

Making gynecological and psychiatric sense out of premenstrual pains, tension and dysphoria

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ABSTRACT

Objective: Millions of women worldwide suffer from a variety of gynecological and psychiatric syndromes that are specifically linked to the late luteal phase of menstrual cycle and hence, need proper treatment for good quality of life. The objective of this qualitative review is to examine the latest developments in the etiology, diagnosis and treatment of premenstrual syndrome and its connections to premenstrual dysphoric disorder.

Methods: A selective search of MEDLINE/PubMed retrieved numerous peer-reviewed papers published in international journals for the past 10 years (the search was ended in 2003), which were screened extensively, but only the latest and most relevant articles were included in this review.

Results: The 2 main premenstrual disorders manifesting tension, dysphoria and pain were

etiologically attributed best to the dysregulation of central serotonergic and GABAergic systems and noxious sex steroid hormonal milieu during normal cyclical ovulation. The women with these syndromes needing proper assessment, investigations and correct diagnosis respond effectively to selective serotonin-reuptake inhibitors, gonadotrophin-releasing hormone agonists, contraceptive pill-Yasmin, cognitive-behavior therapy, life-style changes, and also placebo.

Conclusion: Premenstrual psychiatric syndromes coupled with multiple adverse consequences are important clinical entities in a woman's reproductive life, which need timely intervention and future research especially in Arabian Gulf countries.

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The menstrual cycle, conception and pregnancy, and parturition and lactation are the exclusive privileges of women. However, these special, normal physiological rights of women are often associated with remarkable stresses. But, with particular reference to premenstrual cycle, only a subset of women are known to develop an array of gynecological/psychiatric disorders, such as "pre-menstrual tension" first coined by Frank in 1931¹ and "pre-menstrual syndrome" the term first introduced by Green and Dalton.² Subsequently, many studies have explored extensively several aspects of premenstrual disorders. As a corollary,

several syndromes mushroomed under premenstrual psychiatric spectrum disorders due to considerable overlapping of symptoms and etiological substrates were described in the literature. These are premenstrual syndrome (PMS) or premenstrual tension syndrome (PMTS), premenstrual distress syndrome (PMDS), seasonal premenstrual syndrome (SPMS), and the late luteal phase dysphoric disorder (LLPDD) or, premenstrual dysphoria (PMD) or premenstrual dysphoric disorder (PMDD).^{3,4} The PMS, PMDS, PMTS, and SPMS broadly connote more or less similar meanings and, likewise, PMDD was previously

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known as LLPDD or PMD. However, there appears to be some differences among them. For example, unlike PMS, women with PMDD manifest a specific pattern of symptoms coupled with marked severity and impairment in several aspects of their lives. Similarly, unlike PMS, SPMS has seasonal pattern. Premenstrual distress syndrome is attributed to the stress of approaching menstrual cycle. The patients with PMS usually consult obstetric and gynecological clinics whereas women with PMDD seek help from mental health professionals. However, consultation settings may include primary care clinics, general/specialist hospitals and mental health hospitals. There is a considerable Western database on PMS and further investigations are being continuing for extensively exploring contentious issues surrounding PMS/PMDD. In sharp contrast, there is no published literature on PMS/PMDD in Arabian Gulf countries. By extension the Arabian Gulf medical community is possibly not abreast with the recent research that have produced clinically useful information on PMS and PMDD. Impressively, PMS and PMDD ubiquitous in all cultures of the world are troublesome conditions that, to a very large extent affect adversely the women's mental and physical health. Moreover, the international medical community has prioritized the women's mental health as an important area for extensive research. Notably, since long time the woman's mental health was neglected. Therefore, the authors review the pertinent literature on PMS and PMDD. This brief review will cover the 3 important domains of PMS and PMDD, which relate to etiological, diagnostic and treatment perspectives. Apart from filling the information gap among somatic physicians and mental health professionals, this review may also act as a stimulus to the local researchers for carrying out basic studies on PMS and PMDD.

