PREMENSTRUAL DYSPHORIC DISORDER (FORMERLY PREMENSTRUAL SYNDROME)

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ABSTRACT

Premenstrual syndrome, the recurrent luteal phase deterioration in quality of life due to disruptive physical and psychiatric symptomatology, is a distinct clinical condition caused by an abnormal central nervous system response to the hormonal changes of the female reproductive cycle. Better definition and research based on strict inclusion/ exclusion criteria have allowed the development of successful treatments that are tailored to the severity of the lifestyle disruption and the specific individual constellation of symptoms. Charting and simple lifestyle changes may improve coping skills for many women. However, more severely affected individuals often require medical interventions to augment central serotonin/ norepinephrine levels or to suppress the hormonal changes of the menstrual cycle. For extended coverage of this and related topics, please see our FREE on-line web- text www.endotext.org.

INTRODUCTION

In the past fifty years premenstrual syndrome (PMS) has emerged as a well recognized phenomenon for which effective treatments are available. Unfortunately, because of the widespread public awareness of adverse premenstrual experiences, the term PMS has found usage in popular vernacular as a noun, adjective and verb (I'm PMS ing"). Over-the-counter remedies, often promoted by those who hope to profit by marketing a "sure cure" for a common condition, have exploited the fact that many women believe they suffer from PMS. Researchers have argued that there is a need to discriminate between the usual premenstrual experience of ovulatory women (wherein premenstrual **molimina** forewarn of impending menstruation or where more troublesome symptoms (**PMS**) are an annoyance) from Premenstrual Dysphoric Disorder (**PMDD**) wherein symptoms, particularly psychiatric, lead to major distress that is sufficient to interfere with day-to-day activities and disrupt interpersonal relationships. The challenge to the medical profession is to differentiate between these conditions and to offer appropriate and timely interventions.

Those with annoying premenstrual symptoms should be counseled about simple lifestyle changes that may attenuate these whereas those with marked psychiatric components such as irritability, anger, anxiety, or depression warrant early intervention with medications. Although the literature on PMS has focused almost entirely on women with adverse premenstrual experiences, there is evidence that 5-15% of women may experience positive changes in the premenstrum (1). Rarely do such women present challenges to the clinician. This chapter will review diagnosis, etiologic theories, and therapeutic approaches to adverse premenstrual experiences.

DEFINITIONS AND PREVALENCE:

Molimina, Premenstrual Syndrome [PMS], and Premenstrual Dysphoric Disorder [PMDD]

During the reproductive years, up to 80-90% of menstruating women will experience symptoms [breast pain, bloating, acne, constipation] that forewarn them of impending menstruation, so-called premenstrual ***molimina*.** Over 60% of women report swelling or bloating (2) although objective documentation of weight gain is lacking in most of these women (3). Cyclic breast symptoms affect 70% of women with 22% reporting moderate to extreme discomfort (4). Available data suggest that as many as 30%- 40% of these women are sufficiently bothered by molimina to seek relief.

The term **PMS** continues to be used; however, for the reasons mentioned above it may encompass a wide range of severity and therefore is not particularly useful in defining cohorts for research or in directing the most appropriate therapeutic interventions.

PMDD should be reserved for a more severe constellation of symptoms, mostly psychiatric, that lead to periodic interference with day-to-day activities and interpersonal relationships (5). Women with this degree of symptoms probably comprise 3-5% of women in their reproductive years (6, 7, 8).

Premenstrual Dysphoric Disorder now appears in the Diagnostic and Statistical Manual of Mental Health Disorders (fifth edition) of the American Psychiatric Association. After years of debate about whether this should be included as a distinct psychiatric condition (9,10), the importance of alerting psychiatrists to the critical involvement of the menstrual cycle in psychiatric disorders is now widely accepted (Table 1).

Table 1. Diagnostic Criteria for Premenstrual Dysphoric Disorder (PMDD)

Timing of symptoms

A)
In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week postmenses

Symptoms

B) One or more of the following symptoms must be present:

1) Marked affective lability (e.g., mood swings, feeling suddenly sad or tearful, or increased sensitivity to rejection)
2) Marked irritability or anger or increased interpersonal conflicts
3) Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
4) Marked anxiety, tension, and/or feelings of being keyed up or on edge

C) One (or more) of the following symptoms must additionally be present to reach a total of 5 symptoms when combined with symptoms from criterion B above

1) Decreased interest in usual activities
2) Subjective difficulty in concentration
3) Lethargy, easy fatigability, or marked lack of energy
4) Marked change in appetite; overeating or specific food cravings
5) Hypersomnia or insomnia
6) A sense of being overwhelmed or out of control
7) Physical symptoms such as breast tenderness or swelling; joint or muscle pain, a sensation of "bloating" or weight gain

Severity
D) The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others.

E) Consider Other Psychiatric Disorders The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia) or a personality disorder (although it may co-occur with any of these disorders).

Confirmation of the disorder
F) Criterion A should be confirmed by prospective daily ratings during at least 2 symptomatic cycles (although a provisional diagnosis may be made prior to this confirmation)

Exclude other Medical Explanations
G) The symptoms are not attributable to the physiological effects of a substance (e.g., drug abuse, medication or other treatment) or another medical condition (e.g., hyperthyroidism).

(Adapted from: American Psychiatric Association: Diagnostic and Statistical manual of Mental Health Disorders, 5th edition. Washington D.C.2013) (11)

EPIDEMIOLOGY

It is likely that PMS has emerged as a twentieth century phenomenon in part due to the fact that women's increasing control over reproduction has eliminated the cycle of repeated pregnancy and lactation that formerly characterized the lives of women from puberty to menopause (13). PMS-like behaviour has been reported both in humans and in non-human primates as long as they demonstrate menstrual cyclicity. In the non-human primate, zoologists have noted premenstrual changes in behaviour and appetite similar to those reported by women with PMS (14, 15).

PMS may affect woman at any stage of reproductive life. The common belief that PMS is a disorder of the older woman may have stemmed from the fact that mood swings in the teen are less likely to be considered an effect of menstrual cyclicity and more likely to be

attributed to the “hormonal swings and heartbreaks” of adolescence. Severe PMS may start shortly after puberty and such cases tend to be recognized and brought to medical attention by a parent who recognizes the symptoms from her own experience. Little is known about the inheritance of PMS; however, there is support for a genetic predisposition. Surveys have found that as many as 70% of daughters of affected mothers were themselves PMS sufferers, whereas 63% of daughters of unaffected mothers were symptom free (16). PMS sufferers often relate that symptoms become progressively worse over time, and since women have increasing contact with health care providers for non-pregnancy related concerns in their later reproductive years, this may account for the preponderance of older women seeking help for PMS.

