Aetiology, Diagnosis And Management Of Premenstrual Changes (Pmcs): Current Views

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Abstract

PMCs are a budding issue having both the psychiatry and gynecology-related symptoms with adverse social consequences. It is an affective disorder occuring in the luteal phase (the time between ovulation to the onset of menstrual bleeding) of the menstrual cycle (MC). PMCs range from mild mood fluctuations, called Premenstrual Syndrome (PMS) to severe mental and physical disturbances, called Premenstrual Dysphoric Disorder (PMDD). The exact aetiology of PMCs is largely under-explored. Its diagnosis and management are often difficult. The present article is a short review of current PMCs-research (its aetiopathology, diagnosis and management) with tentative research proposals.

INTRODUCTION

Menstruation is a biological stress for females during their reproductive life. Anxiety, lethargy, household confinement, blood loss, irregularity, weakness, and several deep-rooted cultural taboos make menstruation a regular and nagging, but inevitable event to many of them. Often a series of physical and emotional turmoil are observed in some particular group of females just for few days prior to menstruation, which are apparently vague, bizarre but troublesome called PMCs.

PMCs have gained its importance because of so many possible social implications. As PMCs are thought to be the hypersensitive response of the nervous systems in the body during the luteal phase of menstruation, it is well apprehended that such hyperactivity might induce bad social impacts, e.g., crime[1], suicidal acts[2], accidents[3] or even death from several diseases in the vulnerable females[3].

The present article is a Meta analysis of the relevant literature, available in various Electronic Journal Bases (e.g., MEDLINE/Cochrane Library and MEDSCAPE) providing a lot of aspects of PMCs-research, available till date.

PMS was observed as early as in the year 1931[4], officially reported to the scientific community in 1951 by a physician[5], in 1953 by general practitioners[6] and in the same year by a psychiatrist [7]. Therefore, PMCs shares a common platform of day-to-day medical practice.

PMCs range from Premenstrual Syndrome (PMS), the milder form (approximately 75% of the affected female population) to the Premenstrual Dysphoric Disorder (PMDD), the severe form (approximately 3-8% of the female sufferers)[8]. PMS usually starts in the early twenty years of age but rarely needs treatment until another 10 years[8]. Therefore PMCs usually present during the mid or late thirty and therefore, sometimes it is extremely difficult to determine whether the symptoms are of PMS or Perimenopausal syndrome! Although PMS-symptoms occur only in the luteal phase of the MC and remits approximately three days after the onset of menstruation[8], which is usually not that specific in the patients of perimenopausal syndrome.

SYMPTOMATOLOGY AND DIAGNOSIS

PMC (especially PMS) symptoms (approximately over 150) are complex and multiple. Efforts have been made to classify these symptoms in clusters according to systems involved related to the presenting symptoms[9]. The symptoms of PMS ranges from either alone or in combination of uncontrollable mood swings, irritability, undue anxiety, sense of bloating with associated physical symptoms like lethargy, tiredness, listlessness, mastopathy, sore throat, insomnia, genito-urinary complains, frequent headaches, development of acne and so on. Amidst the crux of symptoms, it is often difficult to diagnose PMCs. Presently some diagnostic tools, e.g., Premenstrual Experiences Calendar, PMS diary, Daily Record of Severity of Problems and many others for screening of PMCs are recommended[8], though no single tool

is absolutely valid and bias free. The bias is autogenerated and stimulated by the questions itself.

The preferred guidelines given by (American College of Obstetrics and Gynaecology) ACOG as to diagnose PMS is as follows[10]:

- Symptoms consistent with PMS (mentioned above),
- Restriction of these symptoms to the luteal phase (the last 2 weeks of the MC)
- Impairment of some major aspects of the female's life, and
- Exclusion of other disorders those may present symptomatic likewise.

The convention given by ACOG is that the diagnosis of PMS is based on diaries maintained by females regularly charting their symptoms, if possible for two to three consecutive months. Reviewing these diaries is mandatory because only a few females visit a doctor for evaluation and treatment of PMS. This is because many other medical conditions are worsened in the late luteal or menstrual phase of the cycle, known as "menstrual magnification"[10]. The disorders commonly affected by menstrual magnification, mistaken for PMS are depression, obsessive-compulsive disorders[11], migraine, headaches, seizure disorders, irritable bowel syndrome, asthma, chronic fatigue syndrome, and various urticarias or allergies[10].

