The Premenstrual Syndrome

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As many as 30% of women who are of reproductive age experience recurrent temporary disruption of their personal and professional lives due to the predictable premenstrual appearance of distressing physical, psychologic, and behavioral changes known collectively as the premenstrual syndrome (PMS). Although marital discord, social isolation, and work inefficiency or absenteeism are the usual sequelae of this psychoneuroendrocrine dysfunction, suicidal or psychotic behavior and criminal activities, ranging from baby battering to theft and murder, may also result.[1] Although there is no clear consensus, most authors agree that the incidence and severity of this condition bear no correlation with either age or parity.[2]

Symptoms

Varying degrees of fatigue, emotional lability, and depression may appear as early as 10–14 days before menses. At this time many women find that they sleep longer, have less energy to devote to household chores, and may cry or have emotional outbursts for apparently little reason. More severely affected individuals may become completely withdrawn from family and friends, confining themselves to their beds and canceling all social engagements. Painful swelling of the breasts, lower abdominal bloating, and constipation set in about the same time and may require some women to change to looser clothing as the menses approach. Although these symptoms frequently are interpreted as manifestations of a generalized swelling, true weight gain and edema occur in a few women with PMS. In rare circumstances fluid retention in the 2–3 days before menses may reach impressive proportions. Many women note a dramatic increase in appetite or specific cravings for sweet or salty foods in the premenstrual week and episodes of binge eating at this time are common.

Late in the cycle, feelings of anxiety, inward tension, and anger supervene, leading to physical unrest, insomnia, irritability and combativeness. This unchanneled energy and emotion that manifests as a hair-trigger temper may lead to repeated angry confrontations about relatively trivial mat-

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ters with inevitable deleterious effects on interpersonal relationships. Other factors, such as difficulty in concentrating, forgetfulness, impaired judgment, motor incoordination, and susceptibility to accidents, frequently compound the scope of the problem in the final days of the cycle. Sensing that their behavior may become irrational or uncontrolled at this time, some women become fearful of driving the car, postpone important decisions, and may even relinquish all parental responsibilities to their spouse. The appearance of acne or the onset of headaches often precede menstruation by 1-2 days, while the onset of crampy low back pain and the return to a normal or loose pattern of stool generally indicate that the menses are imminent. With the onset of menstruation most women report prompt relief from psychologic distress, although somatic symptoms, particularly headache, may persist for a further 1-3 days. Dysmenorrhea, which is frequently, though not always, associated with PMS,[2] may prolong or intensify the perceived summation of premenstrual and menstrual distress.

Four patterns of premenstrual symptoms have been identified (Fig. 1).

The existence of a symptom-free interval following the menses is important to establish that premenstrual symptoms are not merely an exacerbation of some chronic condition such as idiopathic edema, fibrocystic breast disease, endogenous depression, or anxiety neurosis. Premenstrual pelvic pain is seldom a feature of PMS and may be indicative of endometriosis or dysmenorrhea.

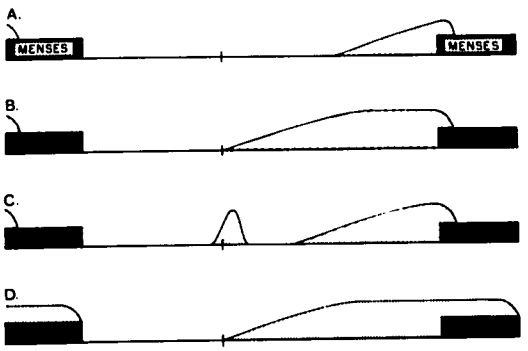

FIG. 1. *Patterns of premenstrual symptoms. The onset of midcycle symptoms in Pattern C are abruptly coincident with the fall in serum estradiol after ovulation.*

