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REVIEW

Premenstrual Syndrome (PMS)

Wicharn Choktanasiri MD.

Department of Obstetrics and Gynaecology, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand

ABSTRACT

Premenstrual syndrome (PMS) was first recognized by RT Frank in 1931. However, it was not until 1983 that PMS diagnostic criteria was rather clearly established by The American Psychiatric Association (APA). Various aetiologies have been proposed and recently many studies suggest a deficiency of serotonin in the central serotonergic system. Diagnosis of PMS must be made by prospective recording of the luteal phase related symptoms. Other medical and psychological disorders should be excluded and managed accordingly. Patients with predominantly specific physical symptoms may be treated with specific therapy. Pain-related symptoms should be treated with prostaglandin synthetase inhibitors. Mastalgia may be treated with bromocriptine and significantly weight gain in luteal phase with spironolactone. Psychotropic drugs, especially fluoxetine or alprazolam, may be the first line treatment of severe PMS because of ease of administration and tolerability. Ovulation suppression agents should be preserved for patients who cannot tolerate or do not respond to psychotropic agents. GnRHa with estrogen and progestin add-back may be a good choice for this purpose .

Key words : premenstrual syndrome (PMS), aetiology, diagnostic criteria, treatment

Premenstrual syndrome was first recognized by RT Frank in 1931 to describe a constellation of physical emotional and behavioral symptoms occurring for up to two weeks prior to menses with relief soon after the onset of the menstrual period. Since then, many theories and treatment regimens have been proposed. However, there is no single intervention that will uniformly eradicate premenstrual syndrome and its aetiology remains unknown. There are some main problems associated with the research literature on PMS :

1. Subject selection issues : It was not until 1983 that PMS diagnostic criteria was rather clearly established.[1] Studies prior to 1983 did not incorporate appropriate diagnostic criteria, and therefore suffer from inaccuracy and heterogeneity. Early studies usually admitted subjects who reported premenstrual symptoms and collection of symptoms were retrospective recalls, which are considered to be unreliable.

Moreover, women with concurrent major psychiatric disorders were usually not excluded.[2]

2. Poorly validated and unreliable symptoms measurement techniques : PMS has a large constellation of symptoms (over 100) which almost all are subjective ones. Comparison of treatment results from different studies are very difficult and may be inconsistent.

3. Placebo response rates : Because of high placebo response rate in PMS treatment, any research in treatment of PMS should be a double - blind, placebo-controlled, crossover study. However , the choice of placebo itself can still be a problem. For example, in a placebo-controlled trial of a diuretic or an antidepressant, subjects could probably identify the period of treatment with the active drug because of its adverse effects. If they do, the blind is broken and the study becomes open to expectation bias.[2]

DEFINITION

The simplest definition of the premenstrual syndrome (PMS) is the cyclic appearance of one or more of a large constellation of symptoms (over 100) 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. Symptoms usually occur in the last 7 to 10 days of the cycle. The diagnosis is made by prospectively and accurately charting the cycle nature of the symptoms.[1,3]

The American Psychiatric Association (APA) uses the term late luteal phase dysphoric disorder (LLPDD) which appears in the "RESEARCH APPENDIX" of the Diagnostic and Statistical Manual of Mental Disorders, Third edition, Revised (DSM- 3-R). This was published in 1987. These criteria have little modified in 1994 and designated as premenstrual dysphoric disorder (PDD). They are summarized in Table 1.

Table 1. Summary of PDD criteria[4]

A. Symptoms must occur during week before menses and remit a few days after onset of menses
   Five of the following symptoms must be present and at least one must be (1), (2), (3), or (4).
   1. Depressed mood
   2. Anxiety
   3. Lability
   4. Irritability
   5. Decreased interest in usual activities
   6. Difficulty in concentrating
   7. Marked lack of energy
   8. Marked change in appetite, overeating, or food cravings
   9. Hypersomnia or insomnia
   10. Sense of being overwhelmed
   11. Other physical symptoms, e.g., breast tenderness and headaches
B. Symptoms must interfere with work, school, usual activities, relationships
C. Symptoms must not merely be an exacerbation of another disorder
D. Criteria A, B and C must be confirmed by prospective daily ratings for at least two cycles

It should be noted that term PMS and LLPDD or PDD sometimes are used interchangeably. However, acccordingly to the above criteria PDD may be considered a severe form of PMS with predominantly mood symptoms. Some authors also suggested that the aetiology of LLPDD may be different from that of the milder, more somatic forms of PMS and therapeutic strategies will most likely be different.