Unlike PMS, PMDD is included under the domain of psychiatry and the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders, 4[[[th]]] Edition, Text Revision) criteria for its diagnosis are[12]:

In most MCs during the past year, presence of >=5 of the following symptoms for most of the last week of the luteal phase, with remission beginning within a few days after the onset of the follicular phase, and absence of symptoms during the week after menses; inclusion of >=1 of the first 4 symptoms:

- Markedly depressed mood, feeling of hopelessness, or self-deprecating thoughts,
- Marked anxiety, tension, feeling of being "keyed-up" or "on edge",
- Marked affective lability (e.g., feeling suddenly sad or tearful or having increased sensitivity to rejection),
- Persistent and marked anger or irritability or increased interpersonal conflicts,
- Decreased interest in usual activities (work, school friends, and hobbies),
- Subjective sense of difficulty in concentrating,
- Lethargy, easy fatigability, or marked lack of energy,
- Marked change in appetite, overeating, or specific food cravings,
- Hypersomnia or insomnia,
- Subjective sense of being overwhelmed or out of control,
- Other physical symptoms such as breast tenderness or swelling, headache, joint or muscle pain, a sensation of "bloating", weight gain,
- Marked interference with the work or school activities and relationship with others (e.g., avoidance with social activities or decreased productivity and efficiency at work or school),
- Disturbance not a mere exacerbation of the symptoms of another disorder, such as major depressive, panic disorder, dysthymic disorder, or a personality disorder (although possibly superimposed on any of these disorders), and
- Confirmation of three criteria above by prospective daily rating during at least two consecutive symptomatic MCs (diagnosis may be made provisionally before such confirmation).

In nutshell, the diagnosis of PMS or PMDD needs the following things to be checked:

1. The patient is usually of mid or late-thirties,
2. Mental and physical symptoms and signs, mentioned above, are exclusively present in the luteal phase and not in the follicular phase of the MC,
3. This is happening in at least two consecutive MCs,

and

4. Decreasing ability of coping in the professional or social life.

AETIOPATHOLOGY

PMCs are multifactor psychoneuroendocrine disorder. Various factors are identified as the possible causes of PMCs. The present study concentrates on the HPA axis dysregulations, possibly by steroid hormones and biogenic amines during the luteal phase of the MCs behind the emergence of PMCs.

Hypothalamic-Pituitary-Adrenal (HPA) axis is apprehended to be one of the important contributors for the PMCs, as it is typically dysregulated in affective disorders, e.g., major depression[13]. Further, progesterone is a gonadal steroid hormone known to increase the HPA axis response to physical exercise[13]. As PMS patients show less HPA-response related to physical stress than the controls, it is assumed that due to some unknown abnormally low response of progesterone (neither related to its low serum level[14], nor its structural abnormality[15]) in the luteal phase on HPA axis could be responsible for the onset of PMS[13]. Studies are yet to be done to see whether HPA-axis itself was dysregulated so that there is a low progesterone response.

Regarding the functions of other steroidal hormones in PMCs, few studies have hypothesized that oestrogen could be beneficial in reducing the depressive episodes in PMCs by virtue of it's modulatory roles on a) monoamino oxidase, catechoamine, dopamine, serotonin and other metanephrine metabolisms[16] and b) noradrenergic agonistic actions[16] although many recent studies have denied such hypothesis[14].

Adrenocorticotrophic hormone (ACTH) and cortisol are other apprehended biological correlates of PMS. It is found that serum level of ACTH is low in the PMS patients, especially in the luteal phases of their cycles and this is why PMS patients are less able to cope up with the emotional and physical stress, though further studies are needed to confirm it[17].

Apart from gonadal steroids, biogenic amines like a-melanocyte stimulating hormone (a-MSH) synthesizing hormone and ß-endorphine synthesizing hormone cause changes in the brain-hypothalamic-pituitary complex and thus alter mood and behavior. Variable actions of these on the brain-hypothalamic-pituitary system could be the reason for behavior and mood-related disturbances in PMCs[18] and beta-endorphine level co varies with the level of oestrogen[16].

Leptin, another biogenic amine and metabolic regulator of the hypothalamus-pituitary-gonadal axis plays a significant role in the neuroendocrine system in the brain, especially on the emotion[19]. Radioimmunoassay of leptin concentration in the serum of PMS patients shows a significant increment of leptin concentration during the luteal phase of the MC without any correlation between the leptin concentration and the level of oestrogen and progesterone [19].