Pathophysiology

Progesterone Insufficiency or Withdrawal

Progesterone insufficiency or withdrawal resulting in a relative estrogen excess has long been suspected as the cause of PMS, because symptoms are known to intensify as progesterone levels decline late in the luteal phase. Although there have been numerous testimonials by PMS sufferers about the effectiveness of progesterone therapy, this mode of treatment has yet to receive scientific validation. Several groups have recently challenged the use of progesterone for PMS on the grounds that most women with PMS demonstrate evidence of adequate corpus luteal progesterone production and that progesterone is not superior to placebo in controlled clinical trials.[3] However, it should be noted that the doses of progesterone recommended by Dalton[1] are, in most cases, much greater than those needed to achieve normal luteal phase progesterone levels and are greater than those used in previous placebo controlled trials. It remains possible, therefore, that pharmacologic doses of progesterone may have some unknown central effects that could explain the apparent amelioration of PMS.

Fluid Retention

The theory that a generalized fluid retention precipitates the various manifestations of PMS has become firmly entrenched in clinical practice and, as a result, diuretics remain the most widely prescribed treatment for PMS. Careful studies assessing weight

change, total exchangeable sodium, and total body water have failed to uncover a pattern of fluid retention in most women with PMS.[4]

Efforts toward identification of the specific etiologic agent in cases where serial weight determinations suggest the occurrence of true fluid retention have not yet been successful. Sudden increments in the carbohydrate and salt content of the diet have been shown to induce substantial weight gain in some women.[5] Progesterone acting as a partial agonist of aldosterone induces a temporary natriuresis, followed by compensatory increases in the renin-angiotension-aldosterone axis. The finding that the conversion of progesterone to the mineralocorticoid deoxycorticosterone is enhanced during the luteal phase[6] leaves the net effect of progesterone on fluid balance unresolved. Aldosterone levels are not significantly elevated in PMS and to date there is no convincing evidence that prolactin (PRL) has fluid-retaining effects in man. Other unproven but potentially significant factors that may contribute to premenstrual fluid retention include angiotensin and vasopressin (see Reid[4] for review).

Vitamin B_6 Deficiency

Vitamin B_6 (pyridoxine) deficiency has been suggested as the cause of PMS although to date there is no objective evidence to support this contention. Advocates of vitamin B_6 therapy cite the theoretic considerations that it may enhance estrogen clearance or augment biosynthesis of brain monoamines that regulate mood and behavior. The clinical response to pyridoxine has been highly variable, with some women reporting dramatic improvement and others finding no benefit. In the only placebo-controlled trial to date, the beneficial effects of pyridoxine, which were limited to symptoms of anxiety, irritability and tension, extended over both the follicular and the luteal phases suggesting that vitamin B_6 may have some beneficial effects unrelated to the specific correction of PMS.[7]

Hypoglycemia

Hypoglycemia has been invoked as the cause of PMS, based on the finding that oral glucose tolerance curves are flattened with evidence of delayed hypoglycemia late in the luteal phase.[8] Gonadal steroid induced changes in insulin action have been suggested to account for these findings.[9] However, hypoglycemia may occur in women who don't have PMS, and PMS is seldom relieved by ingestion of food, making the likelihood of a causal relationship between these conditions remote.

Endogenous Hormone Allergy

Endogenous hormone allergy is an established entity in dermatology, but the data implicating this as the cause of PMS is limited and controversial (see Reid[4] for review). Although many questions about the effects of gonadal steroids in human allergic response remain unanswered, it seems unlikely that endogenous allergy contributes in a substantive way to the PMS.

Psychosomatic Dysfunction

Psychosomatic dysfunction has been proposed to account for the diverse and apparently unrelated symptoms of PMS and the striking placebo response rate in this disorder. Ganon,[10] following a critical reappraisal of the various studies that have explored the possible psychosomatic origin of PMS, has concluded that there is little evidence to substantiate such a hypothesis.