Methods. To meet these objectives, the database MEDLINE was searched up to June 2003. First, the keyword premenstrual was used as a qualifier and combined with, tension syndrome, distress syndrome, seasonal disorder, late luteal phase disorder, dysphoria, and dysphoric disorder. A second search used the term premenstrual syndrome as a qualifier and combined with etiologies, diagnosis, drug treatment, herbal treatment and psychosocial therapies. A third search used the keyword premenstrual dysphoric disorder as a qualifier and combined with etiologies, diagnosis, drug treatment, herbal treatment and psychosocial therapies. In case, MEDLINE and PubMed did not retrieve any article, the qualifiers or combined keywords were appropriately changed and thereafter search was repeated. Some of the retrieved citations of the past 5 years, in particular review articles were cross-referenced for identifying other relevant

studies. The initial MEDLINE search yielded sundry peer-reviewed citations published over the past one decade. The criteria for including empirical studies were broad and allowed 1) a reasonable diagnosis of PMS/PMDD, 2) a pretreatment systemic assessment of women with PMS/PMDD, 3) a standardized outcome measure, 4) a clear report on the treatment(s) received and whether treatment was controlled or uncontrolled. Notably, randomized controlled trials recruiting women with PMS/PMDD were preferably included in this review. Furthermore, the latest review papers and studies describing etiologies of PMS/PMDD were also included. Indeed, we restricted only to the qualitative review of these studies, as our objective was to highlight the new etiological, diagnostic and treatment developments in PMS/PMDD. We did not attempt a meta-analysis review of the relevant studies. In view of many published citations, our objective was not to present an exhaustive review of all studies. Similarly, it was impossible to include all citations, more than 5000 related to etiology, diagnosis and management of PMS/PMDD of the past 10 years. It is also understood that, besides each of the aforesaid specific domains of PMS/PMDD others specific issues such as hormonal perspective, role of neurotransmitters, and quality of life associated with such disorders could require review in itself. The studies that did not qualify in terms of the inclusion criteria were excluded from qualitative analysis.

Results. *Epidemiological trends and symptom domains.*

The premenstrual syndrome, characterized mostly by minor symptoms underlying somatic, psychological-cum-affective and behavioral domains (**Table 1**) afflicts approximately 40-75% of reproductive women, mostly in their 20s and 30s. Approximately 3-18% of them qualify for PMDD, due to its marked severity of symptoms associated with multiple impairment in their lives.^{5,6} The PMS and PMDD are associated with considerable economic burden, and also have adverse impact on quality of sufferers, family and the society as well.⁵ On severity scale, PMS/PMDD could be categorized into mild, moderate and severe disorders and then each of them requires relatively different treatment approaches.⁷ Typical symptoms of PMS, among over 100 symptoms include dyspareunia, tension, pelvic discomfort, irritability, anxiety, depressed mood, carbohydrate craving and dysmenorrhea. On a premenstrual distress scale, Chang et al reported that women from western cultures express more negative affective features as compared to Chinese women who predominantly relate their premenstrual distress through aches and pains.⁸ Cultural learning experiences and meaning of menstruation/premenstruation symptoms may also

determine the reporting of PMS symptoms and may offer new insights into the phenomenon of PMS.⁷ The PMS indicates normal cyclical ovarian function surrounded by hormonal imbalance or sensitivity to in particular sex steroids-progestogens and progesterone together with estrogen and is further linked to abnormalities in central serotonergic regulation and gamma-aminobutyric acid system.¹⁰ Simply, PMS reflects the cyclical 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 by a period of time entirely free of symptoms. Cyclical symptoms both of PMS and PMDD recur during the late luteal phase of most menstrual cycles and typically remit by mid-menstruation. The most stable symptoms reported in PMS are mood symptoms-anxiety, irritability, and labile affect and, therefore, some researchers have included PMS within the spectrum of mood disorders (MD).¹¹ Symptoms usually worsen with age until relieved by the onset of menopause. Like seasonal mood disorders, seasonal pattern of symptoms are also reported in PMS and PMDD, which respond to light therapy and sleep deprivation,¹² which are the standard therapies of seasonal mood disorders. In a study, high concentrations of luteal-phase estradiol and

luteinizing hormone (LH) were linked to the severity of premenstrual symptom.¹³ Further, low level of estradiol (E₂) was associated with the exacerbation of premenstrual symptoms of affective, behavioral, and somatic constructs but not of psychotic domain among patients with schizophrenia.¹⁴ The patients with PMDD are more often characterized by obsession traits.¹⁵ Furthermore, women with PMDD but without depression have higher education along with marital disruptive lives. Similarly, highly professional urban women reported more severe psychological symptoms as compared to rural women.¹⁶ But when professional women were excluded from the analysis, their residential backgrounds, urban versus rural do not affect premenstrual symptom.¹⁶ According to some research, premenstrual socialization influences premenstrual symptom expectation, attitudes, and reporting.¹⁷ Overall, menstrual/premenstrual socialization and also cultural meanings attributed to menarche/menstruation have tremendous impact on the attitude and reporting of PMS/PMDD symptoms by women.¹⁸

Nosological issues. Unlike PMS, PMDD, categorized under Depressive Disorder Not Otherwise specified in Diagnostic and Statistical

Table 1 - Symptoms of premenstrual syndrome and premenstrual dysphoric disorder.