PMS disappears during suppression of the ovarian cycle (for example, during hypothalamic amenorrhea due to excessive physical, or nutritional stress, during lactational amenorrhea, during pregnancy, and after menopause – either natural or induced) (17). It is useful when evaluating a woman with suspected PMS to confirm that PMS symptoms did indeed disappear in these circumstances. Contrary to the popular belief, there is no convincing evidence that PMS begins after pregnancy or tubal ligation. This belief probably originated when PMS symptoms reappeared and seemed acutely worse after the hormonal “protection” of pre-existing pregnancy or lactation.

PMS disappears after natural, medically or surgically induced menopause although the reintroduction of exogenous hormone replacement therapy may be associated with the reappearance of symptoms (18, 19). Typically, the use of sequential progestin triggers PMS symptoms in susceptible women whereas continuous combined hormone replacement therapy is less likely to be associated adverse mood changes.

DIAGNOSIS

In 2008 an international multidisciplinary group of experts met at a face-to-face consensus meeting in Montreal, Canada, to review current definitions and diagnostic criteria for Premenstrual Disorders (PMD) (20). This group defined “Core Premenstrual Disorders (Core PMD) and Variant Premenstrual Disorders (Variant PMD)” as shown in Table 2 below.

Table 2 Classification of premenstrual disorders (PMD)

PMD category	**Characteristics**
Core PMD	Symptoms occur in ovulatory cycles
	Symptoms are not specified—they may be somatic and/or psychological
	The number of symptoms is not specified
	Symptoms are absent after menstruation and before ovulation
	They must recur in luteal phase
	They must be prospectively rated (two cycles minimum)

	Symptoms must cause significant impairment
Variants of PMD	
Premenstrual exacerbation	Symptoms of an underlying psychological or somatic disorder significantly worsen premenstrually
PMD due to non-ovulatory ovarian activity	Symptoms arise from continued ovarian activity even though menstruation has been suppressed
Progestogen induced PMD	Symptoms result (rarely) from ovarian activity other than those of ovulation
PMD with absent menstruation	Symptoms result from exogenous progestogen administration
[a] Work, school, social activities, hobbies, interpersonal relationships, distress	
Adapted from O'Brien PM. Backstrom T. Brown C. et al. Towards a consensus on diagnostic criteria, measurement and trial design of the premenstrual disorders: the ISPMD Montreal consensus. Arch Women's Mental Health 2011; 14(1):13-21	

History

Physicians should make an effort to enquire about premenstrual symptoms as part of the menstrual and reproductive history of all women of reproductive age. For the woman with few symptoms, this provides education about molimina /PMS and may forestall fears that she is “losing her mind” should symptoms emerge in the later reproductive years. For the woman with significant symptoms, this will create the opportunity for counseling and reassurance and will set the stage for establishing the diagnosis and selecting appropriate therapy.

A typical woman with PMDD may relate that she is a productive employee and good mother for most of the month. However, starting sometime after ovulation (often 7-10 days prior to menstruation) she awakens in the morning with feelings of irritability, anger, anxiety, or sadness. At work, she may experience feelings of paranoia and wonder if co-workers are picking on her. Often she will report that she has difficulty concentrating on the task at hand. She may experience menopausal-like hot flashes and night sweats and often reports sleep disruption with vivid dreams. She states that premenstrually she overreacts to things that her children normally do around the house, and this makes her feel like a bad mother. She may feel down but be unable to understand why because she knows she has a good spouse, a good job, and healthy, happy, children. Minor things that her spouse says may be enough to trigger an argument, and nothing the spouse says can appease her. Although she would like to be held and comforted at such times, she reports that she cannot stand to be touched. In severe cases, she may try to isolate herself by locking the door to her room or unplugging her telephone. Occasionally depression, anger and aggression, or anxiety may be extreme, resulting in concerns for the welfare of the affected woman or her family members.

Caution is needed in immediately accepting such a typical sounding history as diagnostic of PMDD. Researchers have found that many other psychiatric conditions worsen premenstrually (so-called premenstrual exacerbation); hence, an individual with an underlying psychiatric disorder may recall and relate the symptoms that were most severe in the premenstrual week while ignoring the lower level of symptoms that exist throughout the month . Only by obtaining a prospective symptom record over a one- to two-month period can the clinician have confidence in the diagnosis. Any calendar used for this purpose must obtain information on four key areas: symptoms, severity, timing in relation to the menstrual cycle, and baseline level of symptoms in the follicular phase (Table 3). Information should be sought about stresses related to the woman's occupation and family life, as these may tend to exacerbate PMDD. Past medical and psychiatric diagnoses may be relevant in that a variety of medical and psychiatric disorders may show premenstrual exacerbation.

Table 3. Key elements of a prospective symptom record used for the diagnosis of PMDD.

1. Daily listing of symptoms
2. Ratings of symptom severity throughout the month
3. Timing of symptoms in relation to menstruation
4. Rating of baseline symptom severity during the follicular phase

Several of the medical interventions described below will work for both PMDD and other psychiatric conditions so that a pretreatment diagnosis is important in determining the most appropriate long term management of the condition.

Typically premenstrual symptoms appear after ovulation and worsen progressively leading up to menstruation. About 5-10% of PMS sufferers experience a brief burst of typical PMS symptoms coincident with the midcycle fall in estradiol that accompanies ovulation (21) (Figure 1). Premenstrual symptoms resolve at varying rates after onset of menstruation. In some women, there is almost immediate relief from psychiatric symptoms with the onset of bleeding while for others the return to normal is more gradual. The most severely affected women report that symptoms begin shortly after ovulation (two weeks before menstruation) and resolve at the end of menstruation. Such individuals typically report having only one “good week” per month (Figure 2). If this pattern is longstanding, then it becomes harder and harder for interpersonal relationships to rebound during the good week, with the result that the condition may start to take on the appearance of a chronic mood disorder. [Whenever charting leaves the diagnosis in doubt, a three-month trial of medical ovarian suppression (see below) will usually provide a definitive answer.]

