Clinical Review

Premenstrual Syndrome

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Symptoms related to the premenstrual syndrome (PMS) are experienced by a large segment of the susceptible population. Its nature and the extent to which it is a problem are not well delineated and are subjects of significant controversy. Its etiology is uncertain. Cortical centers and neurotransmitters appear to play an important role. Its influence on the expression of other diseases and their influence on its presence or its severity have received insufficient study. Various approaches to therapy are commonly used, including birth control pills, diuretics, minor tranquilizers, and bromocriptine, but no single drug therapy is consistently effective. A strong placebo effect has been demonstrated with all medications that have been used.

The physical and emotional discomfort that can occur toward the end of the menstrual cycle is known as the premenstrual syndrome (PMS). PMS has been reported in association with criminal behavior,¹⁻³ suicide attempts,⁴ psychiatric emergencies,^{5,6} accidents,⁷ marital discord,⁸ and child battering.^{9,10} Nevertheless, a precise definition is lacking, and "there continues to be a profound ignorance about the incidence and degree of impairment associated with the periodic phenomena of the human menstrual cycle."¹¹ This paper will review current concepts of its prevalence, pathophysiology, clinical features, and recommended treatment, and will propose additional areas for future investigation.

Several definitions of premenstrual syndrome (PMS) have been proposed. Sutherland and Stewart¹² use "any combination of emotional and physial features which occur cyclically in the female before menstruation and which regress or disappear during menstruation." Using this definition, they classified 97 percent of their cohort of healthy women as having PMS. At the other extreme, Rose and Sacher¹³ require multiple and severe disabling symptoms to diagnose PMS, and estimate that 5 percent of the female population of reproductive age is afflected. Although most investigators include both premenstrual alterations of mood and behavior and physical symptoms, se-

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verity of symptoms has generally not been included in the process of evaluation. "Clearly it is necessary to distinguish between women who notice changes which they regard as tolerable and those who regard themselves as ill."¹⁴

Symptoms usually begin 2 to 7 days prior to menses and abate on the day flow begins. The discomfort includes negative affect, decreased cognition and motor coordination, autonomic nervous system symptoms, abdominal pain, and fluid compartment alterations.^{15,16} Although PMS may be associated with dysmenorrhea, the latter occurs only with ovulation, whereas PMS can occur with anovulatory periods. Most reports do not separate PMS from premenstrual aggravation of existing psychopathology such as antisocial behavior, depression, hypomania, and schizophrenia.^{5,17-21,22}

Prevalence

Data on PMS were not available from the National Ambulatory Medical Care survey prior to 1977²³ because the classification used (International Classification of Diseases–Adapted—Eighth Revision)²² did not contain that diagnostic title. The ninth revision (ICD–9–CM)²⁴ does include PMS as a separate diagnostic title, and preliminary data from the National Ambulatory Medical Care Survey for the year 1980²⁵ revealed that of a total of 346,105,937 visits to physicians by women, there were 719,000 visits for all menstrual problems, and 22,000 visits for premenstrual tension syndrome.

Among the classifications used in the ambulatory setting, PMS was first included as a separate diagnostic title in the International Classification of Health Problems in Primary Care (ICHPPC)²⁶ and, therefore, previous morbidity surveys using older ambulatory care classifications (RCGP)27 did not include data on this syndrome. Froom (personal communication, November 1983) found that only 44 instances of PMS (classified according to ICHPPC) were recorded in 105,245 diagnostic encounters in an ambulatory setting. Thus, prevalence data from morbidity surveys indicate either that women fail to bring this problem to their physician or that physicians do not consider the diagnosis of sufficient importance to record it.28-30 On the other hand, prospective studies reveal an entirely different picture. Smith³¹ reports that 30 to 60 percent of women note a major mood change during the luteal phase, and Sturgis³² reports that 95 percent of women are aware of the approach of a period and 2 to 5 percent are incapacitated by it. Rose and Sacher¹³ stated that 25 to 35 percent of women have one or more symptoms, and 5 percent report multiple or severe symptoms. In a review of questionnaire reports,33 it was concluded that 70 to 90 percent of the female population experience recurrent premenstrual symptoms and 20 to 40 percent report some degree of impairment. Parker³⁴ estimates that work absenteeism association with menstrual disorders causes a yearly loss of about \$5 billion. Menstrual dysfunction, however, does not appear to be associated with the level of job responsibility.35