Domains	Symptoms*
Premenstrual syndrome	
Psychological	Irritability, depression, tension, anxiety, restlessness, tiredness, lethargy, reduction in libido, labile moods, decreased concentration and reduced appetite.
Behavioral	Reduction in work performance, suicidal ideation, accident proneness, criminal activities.
Somatic	Hot flushes, mastalgia, nausea, dizziness, palpitations, sensations of weight gain, abdominal bloating, visual disturbances, headache.
Others	Exacerbation of epilepsy, asthma, allergies, and migraine.
DSM-IV Premenstrual dysphoric disorder	
Psychological	Feeling sad, hopeless, or self-deprecating, feeling tense, anxious or "on edge", marked lability of mood interspersed with frequent tearfulness, persistent irritability, anger and increased interpersonal conflicts, decreased interest in social relationships, difficulty concentrating, feeling fatigued, lethargic or lacking in energy, marked changes in appetite, which may be coupled with binge-eating or craving for certain foods, hypersomnia or insomnia, a subjective feeling of being overwhelmed or out of control
Behavioral	Marked impairment in the ability to function socially or occupationally, manifested by marital discord or problems with friends and family members, suicidal thoughts
Somatic	Breast tenderness or swelling, headaches, sensations of bloating, weight gain with tightness of fit of clothing, shoes or rings, joint or muscle pains
DSM-IV - Diagnostic and statistical manual of mental disorders. *Psychotic symptoms such as delusions or hallucinations are rarely reported. For the diagnosis of premenstrual syndrome, report of one symptom during luteal phase is sufficient.	

Manual of Mental Disorders (DSM-IV),¹⁹ has proposed research criteria for further study. Premenstrual dysphoric disorder is yet to receive official recognition, as it lacks sufficient information. There should be a total of 5 specified symptoms with one severe mood symptom for the diagnosis of PMDD. In the International Classification of Diseases (ICD-10),²⁰ PMTS when determined only by psychological factors, is grouped under psychological or behavioral factors associated with disorders or diseases classified elsewhere in mental disorder section (F54) plus physical disorder section-N94.3 under 'pain and other conditions associated with female genital organs and the menstrual cycle'. However, PMDD is not mentioned in ICD-10. Notably, according to ICD-10 there must be only one distressing symptom for the diagnosis of PMS.²⁰ The American College of Obstetricians and Gynecologists states that there should be at least one moderate to severe mood symptom and one physical symptom for the diagnosis of PMS.²¹ Further, there must be functional impairment attributed to severity of symptoms that differentiates clinically significant PMS from normal menstrual cycle changes.²² According to some researchers, the diagnostic criteria for PMS must recognize the broad range of symptoms, the temporal pattern of symptoms and the critical issue of symptom severity.²² Symptoms must be present for 1-2 weeks premenstrually with relief by day 4 of menses and should be documented prospectively for at least 2 cycles using a daily rating form. It is worthwhile that the researchers should consider both ICD-10 and DSM-IV criteria in making the diagnosis of PMS/PMDD.

According to some studies, clinicians should consider the following categories with regard to a patient with PMS-PMDD (i) PMS should meet ICD-10 criteria for PMS but not DSM-IV criteria for PMDD. Criteria include mild psychological symptoms, bloating, weight gain, breast tenderness, swelling, ache and pains, poor concentration, sleep disturbance and appetite change. One of these symptoms must present during the late luteal phase but all must cease after menses, (ii) PMDD should meet DSM-IV criteria, which also include presence of symptoms during most premenstrual cycles over the past 12 months. The prospective rating should show symptom worsening in minimum of 2 consecutive premenstrual cycles, (iii) other diagnosis only means either psychiatric or medical diagnosis but no relationship with premenstrual cycle and (iv) no diagnosis means symptoms are disruptive but not meeting criteria for any diagnosis.²³ According to some researchers, the methods of operationalizing diagnostic criteria of PMDD should be described in studies on PMDD.²⁴