Hyperprolactinemia

Isolated reports of hyperprolactinemia in women with PMS and the erroneous, though frequently cited, assertion that PRL has fluid-retaining properties in man have led to considerable confusion surrounding the role of PRL in PMS. Available evidence now indicates that women with PMS do not have elevated PRL levels and, conversely, that women with hyperprolactinemia rarely suffer from PMS.[11] The initial studies that suggested that PRL had important osmo-

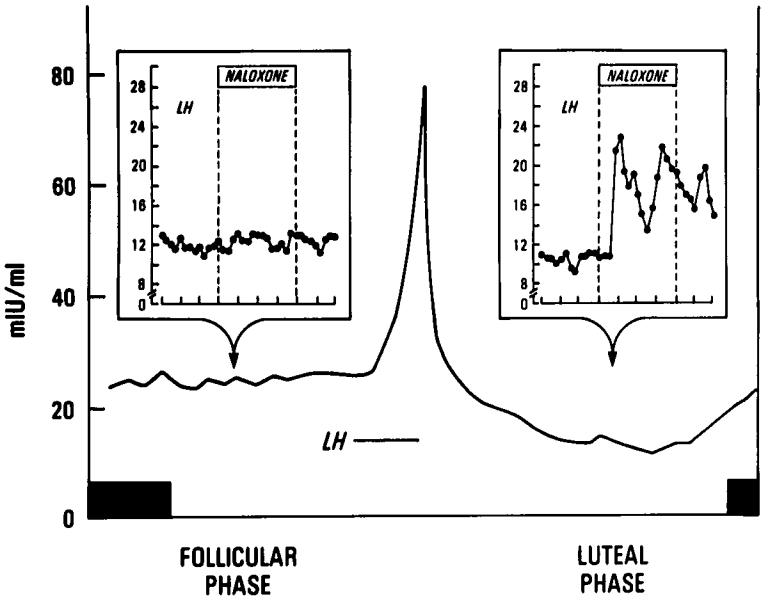

FIG. 2. *Schematic diagram of serum LH concentrations throughout the normal menstrual cycle, with* insets *showing the LH response to 4-hour infusions of naloxone (1.6 mg/hr) on separate days in the early follicular and mid luteal phases. Marked increments in the serum LH level during the mid luteal phase suggest EOP activity is maximal at this time. The* shaded boxes *indicate menstruation. (Modified from Quigley et al.*[12] *By permission.)*

regulatory effects in man have been largely discredited (see Reid[4] for review). Therapeutic trials aimed at PRL suppression employing the dopaminergic agonist, bromocriptine, have found that this treatment uniformly relieves breast symptoms but has less certain benefits as far as other symptoms are concerned.[11]

Endogenous Opiate Peptide Hypothesis

Recent evidence points to the possibility that cyclic changes in endogenous opiate peptide (EOP) activity during the menstrual cycle may be important in the pathophysiology of PMS. Based on evidence that indicates an inhibitory effect of EOPs on gonadotropin secretion, changes in the concentration of luteinizing hormone (LH) in response to administration of the opiate receptor antagonist naloxone have been used to deduce the apparent levels of central EOP activity during the different phases of the human menstrual cycle.[12] During the early follicular (or menstrual) phase of the cycle, naloxone causes no increment in the level of LH, suggesting that EOP inhibition of gonadotropin release is minimal at this time (Fig. 2). In contrast, during the luteal phase of the cycle, when gonadotropin levels are normally low, naloxone results in the greatest increments in serum LH concentration, suggesting that EOP inhibition of gonadotropin release is maximal at this time (Fig. 2). Direct measurement of β-endorphin concentrations in the portal-hypophyseal blood of the rhesus monkey have revealed that the levels of this EOP are also high during the mid-luteal phase and undetectable at the onset of menstruation (Fig. 3).[13] These findings suggest that progesterone acting either alone or in combination with estrogen can increase central EOP activity, resulting in a characteristic cycle of exposure to and subsequent withdrawal from EOPs during the normal luteal phase (Fig. 4). Excessive exposure to, or abrupt withdrawal of, this EOP stimulus may trigger the subsequent psychoneuroendocrine manifestations of the PMS. Indeed, the opiate receptor antagonist, naloxone, when administered in