EPIDEMIOLOGY

Most reproductive-age women appear to experience recurrent premenstrual physical and/or emotional symptoms, although the overall prevalence reported varied between 30 and 90%.[5] In 17 to 40% of women report significant or worrisome problems related to their cycles.[5] Approximately 2.5 - 5% of women of reproductive age meet criteria for PMS.[6] PMS has been reported in all reproductive age groups. No consistent association has been found between PMS and demographic or dietary variables, amount of exercise, level of psychological stress, menstrual cycle characteristics.[5,7,8] The only clinical variable that has been shown to be associated with PMS is mental disorders, both concurrent and lifetime, are high.[9] The strongest association seems to be with lifetime prevalence of affective disorder, especially major depression.[10] Studies also suggested an elevated frequency of postpartum depression up to about 40%.[10] However, Pop VJ et al found that PMS was significantly related to postpartum depression only at the time of the women resumed menstruation (post - puerperium) and suggested that screening on postpartum depression partly involves screening on depressive symptoms related to PMS.[11] Studies in twins suggested increased concordance for heritability of PMS.[12]

AETIOLOGY

Many theories have been proposed to be the aetiology of PMS. These theories are[1] :

Low progesterone levels
High estrogen levels
Falling estrogen levels
Changes in estrogen : progesterone ratios
Increased aldosterone levels
Increased renin - angiotensin activity
Increased adrenal activity
Endogenous endorphin withdrawal
Central changes in catecholamines
Vitamin deficiencies .... etc .

These can be grouped into the following categories :

1. Hypothalamus - pituitary - ovarian axis

The close association of the symptoms of PMS with the luteal phase of the menstrual cycle has led to the postulate that PMS reflects either a physiologic abnormalities or an abnormal to the normal hormonal changes during the luteal phase. Most studies reported no different plasma level of progesterone in PMS patients compared to control.[13,14] Even if some reported lower progesterone level in PMS patients, almost all were the studies before 1983 and the administration of progesterone during the luteal phase of the menstrual cycle in women with PMS has not been more therapeutically effective than placebo.[15,16] Moreover, a significant study by Schmidt et al using the progesterone antagonist (mifepristone) to induce menses or luteolysis suggested that symptoms of PMS could occur even in the absence of the luteal phase. They concluded that endocrine events during the late luteal phase do not directly generate the symptoms of PMS.[17] In another study, Chan et al found that luteal phase administration of low - dose RU 486 does not significantly reduce

the physical or behavioral manifestations of PMS and suggested that progesterone or progesterone receptors are not important mediators of PMS.[18]

Recent studies have reported luteal abnormalities in amplitude and frequency of pulsatile luteinizing hormone secretion.[19] However, the others did not confirm this result.[20] In general most studies have failed to demonstrate differences between women with PMS and control for all hormonal level throughout the menstrual cycle, including estrogen, progesterone, testosterone, follicle - stimulating hormone (FSH), luteinizing hormone (LH), prolactin, and sex hormone binding globulin.[21] However, in anovulatory cycles whether spontaneous or induced by medical or surgical intervention are associated with disappearance of symptoms in PMS.[22,23] This is obvious that hypothalamus - pituitary - ovarian axis must be involved in pathogenesis of PMS .