Co-morbid disorders. Premenstrual syndrome/PMDD is reported to co-morbid with

other psychiatric disorders including major depression, rapid cycling mood disorder, seasonal affective disorder, dysthymic disorders, schizophrenia, obsessive-compulsive disorder, panic disorder, somatoform disorders, bulimia nervosa, substance use disorders and personality disorders.^{25,26} In one study from Taiwan, Hsiao et al²⁷ found co-morbid psychiatric disorders in 86% of women with PMS. In another study, Chau et al²⁸ reported high level of trait anxiety in Chinese adolescents, which was related to an increase in premenstrual symptom. Unlike physical disorders, clinicians face diagnostic dilemmas when they examine patients with multiple psychiatric diagnoses, which have no specific diagnostic laboratory tests. Notably, like panic but unlike major depression, patients with PMDD are highly sensitive to CO₂ inhalation,²⁹ which could help in distinguishing PMDD from mood disorders. In 40% of patients, symptoms of co-occurring psychiatric disorders including postpartum depression, dysphoric effects of contraceptive medication and dysphoric mood observed during sequential hormonal replacement therapy (HRT) may exacerbate during premenstruation.^{14,30} Similarly, there are also reported exacerbation in the symptoms of certain medical conditions, which include hypertension, seizure disorders, endocrine disorders, cancer, systemic lupus erythematosus, anemia, endometriosis, and various infections. A comprehensive history, specific laboratory tests, and physical examination may help in diagnosing somatic disorders.¹⁹ In a study, Blumer et al³¹ highlighted the similarity between epilepsy-related interictal dysphoric disorder and PMDD and recommended a combination of antidepressant and antiepileptic drugs for patients with PMDD coupled with epilepsy. The exacerbation of psychiatric and physical co-morbid disorders of PMS and PMDD is known as premenstruation magnification (PMM)²³ that should not be confused with PMS and PMDD, as the symptoms of co-morbid disorders persist even after menstruation. Notably, the treatment of PMS and PMDD may be unsuccessful if the underlying psychiatric or medical conditions are not addressed simultaneously.

Etiology. Albeit the exact etiology of PMS is elusive, researchers have proposed an array of biological factors and psychological constructs that partly explain its pathophysiology.^{3,25,29,32-34} There is a reported episodic secretion of progesterone hormone with increased frequency but with reduced amplitude that is temporally related to LH secretion.³⁵ Additionally, women with PMS might have transient or episodic disturbances of the hypothalamic-pituitary-adrenal (HPA) axis, which is corrected by this system's own mechanisms.^{5,6} Women with PMS symptoms appear to have abnormal HPA axis response to progesterone but

not to estradiol. No HPA axis abnormalities as revealed in depression are found in women with PMS/PMDD.³⁶ One study involving patients with PMDD³⁷ reported dysregulation of allopregnanolone, a neuroactive and a metabolite of progesterone that acts via gamma aminobutyric acid (GABA) system and like benzodiazepines, barbiturates and alcohol, its low dosages produce adverse mood effects in humans and animals.¹⁰ However, endocrine studies to date have reported no specific gonadal hormonal abnormalities during luteal phase of menstruation in PMS.³⁶ Notably, there may be some faulty hormonal interactions in early luteal phase heralding the emergence of premenstrual symptoms or a subset of women may have CNS sensitivity to normally circulating gonadal hormones including progesterone and progesterone together with estrogen. More recently, specific animal models of PMDD have supported the important role of neurohormones and GABA (A) receptor in the etiology of PMS/PMDD.³⁸ Although the patients with PMDD and mood disorders³⁴ do not closely share genetic pool with each other, they are more liable to develop MD and vice versa. In a recent study, patients with seasonal affective disorder were reported to share genetic vulnerability with PMDD through polymorphism in serotonin transporter gene promoter region (5HTTLPR).³⁹ Interestingly, flumazenil, a benzodiazepine receptor antagonist is reported to induce panic in women with PMDD reflecting and also further supporting the dysregulation of the GABA-benzodiazepine receptor complex during premenstruation.⁴⁰ Another study reported cortical GABA neuronal dysfunction in terms of increased GABA levels and its modulation by neuroactive steroids in PMDD.⁴¹ Cortisol circadian rhythms, possibly dysfunctioning in PMDD were found to differentiate it from normal control population.⁴⁰ Patients with PMS report unpleasantness and pains, modulated by HPA axis but attributed to lower levels of beta-endorphins that is suggestive of etiological role of endogenous opioids in PMDD.⁴² Furthermore, CCK-B system is reported to play an important role in the pathophysiology of PMDD.⁴⁴ Many studies have reported dysfunction of serotonin and melatonin together with abnormal sleep EEG among patients with PMDD.⁴² Selective serotonin re-uptake inhibitors (SSRIs) are known to directly alter activity of CNS steroid enzyme,⁴⁵ which are possibly at fault in PMS and PMDD. Although there is a converging evidence for dysregulation of either the HPA axis or serotonin control of the HPA axis in women with PMS, there is a little support for luteal phase-specific serotonergic dysfunction. Further, one study demonstrated altered platelet (3H) paroxetine binding characteristics in women with PMDD as compared to controls, which suggested the serotonin