Modulation of gamma aminobutyric acid (GABA) by gonadal hormones is another factor at the backdrop of PMDD, the severer form of PMS. A magnetic resonance spectroscopic (MRS) study shows that oestradiol (the most potent of the available natural oestrogens), progesterone and allopregnanolone possibly disturb the GABA-ergic system at the central cortical level from early follicular to the late luteal phase of MCs in patients with PMDD[20]. A Sleep Electroencepalogram (EEG) study has shown that GABA-inhibitory effects of the steroidal hormones, indicated by low saccadic eye movement and poor sleep in the luteal phase of the PMDD patients, could be the reasons of mood-lability and behavioral disturbances[21]. Moreover, poor sleep pattern in the patients of PMDD may be due the dysregulatory sensitivity at the GABA-A-benzodiazepine receptor complex by certain progesterone metabolites, secreted from corpus luteum in the luteal phase and this may be the underlying mechanism for such mood disorders in the patients of PMDD[22]. Another interesting sleep EEG study has shown that PMS patients with negative symptoms show reduced delta sleep during both the follicular and luteal phase of the MC, markedly shorter rapid eye movement (REM) latency compared to the healthy subjects[23]. Therefore it is the central GABA-ergic and not the PBR is significantly associated with PMS pathology. Apart from the ‘central' GABA-ergic system, studies have been done to note any relationship between ‘peripheral' benzodiazepine receptor (PBR) complex and the onset of PMDD. It is found that PBR density remains unchanged compared to the normal control and moreover, administration of ovarian steroids does not make any difference to its status [24] (cf. central benzodiazepine receptor complex).

Cerebral serotonin neurotransmitter system (5-HTs) is an important component, involved in a large number of psychiatric illnesses where the affect is disturbed[25]. PMDD is another extreme reflection of the affective disturbances.

Therefore, it is interesting to note whether 5-HTs play any role in the development of PMCs. Studies have shown that post-synaptic serotonergic response possibly is disturbed during the late-luteal-premenstrual phase of the MC or even throughout the cycle in those who have severe vulnerability trait[26]. Though the gonadal hormone (oestrogen and progesterone)-induced modulation of 5-HTs is a known fact at the backdrop of schizophrenia[25], in PMCs, differential effects in the cerebral 5-HTs due to differential hormonal changes in the MC[27,28].

One study[29] investigated whether women with PMDD have any possible genetic correlates of 5-HTs and it has found that there are three polymorphisms in the gene encoding for the platelet serotonin transporter:

I. A 44 base pair insertion or deletion in the promoter region,
II. A variable number of tandem-repeats in the second intron, and
III. A single nucleotide polymorphism in the 3' untranslated region.

The study also analyzed the tentative relationship among these polymorphisms and the platelet serotonin transporter density. It is seen that the density of platelet [(3)H] paroxetine binding sites was alarmingly lower in women with PMDD than the controls, though allele or genotype frequency for any of the three polymorphisms are not different between the patients and the controls. Thus it corroborates that PMDD is a serotonin-related psychiatric disorder and that may be associated with a reduction in platelet [(3)H]paroxetine binding.

To evaluate the possible correlation for severe depression in PMS and PMDD, one SPECT (Single Photon Emission Computed Tomogram) study has shown that regional cerebral blood flow in the temporal region is decreased in patients suffering from PMCs[30].

The article has also proposed a model to note the tentative aetiology of PMCs (vide Model 1 after the reference section).

MANAGEMENT PROTOCOL

Management of PMCs is often extremely difficult. Those who are showing the symptoms consistent of PMCs are advised to monitor their symptoms in the menstrual diary for noting the onset, severity and duration of the symptoms they face. Patients qualified for PMCs could be rated for the symptoms severity under the three-point scale: mild, moderate and severe. According to the symptom rating, the guidelines for the management of PMCs could be adopted as follows:

A. Life style modification including counseling or behavioral psychotherapy for coping up with the symptoms when the symptoms are mild, and

B. Pharmacotherapy when the symptoms, although mild, are not been tackled by simple life style modification or counseling and psychotherapy or the symptoms are moderate to severe and incapacitating.

STRATEGIES TO COPE UP PMCS BY MODIFYING LIFE STYLES:

Doctors often prescribe/advice the followings for their patients with mild PMCs as the first-line of management:

1. Prohibition for caffeine, refined sugars, and crude salt intake31,
2. Avoiding alcohol and related beverages32,
3. Regular exercise, especially isotonic33,
4. Increase carbohydrate intake in the diet34, and
5. Cognitive-behavioral psychotherapy, if required35.