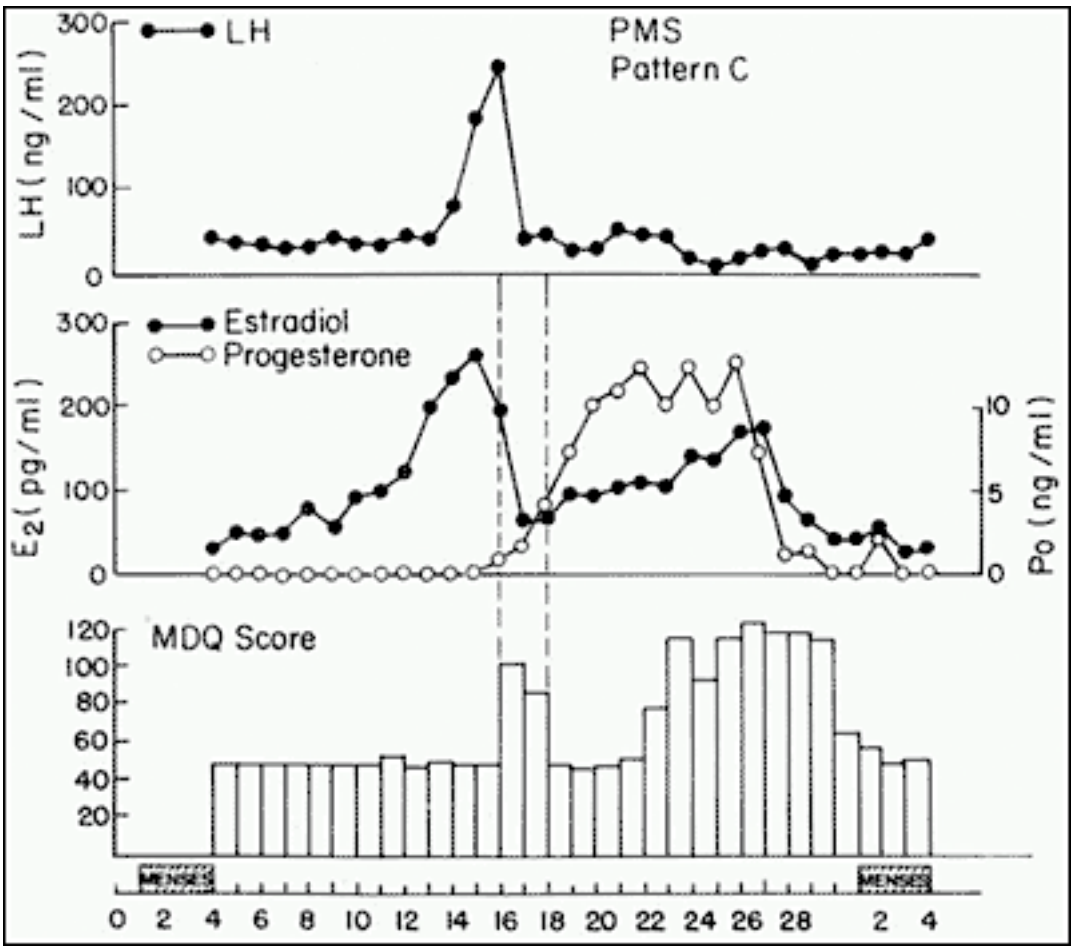

Figure 1

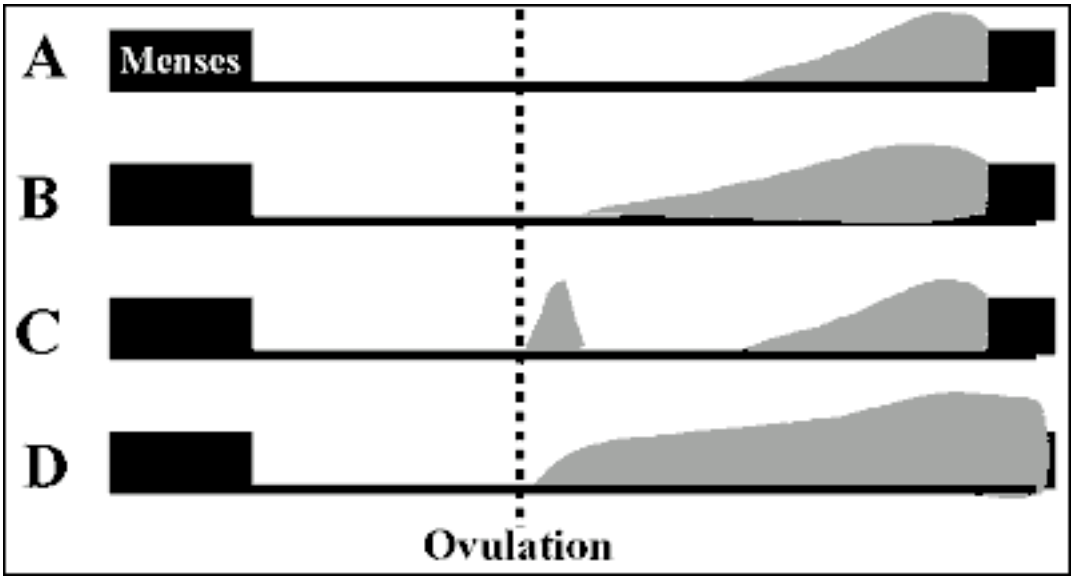

Figure 2

One example of such a calendar record, the PRISM Calendar (Prospective Record of the Impact and Severity of Menstrual symptoms) (Figure 3) (9) allows rapid visual confirmation of the nature, timing, and severity of menstrual cycle-related symptomatology and at the same time provides information on life stressors and current therapies. Although symptoms are rated in severity on a scale from 1-3, the actual interpretation of the calendar requires no mathematical calculations. An arms length assessment of the month-long calendar usually allows a rapid distinction to be made between PMDD and other more chronic conditions (Figure 4). Other charting instruments, including the validated Daily Record of Severity of Problems (DRSP), the Premenstrual Symptoms Screening Tool (PSST), and the Calendar of Premenstrual Experiences (COPE), have been recently reviewed (22).