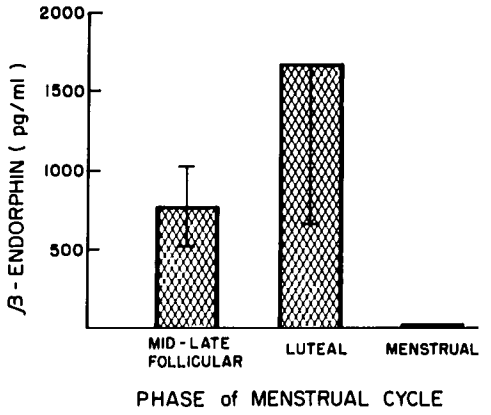

FIG. 3. *Diagram depicting the concentrations of B-endorphin in the hypophyseal-portal venous drainage of the hypothalamus at different phases of the menstrual cycle in the Rhesus monkey. (Modified from Wehrenberg et al.*[13] *By permission.)*

high doses to normal volunteers, has recently been shown to produce a constellation of symptoms almost identical to those of PMS.[14]

Increasing evidence suggests EOP's function as neurotransmitters or neuromodulators with important effects on endocrine secretion, mood, and behaviour. Increased EOP activity in the mid-luteal phase may stimulate appetite, resulting in episodes of binge eating. Fatigue and depression at this time may result from diminished release of norepinephrine or dopamine, occasioned by EOP inhibition of biogenic amine systems[15] (Fig. 5). Acute withdrawal of EOP inhibition as the menses approach may lead to rebound hyperactivity of these neural pathways due to slowly acquired receptor supersensitivity,[15] resulting in irritability, anxiety, tension, and aggression (Fig. 5). Hostile or psychotic behavior, which is frequently linked to premenstrual criminal activity, may result from marked hyperfunction of dopaminergic pathways.[4] Variations in the degree or duration of EOP exposure and the rapidity of withdrawal may account for differences in the severity of PMS from 1 month to the next.

Within the bowel, EOPs are known to inhibit prostaglandin-E_1-stimulated fluid secretion and to decrease muscular propulsive activity, which may account for the constipation and bloating noted by many

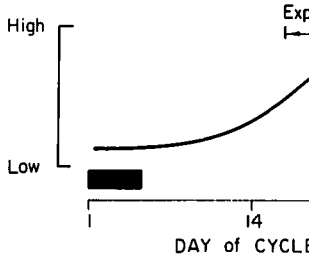

FIG. 4. *Schematic diagram showing proposed cyclic changes in levels of endogenous opiate activity throughout the menstrual cycle. Maximal opiate exposure, which occurs in the mid luteal phase, is followed by acute opiate withdrawal prior to the onset of menstruation (*shaded boxes*).*

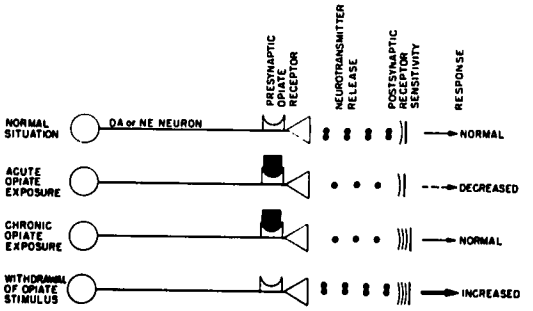

FIG. 5. *Schematic diagram showing the postulated action of endogenous opiates on neurotransmission in biogenic amine systems. The normal level of neurotransmitter release (*top panel*) is dramatically reduced through activation of the presynaptic receptor by endogenous opiates (*second panel*). Prolonged exposure to endogenous opiates results in enhanced sensitivity of the postsynaptic receptor (*third panel*), which subsequently results in an excessive receptor response when levels of endogenous opiates decline and normal levels of neurotransmission resume (*bottom panel*). (Modified from Schwartz et al.*[15] *By permission.)*

women during the luteal phase. Increased prostaglandin activity subsequent to a fall of EOP activity might explain the loose bowel movement that frequently precedes the onset of menstruation.