Though the role of these are quite under tested, the reasons for such age-old prescriptions are probably continuing due to the other benefits and safety[8]. If these are found to be ineffective or inadequate, or the symptoms are severe, pharmacotherapy remains the mainstay of the treatment.

STRATEGIES FOR OPTING FOR THE PHARAMACOLOGICAL AGENTS-

1. Vitamins and minerals as dietary supplements,
2. Psychopharmacologiucal drugs, and
3. Hormonal agents:
4. Vitamins and minerals:

Large body data suggest that vitamin B_6 with a dose of 50-100 mg daily[36], calcium carbonate 1200 mg daily[37] and magnesium salts[38] play a beneficial role in moderating the symptoms of mild to moderate PMS though large multicentric controlled studies are needed before final substantiation. Moreover, pyridoxine must be used with utmost cautious to prevent neurotoxicity. Vitamin E is

another choice, especially for relieving the symptoms due to mastalgia related to PMCs[39].

Psychotropic drugs are prescribed when the above-mentioned measures fail as follows:

PSYCHOTROPIC DRUGS:

Psychotropic drugs are essential components to combat the load of severe PMS and PMDD, where the patient needs the attention of a psychiatrist. Selective serotonin reuptake inhibitors (SSRis) remain the mainstay and the first-line of treatment of severe PMS or PMDD8. Fluoxetine and sertraline remains the most chosen drugs for the treatment of such disorder8. In one study it has been found that fluoxetine in a dose of 20-60 mg daily is superior to placebo for alleviating the mood-related symptoms of PMDD40. On the other hand, sertraline in a dose of 50-150 mg per day is seen effective to reduce PMDD or PMS-induced physical and emotional symptoms[41].

Alprazolam, a benzodiazepine receptor agonist and an anxiolytic agent is also helpful in the treatment of moderate to severe anxiety associated with PMCs[42]. But use of alaprazolam should be judicious otherwise patients may develop physical dependence to it and would abuse it afterwards.

HORMONAL PILLS:

Sometimes it is seen that lone treatment with psychotropics are not sufficient enough to tackle the emotional and physical symptoms related to PMDD or severe PMS. Hormones then remain the alternative approach. Controversy related to OCP in the treatment of PMCs are still prevailing but one study has found that OCP is better choice to treat PMS of moderate to severe symptoms than placebo and drospirenone (a spironolactone like molecule)[43]. The role of oestrogen or progesterone alone in the treatment of PMCs remains disputed, though oestrogen is being claimed as a beneficial agent to treat the physical and emotional symptoms of postmenopausal syndrome [44]. Recent studies have shown that ovulation cessation by down regulating the pituitary-gonadal-axis, using GnRH analogues (e.g., leuprolide) is one of the measures to combat severe PMC-symptoms, not responding to SSRis alone [45], though there are no published studies to see whether GnRH-analogues are helpful in reducing the frequency, intensity and course of depression[14]. Danazol, a synthetic androgen with anti-oestrogen effects is another choice for ovulation suppression as well as cyclic mastopathy related to PMCs, but unfortunately due to its large number of side effects, it is not a very suitable choice to treat PMCs[32].

American College of Obstetricians and Gynecologists has emphasized on daily menstrual card or diary maintenance for two consecutive cycles by the patients who complain the symptoms alike PMCs during the luteal phase of the MCs. If the diagnosis is confirmed, treatment could be best started for moderate to severe PMS or PMDD is with SSRis keeping other prospective treatments in mind.

The article also proposes a model for the management of PMCs (vide Model 2 after the reference section).

CONCLUSION

PMCs are multifactor disorder with a fairly high lifetime incidence rate. PMCs have a lot of adverse social consequence, ranging from criminal activities, social maladjustment, interpersonal conflicts, severe depression, anxiety neurosis and increased suicide incidences.

Its exact aetiology is largely unknown till date. Disturbance of HPA axis in the luteal phase of the menstrual cycle due to the steroidal hormone and biogenic amine dysregulation-related stress is blamed for it. The present literature, however, could not establish any definite relation between psychological stress and development of PMCs.

Screening of patients could easily be done by asking the patients to maintain regular menstrual diary for at least two consecutive cycles to note the target symptoms. Diagnosis is best done according to the guidelines given by ACOG for PMS and DSM-IV TR for PMDD.