2. Hypothalamus - pituitary - adrenal axis

Based on the similarity of symptoms of PMS and those observed in major depression, extensive studies have been made to use biochemical markers in endogenous depression as indicators that might be useful in the diagnosis of PMS.[9,24] Patients with primary affective disorders, such as melancholic depression and anorexia nervosa, during episodes of illness frequently have a hyperactive hypothalamus-pituitary - adrenal (HPA) axis. This is characterized by hypersecretion of Corticotropin-releasing hormone (CRH) and a blunted ACTH response to exogenous CRH.[25] Studies have included sampling of urinary free cortisol, plasma cortisol circadian secretory profiles and responses to serial dexamethasone suppression test (DST). Most have found that there were no significant differences in HPA function between the follicular and luteal phases in women with PMS and between those with PMS and control.[21] Recent studies have conflict results. Rabin et al found that basal evening plasma cortisol in PMS was significantly lower than control and the time-integrated response of plasma cortisol to bovine CRH was significantly increased.[25] While Parry BL et al found that plasma cortisol in women with PMS was increased during midcycle phase and DST showed a 62% overall rate nonsuppression, irrespective of menstrual cycle phase.[26] However, this study had no control subject.

3. Thyroid function

It has been known for some time that hypothyroid patients tend to show symptoms of depression. In 1986 it was reported that 94% of women with PMS were found to have thyroid dysfunction, mostly subclinical hypothyroidism which defined by an augmented response to TSH to TRH. They successfully treated all affected women with L - T4 therapy.[27] They expanded their previous work in a second study and it was clear from this study that the subject selection criteria were insufficient.[28] Almost all subsequent studies have not found thyroid dysfunction in PMS.[29] No significant differences were detected in TSH responsiveness to TRH during both follicular and luteal phases.[29] In addition, administration of L-T4 to treat PMS is not better than placebo.[29,30]

4. Nutritional factors

Nutritional supplements have been used widely as treatment of PMS for many years.[2,31] These were based on various proposed aetiologies. However, an excess or deficiency of dietary factors, vitamins and minerals (magnesium, zinc, vitamin A, vitamin E, thiamine, or vitamin B_6) has not been consistently demonstrated in patients with PMS compare with control subjects. Other studies have mixed results ; these includes zinc deficiency, copper

excess, magnesium and zinc deficiency, calcium deficiency or excess, etc.[31,32] It should be noted that administration of vitamins and minerals to treat patients with PMS is not without harmful effect, especially with high dose. For examples, magnesium supplements could interfere with the absorption of calcium and there is a dose-versus-time relationship (larger doses induce symptoms more rapidly) for the development of neurological symptoms in using of megadose of vitamin B_6.[2] At this time the role of vitamins and minerals in PMS, if any, is only speculative and need further clarification.

5. Central changes in catecholamines

In recent years serotonin function was widely studied. It was known that abnormal serotonin metabolism has been linked with certain types of depressive disorders.[33] Blood platelets are utilized as a model of the serotonergic neuron because serotonin uptake, storage, release and metabolism are postulated to be similar in the platelet and in the serotonergic nerve ending. Patients with depression have decreased uptake of serotonin and this decreased uptake may serve as a marker for decreased central serotonergic activity.[34] Rapkin et al found that serotonin levels of premenstrual syndrome subjects were significantly lower during the last ten days of the menstrual cycle.[35] These studies suggest a deficiency in the central serotonergic system. Several treatment trials utilizing pharmacologic agents that release serotonin or block its re-uptake have been shown to be effective for treatment of PMS. However, the serotonergic system is unlikely to be the only system involved in the pathogenesis of PMS.[33]

6. Others

Studies have also examine the effect of menstrual cycle phase on the opiate system, aldosterone activity and multiple other substances.[3] At present no clear cause has been identified with any of these substances and their relationship to the menstrual cycle. In conclusion, even if the aetiology of PMS is still unknown, research related to PMS has advanced in the last few years. Several factors probably contribute to/or interact in the PMS, and it is expected that the aetiology of PMS will eventually be explained by the interaction of gonadal steroids with the central neurotransmitter (probably serotonin), neuroendocrine and circadian systems that influence mood, behavior and cognition.