Several lines of evidence have implicated EOPs in the regulation of vasopressin release in man, but the significance of these data in relation to cases of premenstrual edema is unknown.

Early Identification of the Patient With PMS

Many women fail to tell their doctors about premenstrual symptoms because they fear they are "going crazy" or because they believe their bizarre symptoms will be a source of embarrassment or ridicule. As symptoms intensify, leading inevitably to deterioration of family life or the alienation of friends, feelings of personal inadequacy, hopelessness, and guilt develop. To avoid this late recognition of the PMS, a few moments should be routinely taken when obtaining a menstrual history to delineate the sequence and severity of premenstrual symptoms in all women of reproductive age. A simple inquiry about "premenstrual symptoms" will often elicit complaints about swelling or "fluid retention" but will seldom yield more detailed information about other physical or psychologic manifestations. Further specific questioning about fatigue, depression, anxiety, irritability, anger, hostility, change in appetite or thirst, constipation, edema, breast or abdominal swelling, and headaches is useful. Patients with premenstrual symptoms often express surprise that their symptoms were correctly anticipated and are reassured to know that other women share their affliction. Such questioning provides the clinician with a better perspective of the scope of PMS and lends an air of legitimacy to premenstrual symptoms that may set the stage for an educational discussion.

When specific troublesome symptoms are identified, further dialogue is needed to establish to what extent these manifestations disrupt activities of daily living. The physician should determine whether the patient turns down social engagements, neglects parental responsibilities, avoids making important decisions, has more minor accidents, refuses to drive the car, stays home from work, has suicidal thoughts or plans, manifests psychotic or aggressive behavior, or takes medication for her symptoms.

Management of PMS

Education and *reassurance* are of primary importance in the management of PMS. The patient and her family should be informed that PMS is a common hormonal disorder in women of reproductive age. When a more detailed explanation is requested, we have found it useful to suggest the possibility that cyclic changes in EOP activity may be responsible. Most patients are familiar with the concept of opiate withdrawal and can readily relate their symptoms to either excessive EOP exposure (constipation, hunger, fatigue, depression) or abrupt withdrawal (irritability, anxiety, tension, hostility) once this association has been suggested to them. Presented for the first time with a plausible explanation for the heterogeneous clinical manifestation of PMS, these individuals and their families experience tremendous psychologic relief. Reassured by the knowledge that their illness is not "all in their heads" (and at times resentful of those whose indifference or derisive comments led them to believe that it was), they often express dismay that they delayed seeking help for so long. A better understanding of the problem by family members and identification on a calendar of anticipated "bad days" helps them to be more tolerant of behavioral lapses and to modify family activities during the premenstruum in a way that minimizes the degree of disability. A nonprofit group* has recently been established to disseminate

*PMS Action, Inc., P.O. Box 9326, Madison, Wisconsin 53715.

information on PMS and to lend support to individuals suffering from this condition.

When premenstrual symptoms are mild and largely somatic in origin, therapy may rely on liberal amounts of education and reassurance and the judicious use of medication. Caution must be taken with the prescription of any drug during the luteal phase if pregnancy is a possibility.

Although some women report dramatic improvement of PMS while on *oral contraceptive steroids*, the superiority of these agents to placebo remains in question.[16] Nevertheless, for the patient younger than age 35 who requires contraception, particularly if dysmenorrhea is an associated feature, oral contraceptives may be an effective therapy.

Antiprostaglandins such as mefenamic acid (250 mg) naproxen sodium (275 mg), or ibuprofen (400 mg) orally every 4-6 hours are also useful for relief of dysmenorrhea but provide little benefit for symptoms confined to the premenstruum.[17]

Analgesics such as acetylsalicylic acid (ASA) or acetominophen with or without codeine may be sufficient to relieve headaches and minor musculoskeletal pains of PMS.