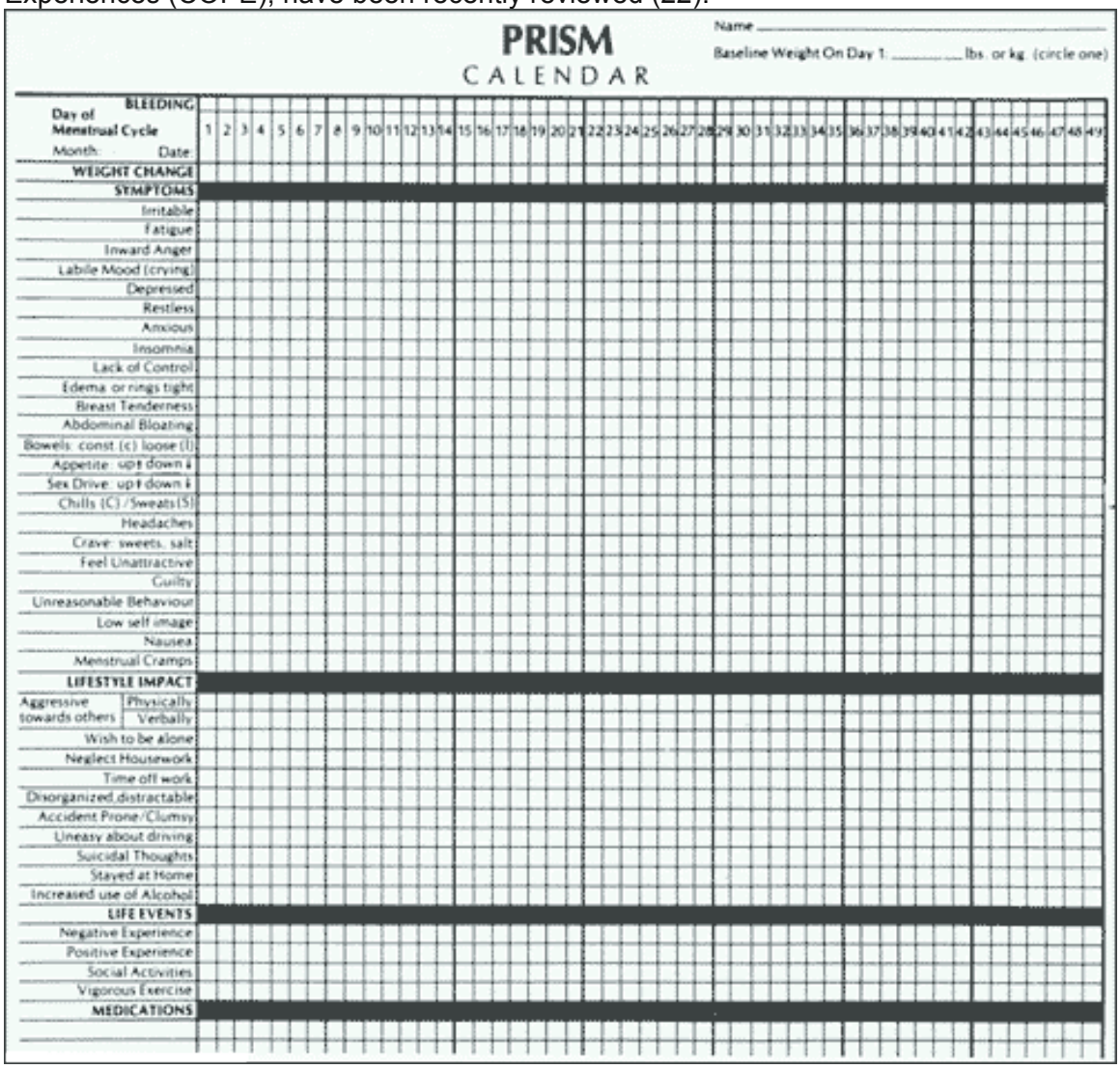
PRISM
CALENDAR
Name
Baseline Weight On Day 1: ____ lbs. or kg (circle one)
BLEEDING
Day of Menstrual Cycle
Month: Date:
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49
WEIGHT CHANGE
SYMPTOMS
Irritable
Fatigue
Inward Anger
Labile Mood (crying)
Depressed
Restless
Anxious
Insomnia
Lack of Control
Edema or rings tight
Breast Tenderness
Abdominal Bloating
Bowels: const (c) loose (l)
Appetite: up↑ down↓
Sex Drive: up↑ down↓
Chills (C) / Sweats (S)
Headaches
Crave: sweets, salt
Feel Unattractive
Guilty
Unreasonable Behaviour
Low self image
Nausea
Menstrual Cramps
LIFESTYLE IMPACT
Aggressive towards others: Physically / Verbally
Wish to be alone
Neglect Housework
Time off work
Disorganized, distractable
Accident Prone / Clumsy
Uneasy about driving
Suicidal Thoughts
Stayed at Home
Increased use of Alcohol
LIFE EVENTS
Negative Experience
Positive Experience
Social Activities
Vigorous Exercise
MEDICATIONS