DIAGNOSIS

According to the definition of PMS and criteria of PDD,[1,4] the pathognomonic for the disorder is the marked fluctuations of symptoms with the menstrual cycle. Symptoms must be confined to the luteal phase. During the time from about the fourth day after the onset of menses until at least cycle day 12, symptoms, if they occur at all, are sporadic and no more frequent than those seen in the general population. Women with cycle that are typically shorter than 26 days in length may have the onset of symptoms slightly earlier than day 12.[6] Women are required to prospectively record their symptoms daily for at least two menstrual cycles. Several prospective rating scales are available.[36] Symptoms associated with PMS include : mood (irritability, mood swings, depression and hostility), somatic (bloating, mastalgia, appetite changes, hot flashes, insomnia, headache, and fatigue), cognitive (confusion and poor concentration) and behavioral (social withdrawal, hyperphagia and arguing). The presence of multiple symptoms is so characteristic that, if the woman has only one symptom, another diagnosis should be considered.[36] Because these symptoms are not unique to PMS, one must

exclude the concomittant medical or psychiatric disorders. The differential diagnosis of cyclic symptoms includes : 1) PMS, 2) PMS plus another disorder, 3) cyclic exacerbation of other disorder, 4) noncyclic other disorder, 5) menstrual - phase symptoms, 6) oral contraceptive use - associated symptoms.[37] The list of "other disorders" is diverse. The most common are psychiatric disorders, especially depression and anxiety. Medical disorders that can present with a luteal - phase pattern include migraine headache, convulsive disorder, irritable bowel syndrome and hypothyroidism.[36] Assessing the symptoms in PMS must also be performed in the absence of any pharmacologic intervention.[6]

Some authors have recognized symptoms of PMS in four patterns, these include : 1) symptoms that gradually increase in severity throughout the luteal phase and abruptly stop with the onset of menses, 2) similar timing of gradually worsening symptoms that continue into the early follicular phase of the next cycle, 3) severe symptoms limited to only a few days in the late luteal phase, 4) two distinct periods of severe symptoms, one around the time of ovulation and a second just before menses.[38]

TREATMENT

Recent advances in the understanding of the pathogenesis of premenstrual syndrome (PMS) have allowed the development of appropriate pharmacological management in PMS. Several well - designed studies with promising results have been conducted that guide the physician's treatment of PMS. Less - proven nonpharmacological modalities (dietary modification, exercise regimens, psychotherapy, etc.) and some medications are quickly supplanted by the use of more - proven medication.[39] Treatment and intervention for treatment of PMS were summarized in Table 2 .

"Placebo response" plays some roles in

Table 2. Summary of modalities in treatment of PMS

Intervention	Method/Dose	Comment	Ref.
1. Non-pharmacologic			
1.1. Diet Modification	e.g. Limit salt intake, eating frequent, small meal with complex carbohydrate, decreased sugar and caffeine, no alcohol, etc.	- can be considered healthful but no evidence of their efficacy in PMS - can gain some control over patient's symptoms - do not clearly indicate a role to treat PMS - need further more well - controlled studies	2, 36
1.2. Relaxation and behavioral therapy	-	- do not clearly indicate a role to treat PMS - need further more well - controlled studies	40
1.3. Light therapy	Bright light (>, = 2,500 lux)	- need further studies	41
1.4. Aerobic exercise	Regular exercise tailored to the	- can be considered healthful but has not been tested directly as a	42