dysregulation.⁴⁶ In another study, Melke et al⁴⁷ support the assumption that PMDD coupled with serotonin dysfunction may be associated with a reduction in platelet (3H) paroxetine binding, which may not be due to certain variants of the serotonin transporter gene. Some researchers provided evidence for the acute efficacy of m-Chlorophenylpiperazine (m-CPP), a serotonin agonist, in the treatment of PMS. These findings, nonetheless, implicate the serotonin system as a modulating factor in PMS.⁴⁸ A positive response to SSRIs by PMS/PMDD patients further supports the etiological role of serotonin in these syndromes. Thyroid axis in terms of hypothyroidism is not reported to be the cause of PMDD.⁴⁹ Other neurotransmitters such as noradrenaline and dopamine have also been reported to be dysregulated in PMDD.^{3,50} In addition to reported hyperprolactinemia and hyperinsulinemia, other biological mechanisms underlying PMS/PMDD are related to deficiency of manganese, magnesium, potassium, and calcium, vitamins B-6, E and B, and prostaglandin PGE1.^{3,6,31-33} Exercise habits, smoking, alcohol use, use of oral contraceptives, a diet high in beef, refined sugar products or caffeine containing beverages and altered fluid balance may also contribute to the development of PMS/PMDD.^{3,4,6,7}

The psychosocial and possibly, cultural mechanisms further explain the psychopathology of PMS.⁵¹ Affection less parenting was found not to be etiological in PMDD.⁵² Chronic stress and trauma in term of sexual abuse is reported commonly in a subgroup of women with PMDD.⁵³ Unlike PMS coupled with more physical symptoms, PMDD manifests relatively with more affective symptoms and these divergent symptoms could be attributed partly to educational level and socio-cultural sophistication of the women. However, such related hypothetical constructs warrant cross-cultural comparisons, which are scarce in the world literature. Other non-biological causative factors of PMS/PMDD may include expectation bias, early abnormal experiences related to menarche, prior knowledge of symptoms and abnormal attitudes towards menstrual cycle.³

Assessment and differential diagnosis. The diagnostic assessment schedules, prospective rating scales, and outcome measures are widely used in research settings, though many difficulties persist as regards the variability related to such measures. Ideally, symptoms must be rated prospectively in order to avoid several inaccuracies such as recall bias, amplification of symptom severity, and under or over reporting of symptoms, which are inherent in retrospective rating. There are many commonly used rating scales in research settings for assessing the treatment efficacy. These include the Menstrual Distress Questionnaire (MDQ) (47 items), the

Premenstrual Experience Assessment (PEA) (88 items), and the Premenstrual Assessment Form (PAF) (95 items). Other important assessment scales are the Premenstrual Tension Scale (PMTS-short version of MDQ), the Daily Record of Severity of Problems (DRSP), and the Prospective Record of the Impact and Severity of menstruation (PRISM). In clinical settings, however, the most acceptable scale is the Calendar of Premenstrual Experiences (COPE). In one study, Budeiri et al⁵⁴ have comprehensively described these scales used among patients with PMS. Recently, Steiner et al⁵⁵ have developed an effective screening tool for operationalizing DSM-IV criteria for PMDD and to understand clinically significant PMS. Several other commonly used scales in psychiatric research such as social adjustment scales, quality of life measures scales, depression and anxiety scales, schizophrenia scales hold promise to measure other components or co-morbid conditions of PMS and PMDD. In PMS and PMDD, the prospective rating of symptoms, their severity and associated impairment is variably increased. According to the National Institute of Mental Health guidelines,⁵⁶ the diagnosis of PMS requires a documentation of at least a 30% increase in severity of symptoms in the 5 days prior to menses compared with the 5 days following menses. Moreover, the significance of prospective assessment lies in the fact that 50% increase in overall scoring reflects severe impairment that entails treatment by drugs. Subjective reports of premenstrual symptoms and associated severity may not indicate true findings. Further, prior knowledge of premenstrual symptoms by a woman may enhance the symptom reporting.³