Figure 3

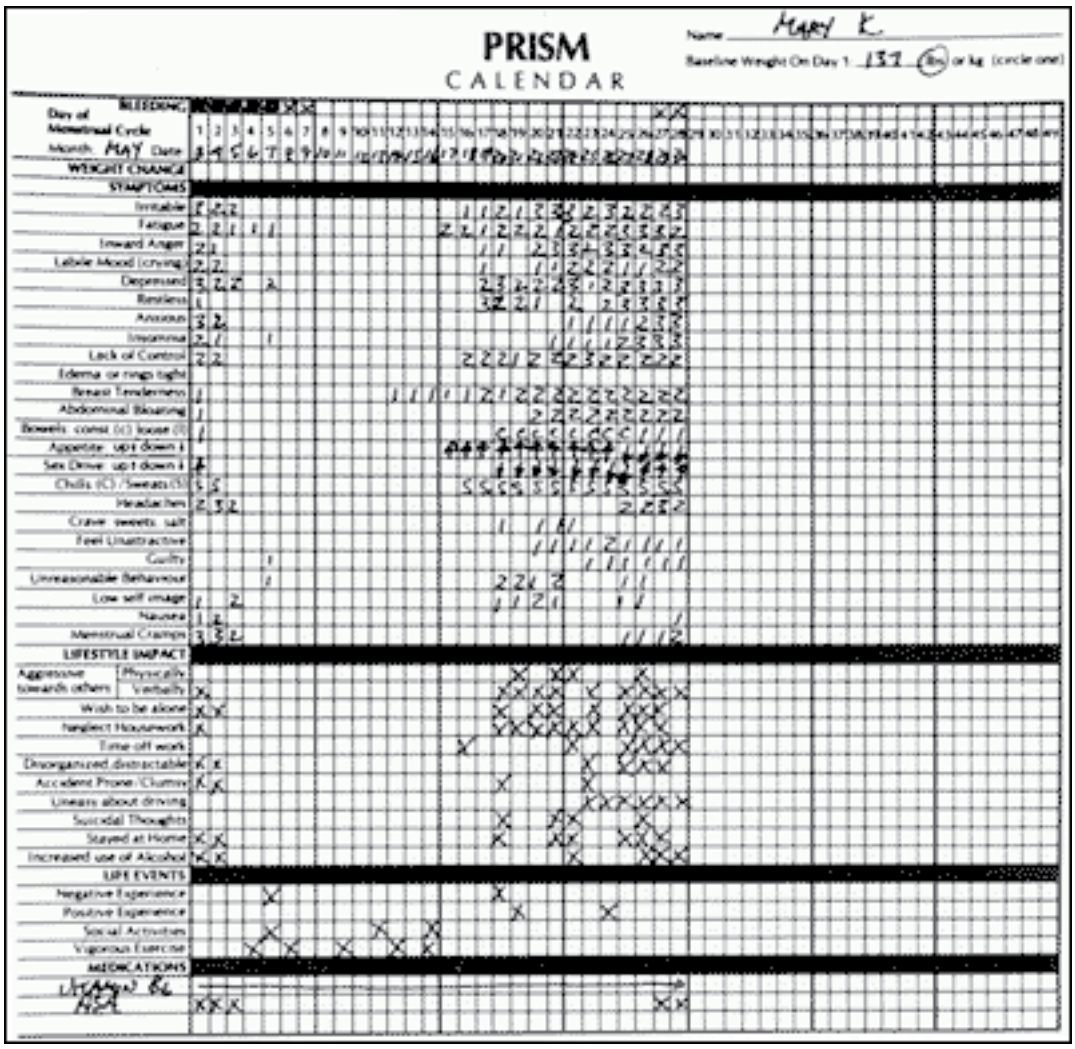

Figure 4

Positive premenstrual changes associated with enhanced mood or performance are reported by up to 15% of women. Increased energy, excitement and well-being have been associated with increased activity, heightened sexuality and improved performance on certain types of tasks during the premenstrual phase. (1)

Physical Findings

There are no characteristic physical findings in women with PMS. When seen in the follicular phase of the cycle, PMS sufferers typically appear entirely normal. Premenstrually, a woman presenting with an acute episode of PMDD may appear anxious, tearful, or angry, depending on the nature of her symptom complex.

A thorough physical exam, including gynecological examination, is recommended in the assessment of all women being evaluated for PMDD. Organic causes of premenstrual symptoms must be ruled out. Marked fatigue may result from anemia, leukemia, hypothyroidism, or diuretic-induced potassium deficiency. Headaches may be due to intracranial lesions. Women attending clinics with premenstrual complaints have been found to have brain tumours, anemia, leukemia, thyroid dysfunction, gastrointestinal

disorders, pelvic tumours including endometriosis, and other recurrent premenstrual phenomena such as arthritis, asthma, epilepsy, and pneumothorax (23).

Blood work

There is no endocrine test that helps in establishing the diagnosis in most circumstances (20). In a woman in whom the natural ovarian cycle has been disguised following hysterectomy, a serum progesterone determination at the time of symptoms may help to confirm the link between symptoms and the luteal phase of the cycle. At times a CBC and/or sensitive TSH may be indicated to rule out anemia, leukemia, or thyroid dysfunction as an explanation for symptoms.

ETIOLOGY

Although many theories of etiology have been proposed and disproved for this poorly understood condition, contemporary work suggests that PMDD is the result of an aberrant response of central neurotransmitters to normal changes in gonadal steroids during the menstrual cycle.

Other theories, while having some biological plausibility, have not or cannot be confirmed with available diagnostic techniques. No one theory has gained universal acceptance although consensus is developing that in some susceptible women normal swings in gonadal hormones appear to mediate changes in the activity of central neurotransmitters, such as serotonin, that in turn incite profound changes in mood and behaviour. Although it is likely that many of the physical symptoms (breast tenderness, bloating constipation) are the direct effect of gonadal steroids, it is intriguing that treatment of PMS with selective serotonin reuptake inhibitors will ameliorate the severity of not only psychological but also physical complaints.

Several lines of evidence from clinical medicine support this interrelationship between estrogen or lack of estrogen effect (perhaps mediated by progestin-induced depletion of estrogen receptors) and central serotonergic activity (24,25). Estrogen has been shown to alleviate clinical depression in hypoestrogenic women in double-blind clinical trials (26). The addition of sequential progestin therapy to estrogen replacement triggers characteristic PMS-like mood disturbance in some susceptible postmenopausal women (19). Anti-estrogens given for ovulation induction may, at times, provoke profound mood disruption. Women with premenstrual syndrome show a surprisingly high frequency of premenstrual and menstrual hot flashes (85% of PMS sufferers vs 15% of non- PMS controls) that are typical of those experienced by menopausal women (27, 28). Selective serotonin reuptake inhibitors (SSRIs) have been shown to relieve hot flashes in breast cancer survivors made menopausal by chemotherapy (29). In each of these circumstances a decrease in exposure to estrogen has been linked to mood disturbance, and in each case a decrease in serotonin activity (inferred from the response to SSRIs) appears to be the proximate cause [Figure 5].