Diuretics are vastly overutilized in the treatment of PMS. Used in a discontinous fashion, they may actually precipitate fluid retention and edema due to the stimulation of the renin-angiotension system that they induce.[5] In those women who show clear evidence of recurrent premenstrual weight gain and edema when they aren't taking diuretics, a reduction in the intake of refined carbohydrates and salt may be helpful.[5] Where these measures are ineffective and symptoms indicate the need for diuretic therapy, spironolactone 25 mg orally, four times a day, may be used in the final week of the cycle.

Studies employing *bromocriptine* (2.5 mg orally, twice a day)[11] and danazol (200 mg orally, twice a day)[18] have shown them both to be effective for the control of breast swelling and tenderness but to be of limited value as far as other symptoms of PMS are concerned. These medications are expensive and may produce troublesome side effects, which limits their usefulness for long-term treatment of PMS.

If PMS is severe or unresponsive to the above symptomatic measures, a different approach to treatment is required. Patients showing marked alterations in mood with manic or severe depressive symptoms and those with psychotic behaviour should have the benefit of a complete psychiatric evaluation before treatment begins. However, it is important to realize that the traditional psychiatric approach to these problems may be inapproriate when applied to a transient premenstrual affliction in an otherwise healthy individual. *Psychotherapy* is not effective for the treatment of PMS, and *tricyclic antidepressants*, because of their delayed onset of action and potential to exacerbate premenstrual manic behavior, should not be used except in individuals who may have endogenous depression with premenstrual exacerbation. *Lithium carbonate* (600-1800 mg per day orally) is sometimes effective for control of recurrent psychotic[19] or cyclothymic behavior.[20] However, troublesome side effects and the need for careful monitoring of renal function and serum lithium levels preclude its routine use in PMS.

Progesterone[1] and *pyridoxine*[7] have received wide acclaim for their effectiveness in treating PMS, but clear scientific proof of their superiority to placebo is lacking. When specific symptomatic measures fail to control PMS or when psychologic or behavioral manifestations predominate, a trial of one of these agents may be helpful. Pyridoxine is usually administered in a dose of 25-50 mg orally, twice a day, although some investigators have used up to 500 mg daily throughout the cycle.[7] Progesterone, 25-100 mg intramuscularly qOD or 200-400 mg OD by vaginal or rectal suppository is given from midcycle until the onset of menstruation.[1] Other than a possible worsening of vaginal candidiasis following progesterone

vaginal suppositories, no adverse effects have been reported with the use of these medications.

Only when PMS is disabling and unresponsive to the above measures or when surgery is indicated by coexisting pelvic disease should termination of cyclic ovarian function by oophorectomy be considered.

Future Directions in the Management of PMS

The possibility that PMS results from an aberration of normal cyclic changes in EOP activity during the luteal phase is intriguing, because it suggests that treatments that can modify EOP activity may be useful in the management of PMS. Further studies assessing the impact of gonadal steroids on EOP activity may shed new light on the role of progesterone therapy in PMS. Luteinizing-hormone-releasing factor (LRF) agonists may prove beneficial in the treatment of PMS by preventing episodic changes in EOP activity through their ability to cause temporary cessation of cyclic ovarian function. Narcotic antagonists such as naltrexone may be useful to counteract features of PMS that result from excessive exposure to EOPs. The α_2 adrenergic agonist, clonidine, which has recently been used to prevent manifestations of opiate withdrawal in addicts undergoing detoxification, may attenuate psychologic and behavior manifestations of PMS resulting from EOP withdrawal late in the luteal phase.

More basic research and adequate testing in controlled clinical trials is needed before these medications can be promoted for treatment of PMS, in order to avoid the addition of more unproven remedies to an already cumbersome therapeutic armamentarium.

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