ from placebo. A later study by the same grp utilized a very large dose 1200 mg daily, also found no difference between P and placebo treatment [49]. P is no better than placebo for the treatment of PMS [33].

Medical and surgical oophorectomy has been described to have dramatic success. A lasting response to surgical TAH with BSO was reported in women unresponsive to medical therapy [34,35]. Gonadotropin releasing hormone agonist treatment has been effective adding E2/P to avoid the side effects of the Gn RH agonists diminished somewhat the improvement in symptoms. However the beneficial effect was still considerable [36-38]. Although medical surgical oophorectomy is undoubtedly effective, it is impossible to blind such treatment and the mechanism is uncertain. In the GnRH agonist steroid add back study, patients receiving a placebo instead of E2/P had a return of symptoms (despite continued GnRH agonist treatment) probably in anticipation of a negative reaction to E2/P. This experience is a strong statement of the power of placebo response, in this case, a negative response. In general, the response to ovarian suppression with Gn RH agonist treatment indicates that the symptoms of PMS represent an abnormal response to normal hormonal changes [39].

The only randomized trials double blinded and placebo controlled, which have had consistent results are those with the selective serotonin reuptake inhibitors and selected antidepressants that have serotonergic activity: fluoxetine, clomipramine, sertraline, paroxetine, citalopram, venlafaxine and alprazolam [32,40-47]. A dose 20 - 60 mg daily of fluoxetine effectively abolished symptoms [40-42]. Further studies established that a 20mg dose of fluoxetine is as effective as higher doses, achieving a rapid response within 2 - 3 months and avoiding the side effects associated with higher doses [45,48]. Treatment can be limited to the premenstrual phase and maybe more effective than continuous administration [49-53]. Alprazolam is a short acting benzodiazepine with anxiolytic, antidepressant and smooth muscle relaxant properties. A dose of 2.5 mgbd-tid during the luteal phase is effective, although some women may require a daily dose of 2.5 mg [32,54,55]. Alprazolam is not the drug of choice, however because of its risk of dependence.

Drospirenone is a progestin that is an analogue of spironolactone. Contraceptive efficacy equal to that of other formulations is achieved in the combination of 3.0 mg drospirenone and 30 µg ethinyl estradiol. Because drospirenone is spironolactone like antiandrogenic and antimineralocorticoid activity it has been suggested that the OC that contains Drospirenone is effective for treatment of PMS. In the only double blind, placebo controlled randomized controlled trial, a statistically significant reduction associated with the OC-treatment was achieved in only one category, the one measuring acne appetite and food cravings [56]. The authors interpreted their results as indicating a general and consistent trend in all symptom groups, suggesting a beneficial effect of this OC. However a close look at the results easily reveals very wide standard deviations around each point and by no point of time this study be considered conclusive or definitive.

**Conclusions**

Premenstrual syndrome (PMS) comprises a range of physical, psychological and behavioral symptoms experienced by many premenopausal women during the luteal phase of their menstrual cycle [57]. The symptoms which are common are irritability, anxiety, depression, mood swings, sleep disorders, fatigue, altered interest in sex, breast tenderness, weight gain, headache, changes in appetite, general aches and pain and feeling bloated [57]. Premenstrual dysphoric disorders (PMDD), a severe subtype of PMS has been defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM) as occurs when a woman suffers from at least 5 distinct psychological premenstrual symptoms [58].

Prevalence estimates of PMS vary depending on the methods used to identify and classify cases. The proportion of women of reproductive age reporting at least one PMS symptom has been reported to range between 50% and 90%, while the percent reporting severe PMS...
symptoms or symptoms which interfere with daily activities range between 10 and 50% and the proportion meeting the strict DSM PMDD criteria of having at least 5 psychological symptoms to range between 1% and 8% [59].

While the proportion of women of reproductive age suffering clinically relevant PMS symptoms appears to be high, the portion of women who seek medical help has been well studied. A survey of 300 women in UK in 1998 classified 31% as having severe PMS symptoms of whom 55% sought medical help [60]. This is similar to 45% and 29% of women with severe premenstrual symptoms seeking medical attention in the USA and France in 1998 respectively, while 49% of women with severe PMS in a separate study in Switzerland reported consulting a doctor between 1986 and 1999 [61].

Evidence-based guidelines for the management of PMS has been published by RCOG [62] and recently by the International Society for Premenstrual Disorders (ISPMD) [63]. The RCOG guidelines suggest the use of exercise, cognitive behavioral therapy (CBT), Vitamin B6, new generation combined OCS (cyclically or continuously) and/or low dose selective serotonin reuptake inhibitors (SSRIs) used continuously or during the luteal phase as 2nd line treatment. Gonadotropin analogues (with back hormone replacement therapy are recommended as 3rd line treatment and TAH with BSO with hormone replacement therapy as 4th line treatment. The ISPMD recommends both SSRIs and all of the oestrogen suppressing treatments listed above but does not recommend different treatment and dosing schedule for specific treatment lines. A study investigating treatment prescribed between 1993 and 1998 in UK found progestogens were the most commonly prescribed treatment and that Vitamin B6 prescribing decreased over the period while SSRI prescribing increased [64].

Sammon, et al. recorded the current prescribing methods in UK and found in last 19 yrs the rate of recording of PMS diagnosis decreased over calendar time from 8.43 in 1995 to 1.73 in 2013. Of the 38614 women without treatment in the 6 months prior to diagnosis 54% received a potentially PMS related prescription on the day of their 1st PMS record while 77% received a prescription in the 24 month after. Between 1995 and 1999, majority of women were prescribed progestogens (23%) or vitamin B6 (20%) on the day of their 1st PMS record; after 1999 these figures fell to 3% for progestogen and Vitamin B6 with the majority of women instead being prescribed a SSRI (28%) or combined OC (17%). Thus they concluded that recording of PMS diagnosis in UK primary care has declined substantially overtime and preferred prescription treatment has changed from progestogens to SSRI and combined OC [65]. On basis of response to sertraline Freeman, et al. divided PMS into clinical subtypes and found PMS and PMDD have similar response to sertraline treatment but symptoms based subtypes have significant different responses to this treatment. Mixed and psychological symptoms subtypes improved while the physical symptom subtype did not improve significantly. Identifying the patients predominant symptoms and their severity is important for individualized treatment and possible response to a selective SSRI [66].

Bibliography


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