Intervention	Method/Dose	Comment	Ref.
	capabilities of the individual woman	therapy for PMS - fewer premenstrual symptoms (molimina) in several studies	
2. Vitamin and Mineral			
2.1. Vitamin E	alpha-tocopherol 150 - 600 unit/day	- insufficient data to support use - not recommend	43
2.2. Vitamin B_6 (pyridoxine)	50 - 500 mg/day	- weak evidence of its benefit - a dose-versus-time relationship for the development of peripheral neurotoxicity - chronic use of as little as 200 mg carries a risk of neurotoxicity	44 36
2.3. Optivite (high dose multivitamin)	12 tabs/day	- equivocal result - at recommended dose has potentially unsafe levels of vit. B_6 (600 mg) and vit. A - expensive and not recommend	45
2.4. Primrose oil	500 mg tid	- not better than placebo - expensive and not recommend	36, 46
2.5. Calcium	1,000 mg of elemental ion	- improved luteal - phase negative mood, fluid retention and pain in some studies - make sense to general health - can be supplemented by natural sources of calcium	47
3. Drugs			
3.1. Prostaglandin inhibitors			
3.1.1. Mefanamic acid	250-500 mg tid (luteal phase)	- effective in pain - related symptoms	48
3.1.2. Naproxen sodium	550 mg bid (luteal phase)	- effective in pain - related symptoms, especially in menstrual migraine	36
3.2. Bromocriptine	2.5 - 5.0 mg OD (luteal phase)	- useful for the treatment of premenstrual mastalgia - high adverse effects such as headache, fatigue, etc.	36
3.3. Diuretics			
3.3.1. Spironolactone	25 - 50 mg bid (luteal phase)	- research data not convincing - may be useful in patient with luteal phase weight gain > 5 lbs. - generally not recommend	49 36
3.3.2. Thiazides	25 - 50 mg bid (luteal phase)	- risk of diuretic dependence and rebound cyclic edema - not recommend	50
4. Hormone			
4.1. Thyroid	levothyroxine sodium	- has no more effective than placebo	28, 29

Intervention	Method/Dose	Comment	Ref.
hormone	0.13 mg/day	in treatment of PMS	
	-	- not recommend	
4.2. Oral contraceptives	monophasic or triphasic pills	- almost all studies focused on premenstrual symptoms, not PMS - a decrease in dysmenorrhea and some molimina was noted but some subjects experienced more depression - Absence of any well - designed, contemporary studies of OCP, especially low dose OCP, use in treatment of PMS - OCP cannot be recommended as PMS treatment at this time	51
4.3. Progesterone	200-800 mg vag.sup. or 300 mg of oral micronized form (luteal phase)	- not better than placebo in almost all studies - should be avoided	15, 16 52
5. Psychotropic Drugs			
5.1. Serotonergic agents			
5.1.1. Antidepressants			
5.1.1.1. Fluoxetine	20 - 60 mg daily (usually 20 mg)	- acts as the selective presynaptic serotonergic reuptake inhibitor - consistently promising results in several well-designed studies for treatment of severe form of PMS or PDD - improvement was found in affective or behavioral than physical symptoms - at low dose (20 mg/day) minimal and tolerable side effects were sexual dysfunction and insomnia - may be considered the first-line treatment for severe PMS or PDD	3, 39 53 - 55
5.1.1.2. Nefazolone	100-600 mg/day	- serotonergic type2 antagonism and serotonin reuptake inhibitor - premenstrual symptoms were improved significantly - needs placebo - controlled studies	56
5.1.1.3. Paroxetine	20-25 mg/day	- selective serotonin reuptake inhibitor - superior to the noradrenaline reuptake inhibitor (maprotiline, another antidepressant) and placebo in severe PMS - needs more studies	57
5.1.2. Fenfluramine	15 mg bid	- stimulates the release of serotonin	58

Intervention	Method/Dose	Comment	Ref.
	(day 14 to day2)	and blocks its reuptakes - significantly decreased carbohydrate consumption and reduced depression scores - needs more studies	
5.1.3. Buspirone	25 mg daily (luteal phase)	- 5HT1A partial agonist - initially suppresses serotonin raphe cell firing, but subsequently potentiate the serotonin system, probably through autoreceptor desensitization - more effective than placebo to treat irritability, fatigue, pain and social functioning	59
5.2. Tricyclic Antidepressants			
5.2.1. Clomipramine	25 - 75 mg/day daily or in luteal phase	- more effective than placebo for PMS or PDD - even at low doses were associated with sedation, dry mouth and constipation	60
5.2.2. Nortriptyline	50 - 125 mg/day	- good therapeutic response in a pilot study, but all subjects noted some adverse effects - needs well controlled studies	61
5.3. Others			
5.3.1. Alprazolam	0.25 mg bid-tid in luteal phase and decreased by 25% daily after initiation menses	- inhibits CNS arousal through potentiation of GABA receptors - short acting benzodiazepine with anxiolytic and antidepressant properties - statistically superior to placebo for specific symptoms such as tension, irritability, anxiety, depression - not effective in one study - may be useful in treatment of severe PMS but must be aware of the adverse effects, tolerance and dependence	16 62 63
5.3.2. Naltrexone	25 mg twice (day 9 to day 18)	- opiate antagonist - associated with significantly fewer symptom than placebo - may be hepatotoxic	2, 64
5.3.3. Clonidine	17 ug/kg/day in 4 divided doses	- effective in reducing psychiatric symptoms, specifically in a subgroup of women with PMS who had cyclic decreases in beta-endorphin levels	65