A differential diagnosis of PMS and PMDD includes a broad range of psychiatric and gynecological/physical disorders that can mimic these disorders. Premenstrual pain due to endometriosis and pelvic infections can be diagnosed by laparoscopy. Cyclical mastalgia needs extensive investigations including sonomammography, mammography, and biopsy, the latter 2 investigations may not always be required. The patients with PMS also require thyroid work-up to exclude hypothyroidism. When pain persists only during menstruation may be diagnosed as dysmenorrhea. All PMS-PMDD patients also need extensive psychiatric evaluation in order to diagnose co-morbid psychiatric disorders as mentioned earlier or their magnification by PMS-PMDD, which may result in increased admission of such patients to psychiatric hospitals. The data is lacking as regards the key points that would help in differentiating PMS-PMDD from other co-existing psychiatric disorders. Finally, PMS and PMDD are diagnoses of exclusion and, therefore alternative explanations for symptoms must be considered before either diagnosis is made.⁷

Treatment modalities. The PMS and PMDD are etiologically heterogeneous disorders. Therefore, multiple empirical therapies,^{2,57} mainly categorized into ovulation suppressants and symptomatic treatments are recommended for their management. The use of danazol, an ovulation suppressant useful in controlling breast swelling and tenderness is limited due to its adverse effects such as raised lipid profile and masculinization. Two gonadotrophin-releasing hormone (GnRH) agonists, namely buserelin and leuprolide are shown to be effective in PMS. But these medications are found to cause unpleasant menopause, managed by non-sequential progesterone and estrogen, and osteoporosis particularly on prolonged use. However, PMS and PMDD per se do not produce osteoporosis. Estrogen, given usually unopposed in hysterectomized patients, should be combined with progestins in PMS.⁵⁸ The addback hormonal therapy, danocrine and estradiol implants or patches with progestin protect the endometrium. Other hormones including progesterone, 200mg daily, and dydrogesterone, 10mg daily, were also reported to be effective in PMS. Bromocriptine, a dopamine agonist, is useful in mastalgia due to breast swelling, an effect of hyperprolactinemia in PMS patients. However, a meta-analytic review did not support the efficacy of progesterone and progestogens among patients with PMS.⁵⁹ Alternatively, Yonkers⁶⁰ recently reported a marginal reduction in symptoms of PMS with the use of progesterone or progestogens.

Other hormonal preparations for severe PMS-PMDD include new oral contraceptive and transdermal patch or implant oestradiol, 100mg/month. This unique oral contraceptive, Yasmin contains a combination of drospirenone (DRSP) 3 mg, a progestogen resembling endogenous progesterone and ethinylestradiol (EE) 30 microg. Drospirenone, derived from 17 alpha-spirolactone is a spironolactone-like progestin with antiandrogenic and antiminerlocorticoid activity. Spironolactone has been shown to be beneficial in PMS. Other oral contraceptives (combination of the estrogen and progestin) have shown conflicting result⁶¹ as they are reported to cause symptoms similar to PMS, such as water retention and irritability. Recently, 2 studies have however reported remarkable effect of this contraceptive pill in women with premenstrual syndrome. Additional benefits were prevention of pregnancy, improvement in dysmenorrhea, acne and seborrhea, and no weight gain and breast tension.⁶³ In another controlled crossover study, Taskin et al⁶³ showed the efficacy of tibolone, a synthetic steroid, in PMS. The main pharmacological treatments include SSRIs, which are the most effective medications added to the therapeutic armamentarium of premenstrual psychiatric

syndrome.⁶⁴ These medications with fewer side effects including withdrawals due to higher doses can be used safely in PMS-PMDD patients. On a caution note, SSRIs should not be combined with hormonal treatments. Selective serotonin re-uptake inhibitors usually inhibit ovulation and are robustly effective among patients with PMDD as compared to placebo.^{2,58} Their intermittent use particularly citalopram in half cycle dosing versus continuous dosing avoid development of tolerance.⁵⁸ However, continuation of small therapeutic dose of sertraline was found to be effective in PMDD.²⁶ Enteric-coated fluoxetine 90mg, given 2 times during the luteal phase of the menses was reported to be effective in PMDD.⁶⁵ The cessation of luteal-phase of fluoxetine results in the recurrence of PMDD symptom.⁶⁶ Other serotonin-enhancing drugs such as nefazodone, D-fenfluramine-serotonin agonist, buspirone and L-tryptophan-serotonin 1a-receptor agonist, yet to be subjected to placebo-controlled studies were also found to be effective in PMS-PMDD patients. Neurosteroid such as progesterone metabolites are reported to speed up the action of SSRIs among patients with PMDD.⁶⁷ Freeman et al⁶⁸ have reported the efficacy of citalopram, 20-40mg/day, given in half-cycle dosing to PMS patients who failed to respond to previous SSRI treatment. Venlafaxine was reported to be effective both in Western and ethnic Taiwanese women with PMDD.⁶⁹ Notably, 60% of patients with PMDD respond to SSRIs⁷⁰ that are known to have good safety and are well tolerated by the patients with PMS/PMDD.⁷¹