The treatment of PMCs is also not very clear, though internationally accredited guidelines of ACOG are available to tackle the problem[46]. The present article, however, proposes that the treatment of mild PMCs may be started with lifestyle modifications through regular exercise, dietary modifications, oral vitamin B_6, vitamin E, magnesium and calcium supplementations for two to three cycles. If no responses with those agents, or the symptoms become more severe, often the drug of choice is the SSRis. SSRis are suitably given during the last week prior to menstrual bleeding and may be continued up to the first couple of days of menstruation if symptoms still persist. The treatment of PMCs is usually continued for two to three cycles till most of the symptoms get relieved, although the duration of therapy may vary from subject to subject. The mean duration of therapy could be determined by double blind time series

analysis on a large body sample. If SSRis fail to show any improvement, GnRH-analogues could be effective but due to oestrogen depleting effect, long-term use of these agents may cause severe osteoporosis and so should be cautiously used. Apart from pharmacotherapy, cognitive-behavioral psychotherapy also helps in reducing the load of PMS in some patients in terms of better coping of PMC-onduced stress [35].

The studies on PMCs, available until now, are largely biological and no studies have shown the socio cultural aspects behind the onset of PMCs. The present article thus recommends a thorough double-blind-control trial study with a large sample of diagnosed PMS patients partaking 1. Socio-economic status, and 2. Culture, especially sharing of such feelings between mother-daughter and sister-sister. Studies are also welcome to evaluate how underlying culture-bound psychiatric illnesses could trigger PMCs.

Figure 1

Model 1

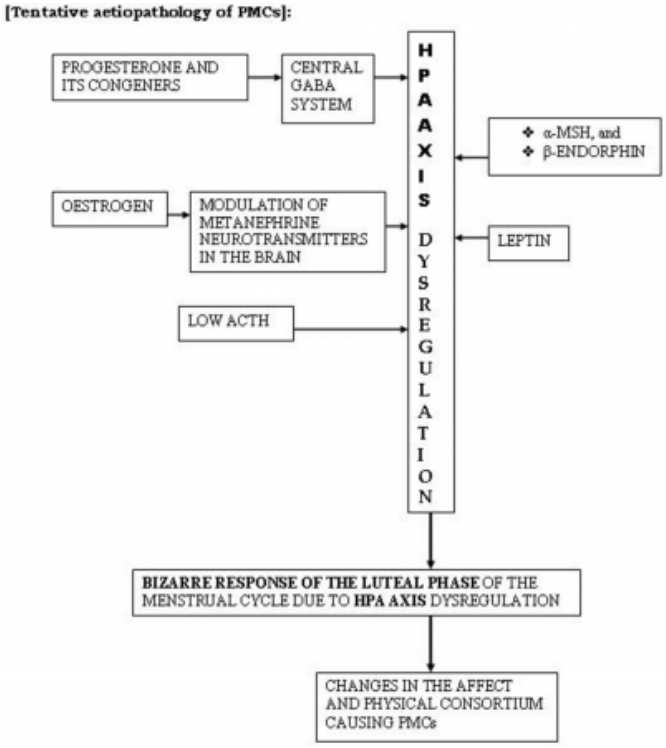
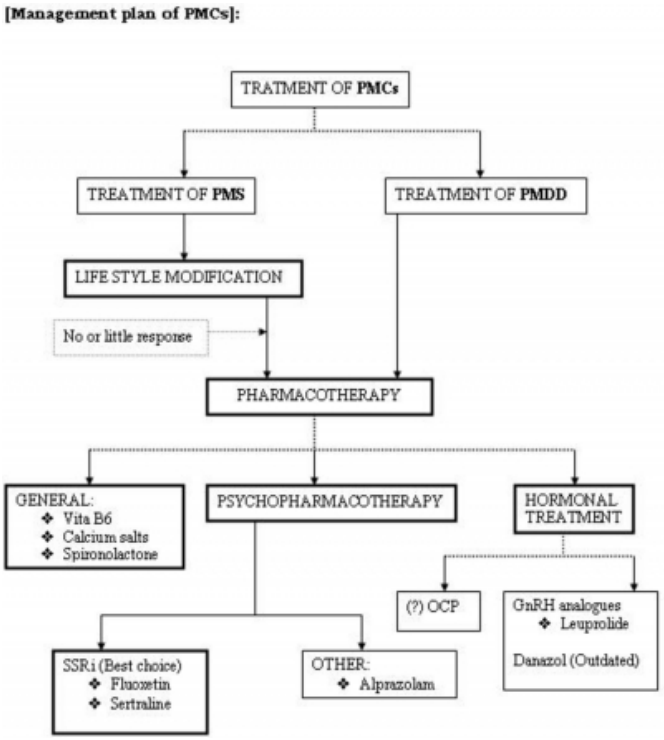


Figure 2

Model 2



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