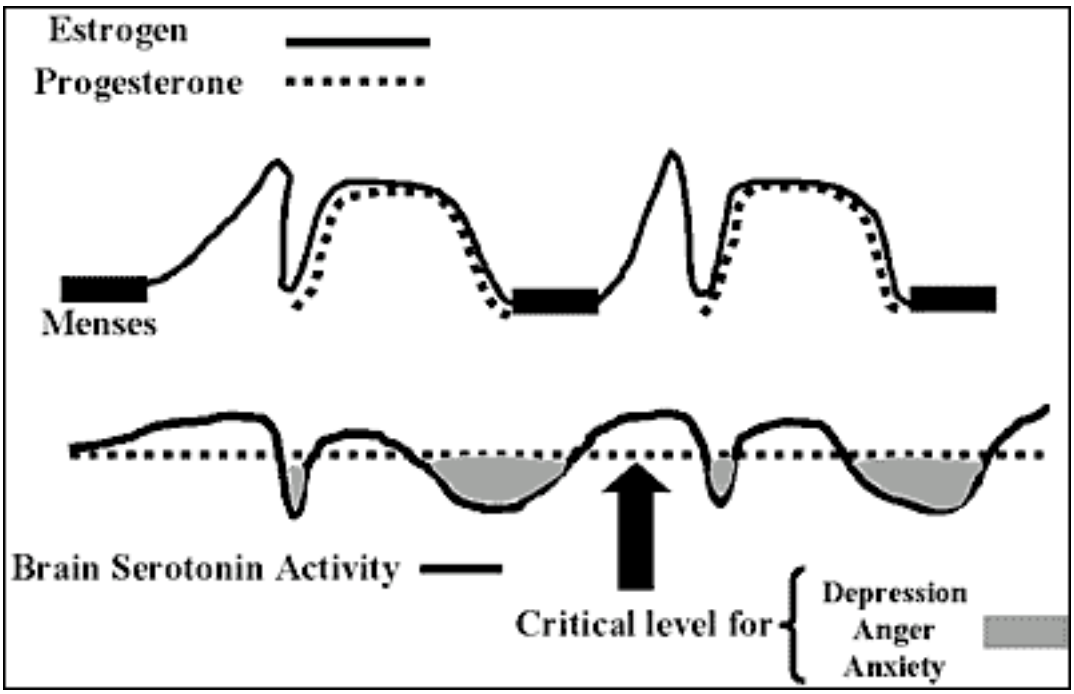

Figure 5

An emerging theory as to causation of PMDD involves a progesterone metabolite, allopregnanolone (ALLO), which acts centrally as a neuroactive steroid. As with progesterone, ALLO increases in the luteal phase and declines just prior to onset of menses. ALLO has a stimulating effect on the GABA-A receptor similar to alcohol and benzodiazepines with anxiolytic and sedative properties. One possibility is that women with PMDD have developed tolerance to the sedating GABA-a enhancing effects of ALLO (30). Preclinical and early clinical work have suggested that blockade of the production of ALLO with a 5-alpha reductase inhibitor can attenuate symptoms of PMDD (31).

THERAPY

Many women suffering from PMDD have suffered the fate of those with other poorly defined illnesses that lack a discrete diagnostic test. All too often their concerns have been dismissed as “a normal part of being a woman” and therapy has been denied. Typically affected women will suffer for long periods before seeking treatment, and most will have tried a variety of ineffective over-the–counter “PMS remedies”. Like other areas of confusion and uncertainty, the area of PMS is an attractive one for those promoting unorthodox treatments for personal gain. Many of the theories about causation of PMDD in the past 50 years appear to have emerged as a means to market specific therapeutic products. Much effort has been expended by conscientious investigators in an effort to rigorously evaluate the promotional claims of others. Randomized controlled trials have failed to confirm the efficacy of most of these purported treatments.

Lifestyle modification:

1) Communication strategies

When an individual is suffering to a degree that requires more than simple counselling and reassurance, measures aimed at lifestyle modification should first be explored. She should be encouraged to discuss the problem with those individuals who are central to her life, including spouse, other family members, and even a sympathetic co-worker. Often confrontations can be avoided if an understanding spouse or friend recognizes the cause for her upset and defers discussion of the controversial subject until another time. Strategies for stress reduction can be helpful. Communication skills and assertiveness may be improved with counselling. Group counselling in a program supervised by a clinical psychologist may be invaluable. While it is useful for PMS sufferers to learn to anticipate times in the month when vulnerability to emotional upset and confrontation may be greatest, the strategy of making important decisions "only on the good days" falls apart if premenstrual symptoms last for more than just a few days per month. For some women distressing premenstrual symptoms may last for a full three weeks, and advising them to restrict their important activities to the remaining days of the month is neither helpful nor warranted. Interventions aimed at reducing symptoms are more appropriate in this circumstance.

2) Diet

While there have been many books written which describe specific "PMS diets," few of the recommendations contained therein are founded on scientific fact. Several simple dietary measures may afford relief for women with PMS.

Most women with PMDD, despite feelings of bloating and tension, show no absolute increase in weight, no change in girth and no signs of peripheral edema (3, 20). Sudden shifts from low-sodium, low-carbohydrate intake to a diet high in these constituents can account for weight gain of as much as 5 kg in 24 hours in rare cases (32). Cravings for salty and sweet foods are commonly reported by women with PMDD, and these dietary alterations may account for unusual cases of premenstrual edema. For this reason reduction in the intake of salt and refined carbohydrates may help prevent edema and swelling in occasional women with this manifestation of PMS.

Although a link between methylxanthine intake and premenstrual breast pain has been suggested, available data are not convincing (33, 34). Nevertheless, a reduction in the intake of caffeine may prove useful in women where tension, anxiety, and insomnia predominate.

Several lines of evidence indicate that there is a tendency to increased alcohol intake premenstrually (35), and women should be cautioned that excessive use of alcohol is frequently an antecedent factor in marital discord.

Anecdotal evidence suggests that small, more frequent meals may occasionally alleviate mood swings. Based on recent evidence that cellular uptake of glucose may be impaired premenstrually, there is, at least, some theoretical basis for this dietary recommendation (36). Carbohydrates may exhibit mood altering effects through a number of mechanisms (37), but attempts to improve premenstrual symptoms through dietary supplements have met with limited success (38). Calcium supplementation has been shown to be marginally superior to placebo in a randomized placebo controlled trial (39, 40).

3) Exercise

Exercise is reported to reduce premenstrual molimina in women running in excess of 50 km/cycle (41). Lesser amounts of regular aerobic exercise may relieve symptoms, at least temporarily, in many women (42). As part of an overall program of lifestyle modification, exercise may reduce stress by providing a time away from the home and by providing a useful outlet for any anger or aggression. Some PMS sufferers report that exercise promotes relaxation and helps them sleep at night.

Medical interventions

The primary factor directing the selection of therapy should be the intensity and impact of premenstrual symptoms. Symptoms that are causing major disruption to quality of life rarely respond to lifestyle modification alone, and efforts to push this approach often do nothing more than delay effective therapy. Conversely, minor symptoms or symptoms that are short-lived each month seldom justify major medical interventions.

Attention should always initially be directed to symptoms for which simple, established treatments exist. For example, dysmenorrhea or menorrhagia may be satisfactorily relieved with prostaglandin synthetase inhibitors or oral contraceptives.

Mefenamic acid (500 mg tid) in the premenstrual and menstrual weeks has outperformed placebo for the treatment of PMS in some, but not all, clinical trials (43,44). It is likely that many of the end stage mediators of premenstrual symptomatology are prostaglandins; hence, this prostaglandin synthetase inhibitor may be working through a general inhibition of prostaglandin activity. Due to this, it is an ideal adjunct for any woman with coexisting dysmenorrhea and menorrhagia. In practice, however, its effectiveness for PMDD where psychological symptoms predominate is disappointing. Mefenamic acid is contraindicated in women with known sensitivity to aspirin or those at risk for peptic ulcers.

Until relatively recently trials comparing oral contraceptive therapy to placebo have not shown a beneficial effect on mood in most circumstances (45), although extended cycle combined hormonal contraceptives (46) and oral contraceptives containing the progestin drospirenone (47) have proven superior to placebo in randomized clinical trials. . When contraception is required in a woman with PMDD, especially in teens and if there is coexisting dysmenorrhea or menorrhagia, extended cycle hormonal contraceptives or those containing drospirenone can be tried initially.