Pathophysiology

Self-Report Studies

The Menstrual Distress Questionnaire (MDQ) is designed to produce uniform symptom reports regarding PMS. It is the most commonly used instrument to study self-reports of PMS. Part A lists 47 symptoms that can occur during the entire cycle. Part T requests symptoms that are present within 24 hours of the time of test administration. In a study of 839 wives of graduate students, Moos¹⁵ concluded that symptoms of negative affect were not unique to the premenstrual period; rather, they were an exaggeration of those that occur throughout the cycle. Moos suggested that women who suffered only from symptoms due to fluid retention had a different physiologic alteration from that experienced by those with symptoms of negative affect. Rouse³⁶ used the MDQ to test 392 British women and reported that the respondents found the instrument confusing and time consuming. She concluded that the MDQ was of limited use in its present form, but reported significant difference between parts A and T of the MDQ, particularly for pain, water retention, and the negative-affect scales. She concurs with others that "the measurement of menstrual disorders has baffled many but left none triumphant." She noted, however, that women on birth control pills had a lower incidence of PMS symptoms than those using other forms of contraception.

Haskett et al²¹ found that volunteers who re-

sponded to a newspaper advertisement suffered more severe PMS symptoms than those who were selected at random. Ruble37 administered part T of the MDQ to 44 female undergraduates aged between 18 and 24 years and found that those susceptible to the suggestion that they were within one to two days of onset of a period (when, in fact, it was a week or so away) had higher scores than otherwise. She stated "it appears that learned association of belief might lead a woman either to overstate what she is actually experiencing or to perceive an exaggeration of naturally fluctuating bodily states." She concluded that physiological factors influence self-reporting of menstrualrelated symptoms and that the effect of physiological changes that accompany the premenstruum is questionable.

Ruble and Brooks-Gunn³⁸ reviewed the literature of self-reported PMS symptoms. They found serious methodological problems and statistical deficiencies in most of the studies and suggested that "symptom associations may originate and be maintained by biases in the processing of information about cyclicity." It was their impression that menstrual symptomatology cannot be fully accounted for by physiological factors and is more easily explained by biased beliefs associated with the menstrual cycle.

Behavioral Studies

During 1980 three British women successfully pleaded that crimes of manslaughter, arson, and assault were related to PMS. Each had a long history of repeated misdemeanors that appeared to be related to the premenstrual phase and that improved with administration of natural progesterones.³

The first recorded association of violence and PMS appears to have been by Lombroso and Ferrero³⁹ in 1894. In another report² of 50 women charged with violent crime, 44 percent of the crimes were committed during the paramenstruum (the four days before and the first four days of the period), although an unusually low incidence of premenstrual complaints occurred among this group. After a careful review of criminal activity in relation to PMS, Horney⁴⁰ concluded that there was insufficient evidence to change the current concept of responsibility for acts committed in relationship to the menstrual cycle.

An analysis⁴ of telephone calls to the Los

Angeles Suicide Prevention Center revealed that the majority of women called during the four days before and the four days after the onset of menstrual flow. Nineteen of 22 Hindu women who had committed suicide by burning themselves with kerosene were found to have been menstruating when examined at necropsy. Autopsies on suicide and accident victims showed that 52 of 58 uteri examined were in the last half of the menstrual cycle⁴¹ Glick and Stewart¹⁹ report severe premenstrual exacerbation of disease in three schizophrenics who required hospitalization.

Berlin et al²⁰ report a 15-year-old with periodic psychosis during the luteal phase, observed over a three-year period, in whom weekly injections of progesterone resulted in no further recurrence during a year of therapy.

Endicott et al¹⁸ compared for differences in symptoms during the premenstruum those patients with an effective disorder and those who had a panic disorder. Those with an affective disorder reported an increased anxiety and more physical changes, while those with panic or generalized anxiety disorder reported no increase in the frequency or severity of such symptoms.

Tuch⁴² found that women were more apt to bring their children to a pediatric outpatient department during the premenstruum, and that the children had less illness, were ill for shorter periods, and had different types of illnesses than when the mothers were at different phases of the menstrual cycle.