Intervention	Method/Dose	Comment	Ref.
6. Ovulation Suppression			
6.1. GnRH Agonist	3.75 mg leuprolide IM , monthly or 3.6 mg goserelin SC monthly or 50 ug buserelin SC daily or 400-600ug buserelin intranasal, daily	- suppression of ovulation - effective for both behavioral and physical symptoms in severe PMS or PDD (in most well- controlled studies) - risk of osteoporosis and other unpleasant symptoms of hypoestrogenemia	66, 67
6.2. GnRH a + add back	(6.1) + CEE 625mg D1-25+ MPA10mg D16-25 * start CEE + MPA after GnRHa 2 months	- may extend safety and efficacy of GnRHa for treatment of severe PMS - further research is being studied	68, 69
6.3. Estrogen	- estradiol implant 100 mg + cyclic progestin	- more effective than placebo in severe PMS - some developed PMS-like symptoms during progestin administration - high adverse effects from progestin	70
	- transdermal estradiol 1-200ug twice weekly + cyclic progestin	- more effective than placebo in severe PMS - 100 ug dose is effective and better tolerated - this regimen appears promising	2, 71
6.4. Progestin	MPA 1-30 mg daily or DMPA 150 mg IM every 3 months	- significant improvement in mood and less breast discomfort in one study - generally has not been tested in well- controlled studies - can induce PMS - like symptoms itself	1, 2, 36
6.5. Danazol	200 - 400 mg / day	- superior to placebo in many symptoms (depression, tension, irritability, mastalgia, swelling, etc.) - relatively high side effects and potential long term risks (from both hypoestrogenic and androgenic effects) - needs long term studies of the safety and efficacy)	2, 72
7. Hysterectomy with bilateral ovariectomy	(supplement with low dose estrogen after operation)	- may be indicated for a small, selected group of women who do not respond to conventional therapy	22, 23

PMS in all studies. Some authors recommended to replace this term by "the response to care" or "the response to the doctor" or "the healing response" this is to emphasize that it is a) powerful b) no less than drug actions and c) embedded in every therapeutic transaction.[1] PMS is chronic, very bothersome and varying in severity and symptoms. Physicians should keep all these in mind. Diagnosis of PMS by prospective recording of the luteal phase related symptoms is the very important step in the management of PMS. Other medical and psychological disorders must be excluded and managed accordingly. Meanwhile this is the time to create the doctor-patient relationship. Patients with predominantly specific physical symptoms ay be treated with specific therapy.[1,36] Pain-related symptoms should be treated with prostaglandin synthetase inhibitors, mefanamic acid or naproxen sodium. Mastalgia may be treated with bromocriptine and significantly weight gain in luteal phase may be treated with spironolactone. Psychotropic drugs, especially fluoxetine or alprazolam, may be the first line treatment of severe PMS or PDD because of ease of administration and tolerability.[3] Ovulation suppression agents should be preserved for patients who cannot tolerate or do not respond to psychotropic agents. GnRHa with estrogen and progestin add-back may be a good choice. Hysterectomy and bilateral oophorectomy is rarely indicated and should be done only if all of the following stringent criteria are met.[22,23,36]

1. No response to any therapy except danazol or GnRHa suppression
2. Complete resolution of symptoms while receiving one of these two regimens for a minimum of 4 - 6 months
3. Childbearing completed
4. At least 5 years of menstrual functioning remain and preferably 10 - 15 years.

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