Published data in regard to the efficacy of pyridoxine (Vitamin B6) have been contradictory (48); however, this medication in proper dosages (100 mg OD) is, at worst, a safe placebo that becomes one part of an overall management plan for the women with distressing molimina that should include lifestyle modification and changes in diet. Patients should be cautioned that these medications do not work for all women and that increasing the dose of pyridoxine in an effort to achieve complete relief of symptoms may lead to peripheral neuropathy. Pyridoxine should be discontinued if there is evidence of tingling or numbness of the extremities.

Neither progestin therapy (49, 50) nor oil of evening primrose (51) have been shown to be efficacious for PMDD in controlled clinical trials.

Premenstrual mastalgia which affects up to 70% of women in reproductive age may occur in isolation from other distressing premenstrual symptoms and, as such, should be considered a moliminal symptom. Low dose danazol (100 mg OD) for several cycles followed by maintenance doses in the luteal phase only (50 mg OD) (52) can bring about dramatic relief of mastalgia in most women; however, higher dosages (400 mg OD) may be required to relieve other symptoms of PMDD (53). Mastalgia may also respond to tamoxifen (10 mg daily) (54), but has not been shown to respond to diuretics, medroxyprogesterone acetate, or pyridoxine.

The routine use of diuretics in the treatment of PMS should be abandoned. Most women show only random weight fluctuations during the menstrual cycle despite the common sensation of bloating. In the absence of demonstrable weight gain it is likely that this symptom may result from constipation and/or bowel wall edema rather than from an overall fluid accumulation. In rare cases, ingestion of salt and refined carbohydrates has been shown to result in true fluid retention. In cases where a consistent increase in weight can be documented or where edema is demonstrable, limitation of intake of salt and refined carbohydrates should be tried first. If such dietary restrictions fail to relieve premenstrual fluid accumulation, use of a potassium-sparing diuretic, such as spironolactone, may be considered (55). Continued use of a diuretic activates the renin–angiotensin–aldosterone system resulting in rapid rebound fluid accumulation as soon as the diuretic is discontinued. Weight takes approximately two to three weeks to return to normal after discontinuation of a diuretic in some people. Unfortunately this leaves the affected women with the impression that she must use a diuretic to maintain normal fluid balance.

Some women report overriding symptoms of anxiety and tension or insomnia in the premenstrual week (56). New short-acting anxiolytics or hypnotics such as alprazolam (.25 mg po bid) or triazolam (.25 mg po qhs) may be prescribed sparingly for such individuals (57, 58). Buspirone has also proven useful for anxiety and may be particularly helpful in circumstances where SSRIs evoke sexual dysfunction (59).

Estrogen withdrawal has been implicated in menstrually-related migraines, and recent evidence indicates that estrogen supplementation commencing in the late luteal phase and continued through menstruation may alleviate headaches in some women (60, 61, 62). As discussed below, if headaches are severe and are unrelieved by short term estrogen supplementation, they can often be nicely controlled by intramuscular or oral sumatriptan therapy (63) or by medical ovarian suppression with GnRH agonists (64, 65) and continuous combined hormone replacement therapy.

Antidepressant Therapy

A range of newer antidepressant medications that augment central serotonin activity have been shown to alleviate severe premenstrual syndrome (66, 67). Since these agents will also relieve endogenous depression, a pretreatment diagnosis, achieved by prospective charting, is very important. Practically speaking, many women who attend a gynecology clinic to seek relief from premenstrual symptoms express reservations about taking an antidepressant, particularly if a short-term endpoint (3-6 months away) is not

likely. Long term therapy may be required to control symptoms of PMDD from the late 30s until menopause.

For patients in whom psychiatric symptoms predominate antidepressant therapy may provide excellent results (Figure 6). Selective serotonin re-uptake inhibitors, such as fluoxetine, sertraline, paroxetine, fluvoxamine, and venlafaxine (a serotonin and norepinephrine re-uptake inhibitor) have all been successfully employed.

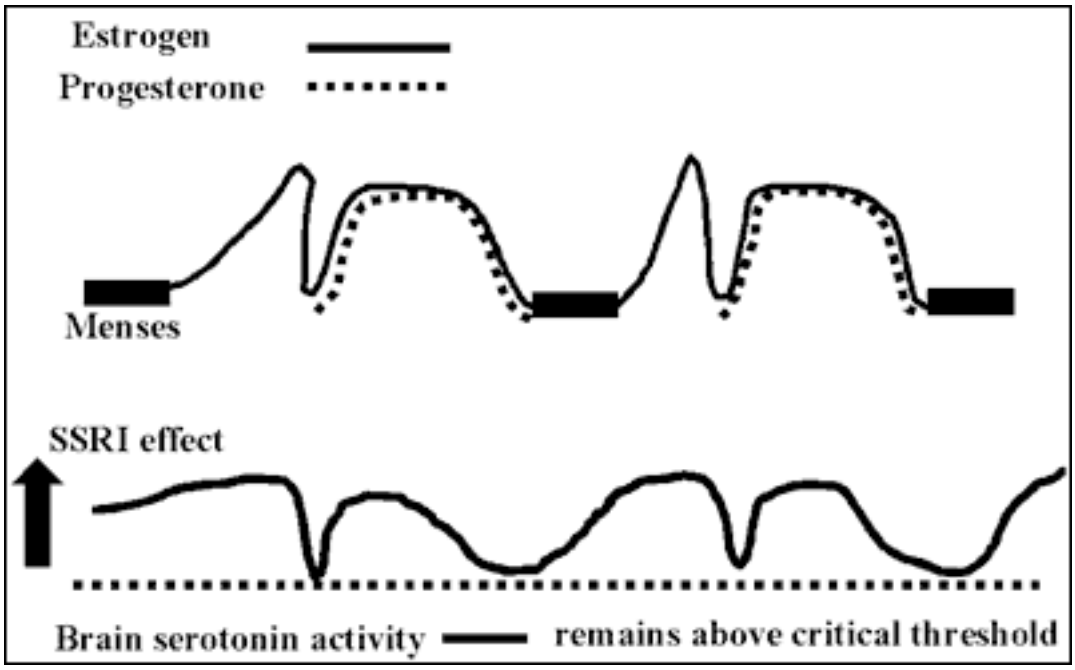

Figure 6

Symptom profiles may help in selecting the most appropriate agent (i.e., fluoxetine in patients where fatigue and depression predominate; sertraline if insomnia, irritability, and anxiety are paramount). SSRIs have been associated with loss of libido and anorgasmia, which are particularly distressing to this patient population, and appropriate pretreatment counseling is essential.