There are many other miscellaneous medications used in PMS patients. Evening Primrose Oil (Primosa) is recommended for mastalgia and bloating while low salt-diet and diuretics for fluid retention. Non-steroidal anti-inflammatory drugs and anti-prostaglandins such as mefenamic acid, naproxensodium and ibuprofen are given for pain, headache and dysmenorrhea. Alpha-tocopherol (vitamin E), naltrexone and alprazolam were also found to be helpful in PMS clients.^{3,6,67} Primosa, a non-hormonal preparation with anti-inflammatory effects, is a rich source of polyunsaturated essential fatty acids such as linoleic and gamma linolenic acids. It produces PGE1, which improves symptoms of PMS. Alternatively, PGE2 from natural dietary arachidonic acid mediates vasodilatation and worsens the PMS. All these medications need further rigorous controlled studies. Further, these drugs should not be used for prolonged period because of their adverse effects such as hyperaldosteronism and electrolyte imbalance by spironolactone and iatrogenic dependence caused by alprazolam. Pyridoxine, 100mg/day, can be used safely and successfully in clients with PMS manifesting predominantly psychiatric symptoms including depression. It is worthwhile to note that

higher doses of B-6 are coupled with neuronal damage. B-6 is a co-factor in the synthesis of serotonin and dopamine; both implicated in the regulation of mood and behavior. Micronutrients such as magnesium, potassium and calcium (1200mg daily), deficient in PMS, were found to be effective in open trials.²¹ In a prospective, placebo-controlled study, Schellenberg reported the efficacy of *Vitis agnus castus* fruit extract, a homeopathic remedy in PMS.⁷² Ginko biloba extract has also been found to be effective in the management of congestive and neuropsychological symptoms of PMS.⁷³

Non-pharmacological therapies may be categorized into life style changes and specific modes of treatment such as counseling, social supports and networks, and cognitive-behavioral therapy (CBT). Regular daily exercises including sporting activities coupled with weight reduction, and aerobic training particularly high intensity are known to reduce symptoms of PMS, though the underlying mechanisms are yet to be explored.⁷⁴ Further, it is advisable for patients with PMS-PMDD to reduce intake of caffeine, alcohol, salt, and unrefined sugar and eating frequent small carbohydrate-rich snacks with lesser proteins may increase the dietary availability of tryptophan, which in turn increases serotonin synthesis. Furthermore, potassium-rich fruits and foods may improve symptoms of PMS. Relaxation training, important component of behavioral programs, is associated with good improvement in PMS.²¹ Support groups are found to have beneficial effects in PMS patients. Their focus is either on psycho-education or problem-solving techniques or empathic listening. Cognitive-behavioral therapy is relatively a very powerful method of treatment of patients with PMS manifesting in particular negative cognition on menstrual cycle. Cognitive-behavioral therapy, consisting of maximum of five sessions, should involve a sound therapeutic relationship between therapist and the patient, a dismissal of irrational thoughts, the identification of self-defeating patterns of behavior, and a dismissal of early life experiences.³ For detailed information on complementary and alternative medicines in the treatment of PMS/PMDD, readers are referred to a review article.⁷⁴

Finally, surgical interventions, such as oophorectomy and hysterectomy, are needed in most severe cases of PMS and PMDD, unresponsive to other treatment options.⁷⁵ It is valuable to note that, such as patients with depression and mania, the patients with PMS also are reported to show a placebo response, 20-40% that could be attributed to multiple factors.^{3,76} There appears to be an inverse relationship between severity of PMS and placebo response.⁷⁶