Tricyclic antidepressants (TCA) have not generally been effective with the exception of clomipramine, a TCA with strong serotoninergic activity. Intolerance to the side effects of TCAs is common.

Most women with PMDD would prefer to medicate themselves only during the symptomatic phase of the menstrual cycle. Recent studies have demonstrated that luteal phase therapy and even symptom-onset therapy may be effective for many women with PMS (68, 69). Practically speaking, it makes sense to start a trial of SSRI therapy with continuous use. After a woman has determined the optimal response that can be achieved with continuous therapy, it is reasonable for her to try luteal phase-only or symptom-onset therapy (70) to determine if the benefit is maintained.

Medical Ovarian Suppression

Suppression of cyclic ovarian function may afford dramatic relief for the woman with severe and long lasting symptoms (71, 72) (Figure 7). In each case, therapy should be directed toward suppression of cyclic ovarian activity while ensuring a constant low level of estrogen sufficient to prevent menopausal symptomatology and side effects.

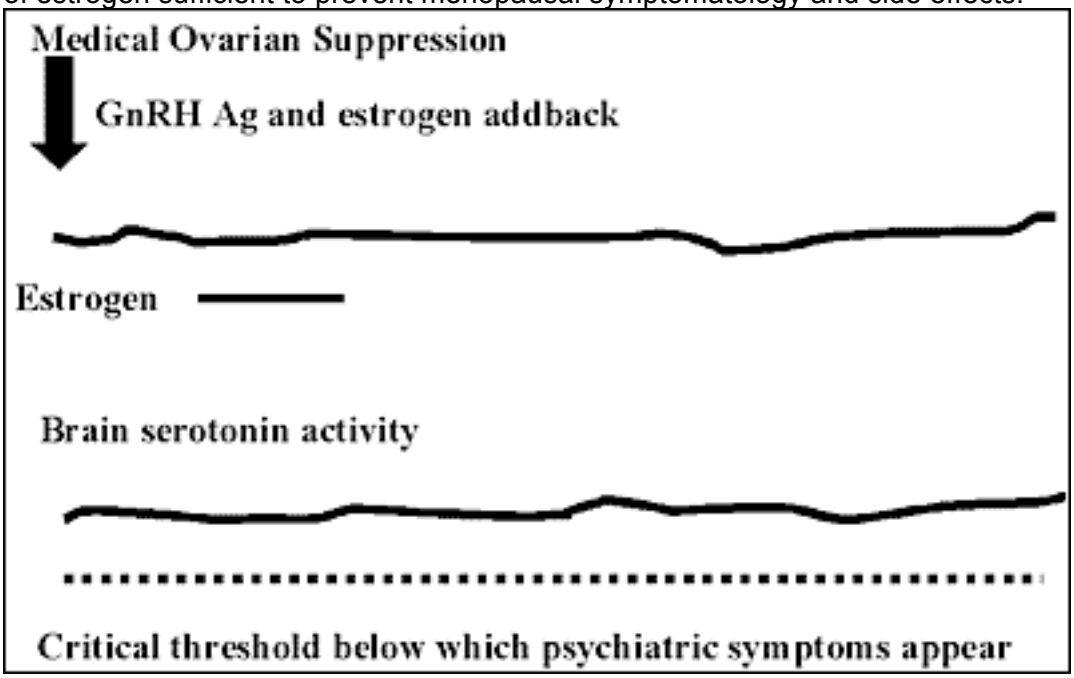

Figure 7

Danazol (200 mg bid) will effect ovarian suppression in approximately 80% of women with prompt relief from symptoms (53). It also reduces breast pain and menstrual flow. However, danazol is an impeded androgen and at a dosage of 200 mg bid may have side effects that limit its use, such as hot flashes, muscle cramps, hirsutism or a worsening of the lipid profile. Because of this, the use of danazol has been largely supplanted by ovarian suppression with gonadotropin-releasing hormone agonists (GnRH Ag).

Gonadotropin releasing hormone agonists effect rapid medical ovarian suppression, thereby inducing a pseudo-menopause and affording relief from PMS (71, 72). This approach may effectively alleviate other less common menstrual cycle-related conditions such as asthma, epilepsy, migraine and irritable bowel syndrome (65). This approach is unsatisfactory in the long term, not only because of the troublesome menopausal symptoms it evokes, but also because if creates an increased risk for osteoporosis and ischemic heart disease. When combined with continuous combined hormone replacement therapy, GnRH Ag afford excellent relief from premenstrual symptomatology without the attendant risks and symptoms resulting from premature menopause. The major drawback to this therapeutic approach is the expense of medication and the need for the patient to take multiple medications on a long-term basis. For women approaching menopause, this therapy (a GnRH Ag and continuous combined hormone replacement therapy) can be maintained until menopause with satisfactory symptom control. Some women, despite complete relief of symptoms, cannot afford or choose not to take this combination of medications for prolonged intervals (as long as 10-15 years from diagnosis until menopause in some cases).

Though less well studied depo-medroxyprogesterone acetate (depo-MPA) (150 -300 mg IM q3m) may provide a cheaper way to attenuate symptoms of PMDD in women who require contraception. The major drawback to this approach is that a substantial percentage of women will get irregular bleeding and gradual weight gain. Patients should always be counseled about the potential for protracted anovulation following use of this medication.

Surgical Therapy

Medical approaches to PMS should be considered and explored prior to any consideration of surgery for PMDD. For the woman in whom there is unequivocal documentation that premenstrual symptoms are severe and disruptive to lifestyle and relationships, and in whom conservative medical therapies have failed (either due to lack of response, intolerable side effects, or prohibitive cost), the effect of medical ovarian suppression should be tested.

Where the family is complete and permanent contraception is desired, the pros and cons of oophorectomy for lasting relief from premenstrual symptomatology should be discussed with the patient (if she has failed other medical treatments and responded to a clinical trial of medical ovarian suppression). Clinical trials have clearly shown that oophorectomy with subsequent hormone replacement therapy is effective in the treatment of PMDD (73, 74, 75). Concomitant hysterectomy will avoid the need for progestin as part of the hormone replacement regimen and may avoid irregular bleeding and progestin-induced recrudescence of symptoms. An international group of specialists with clinical experience in management of PMDD has recently published a detailed consensus document which reviews the efficacy of existing therapies (76).

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