DISCUSSION. The occurrence of monthly menstrual cycle is a normal physiological phenomenon in the life of a woman. However, a subset of women tend to develop, in decreasing frequency, an array of psychopathological syndromes including premenstrual syndrome, premenstrual dysphoric disorder, seasonal premenstrual syndrome that are etiologically attributed to biopsychosocial and cultural factors. Moreover, some atypical psychotic disorders such as "atypical psychosis", "periodic psychosis", and "cycloid psychosis" were also reported to occur during premenstrual cycle.⁷⁷ Collectively, these syndromes typically recur during premenstruation and essentially remit following initiation of menstruation during follicular phase. But a minority of women tends to have premenstrual-like symptoms throughout the month. Furthermore, certain psychiatric disorders and gynecological/physical conditions may co-morbid with those premenstrual syndromes, but 26% of patients with PMS-PMDD have no associated disorder. Moreover, premenstrual syndromes may complicate co-morbid psychiatric and physical conditions, which in turn negatively affect the outcome of PMS. The clinical implication of this finding as also highlighted earlier is that co-morbid disorders should be distinguished and addressed simultaneously in order to treat the patient successfully.⁷⁸ Further, the premenstrual psychopathological syndromes cause mild discomfort to severe impairments in several aspects of sufferer's life. Suicidal preoccupation, interpersonal conflicts, marital problems, occupational difficulties, neurocognitive impairment such as psychomotor slowing are common among patients with severe PMS and PMDD. Moreover, the patients with PMDD increasingly utilize health services and frequently tend to be hospitalized.⁷⁹ Therefore, these premenstrual disorders of public health magnitude need prompt management and careful follow-up. The premenstrual syndromes require an integrated treatment approach. There are numerous pharmacological-psychiatric and non-psychiatric, and non-pharmacological therapies that are used effectively in premenstrual syndromes. In contrast to the limited and conflicting use of ovulation suppressants and hormonal preparations, new contraceptive (Yasmin) is a source of relief to PMS patients. Surprisingly, in a survey about prescribing patterns in PMS, progestogens including progesterone and estrogens followed by SSRIs and B-6 were the most commonly prescribed drugs.⁸⁰ Selective serotonin re-uptake inhibitors are now drug of choice in the treatment of patients with PMS and PMDD. Aside reducing PMS-PMDD symptoms, SSRIs administered in different dose schedules also improve premenstrual psychosocial functioning. The mode of action of SSRIs reflecting

quick and early response in PMS-PMDD patients may be through other serotonergic synapses,⁸¹ which differs from mechanisms underlying antidepressant response of mood disorder clients who tend to show clinical improvement only after 2-3 weeks. It is worthwhile to note that SSRIs are also associated with some troubling adverse effects such as anxiety, headache, nausea, and sexual dysfunction. Non-serotonergic antidepressants such as maprotiline, bupropion and desipramine are reported to be less helpful as compared to SSRIs.^{58,67} Serotonin antagonists such as metergoline are found to worsen the PMDD.⁸² Notably, patients with premenstrual magnification of depression require premenstrual escalation of antidepressant dosing.⁸³

Furthermore, several psychosocial and behavioral therapies such as support groups and CBT are advocated for the management of premenstrual gynecological (PMS) and psychiatric syndromes.^{3,84} It is worthy to remember that appropriate drugs should be combined with one of the suitable psychotherapies, life style changes and stress management strategies in the treatment of moderate to severe premenstrual syndromes, probably for better outcome, psychosocial functioning and good quality life. Patients with mild degree of PMS/PMDD may just require life style changes. Notably, depressed mood at baseline predicts poor outcome in PMDD.⁶ Notably, PMDD has been viewed as major depression,¹⁹ though it is a distinct clinical entity with irritability and labile affect rather than depressed mood or anxiety as most characteristic features.⁸¹ Further, there may be subtypes of PMDD more closely related to depression or anxiety disorders than the most common form of the PMDD syndrome.⁸¹

In summary, over two-third of women in their reproductive age develop minima of premenstrual syndrome but only 45% of them demonstrate functional impairment. Unlike PMS, PMDD afflicts only 3-18% of women but both syndromes necessitate treatment with SSRIs, psychosocial modalities, and complementary therapies. Other promising drugs include novel contraceptive Yasmin, gonadotrophin-releasing hormone agonists, and a synthetic steroid Tibolone. The therapeutic use of steroid hormones in PMS/PMDD is disputatious because of their adverse effects. Oophorectomy and hysterectomy may be the last option in severe cases of PMS/PMDD not responding to drug regimens. At international level, there is a further need to define distinctively the etiopathogenesis of PMS/PMDD and also to develop effective drugs with better clinical profile. In Arabian Gulf countries, there is a fitting need to explore individual aspects of premenstrual syndrome and its biopsychosocial connection to other premenstrual psychiatric spectrum disorders. Therefore, authors suggest forming an Arabian Gulf

PMS/PMDD Research Group for exploring premenstrual psychiatric spectrum disorders, puerperal psychosis, post-partum depression, and other post-partum psychiatric disorders.

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