Neuroendocrine Influences

Reid and Yen³³ postulate that the various manifestations of PMS are a result of a cascade of hormonal and neurotransmitter changes that occur during the luteal phase, but that no hypothesis yet proposed can adequately explain the pathogenesis of PMS. A negative affect or depression can occur when estrogen levels are low, as in the premenstruum, menopause, or the postpartum periods, perhaps by interfering with the amine oxidase activation of norepinephrine at the synaptic site.^{43,44} Andersch and Hahn⁴⁵ believe it unlikely that PMS will be found to be due to a single hormonal aberration, but that the defect probably relates to central nervous system neurotransmitters.

The hypothalamus is a terminus where chemical neurotransmitters are modulated by the formation Continued on page 674

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and release of substances that stimulate or inhibit the discharge of specific pituitary hormones or other messenger substances. Some neurons have become so specialized as to assume a quasiendocrine function.⁴⁶ Although they have dendrites and axons, they do not discharge neurotransmitters to trigger other neurons. Swanson and Sawchenko⁴⁷ have demonstrated that cells of the hypothalamus project directly into the pituitary, the brain stem, and the spinal cord. These cells probably play a direct role in the regulation of the autonomic as well as the endocrine effector mechanisms.

Kreiger and Martin⁴⁸ have demonstrated that inhibiting and releasing factors, originally thought to be solely of hypothalamic origin, are in fact widely distributed throughout the central nervous system and other tissues. Such neurotransmitters influence and in turn are influenced by behavior; both can produce alterations in the menstrual cycle⁴⁹ such as the amenorrhea associated with pseudocyesis and anorexia nervosa.

Steiner and Carrol,⁵⁰ in their review of psychoendocrine mechanisms, find that all recent attempts to formulate a working hypothesis of premenstrual dysphoria have been unsuccessful. Andersch and Hahn⁴⁵ state that there is no evidence in the literature to indicate that PMS is related to high prolactin levels. They feel strongly that the defect will relate to the neurotransmitters of the central nervous system. Some of the women whom they studied were anovulatory at the time that they were suffering from significant PMS symptomatology. They concluded that neither prolactin nor progesterone plays a role in the etiology of this syndrome.

Boyden et al⁵⁰ studied menstrual cycle changes and prolactin responses in female runners. They report an increase in prolactin levels, frequent oligomenorrhea, but no amenorrhea. They did not, however, study PMS in this group.

Fluid retention is one of the few objective findings associated with PMS, and localized vascular edema is thought to be responsible for symptoms referable to the intestinal tract, brain, and breast. Fluid transudation across capillaries has been reported to be greater in PMS subjects than in controls. Although renin and angiotensin levels are elevated during the luteal phase, differences between PMS sufferers and subjects without PMS have not been demonstrated.⁵¹ Furthermore, there is no consistent pattern of weight gain in the premenstruum and a poor correlation between weight gain and behavioral symptomatology.^{17,52}

Diagnosis

Specific Manifestations. Almost 150 different symptoms have been linked to the premenstrual period.¹⁵ These symptoms vary, not only from individual to individual, but also over time in the same individual. Although PMS may occur at all ages during the reproductive years, it is more frequent and more severe in those aged over 30 years.⁷

Behavioral Manifestations. These are the most frequent and distressing symptoms. Negative affect is manifested by variable levels of irritability, lethargy, depression, agitation, and inability to concentrate. Although a few note increased energy toward the end of this phase, others complain of diminished motor coordination and being accident prone.³³

Somatic and Autonomic Manifestations. These include changes in appetite, thirst, bowel habits, abdominal bloating, pelvic heaviness, faintness, headache, and rheumatic pains.^{34,51}

Fluid Compartment Alternations. Weight gain, generalized edema, breast engorgement, and headache are frequent and, at least in part, due to localized edema.⁵¹

Psychomotor Testing

The results of psychomotor tests are variable and contradictory. Decreased classroom test performance by teenaged English schoolgirls during the premenstruum has been reported by Dalton,⁵⁴ but Sommer⁵³ found no difference in performance of intellectual tasks by college women tested during various phases of their menstrual cycle. In their study of 26 college women during the ovulatory and premenstrual cycles, Ivey and Bardwick⁵² found that scores for anxiety and hostility were greater in the premenstrual period compared with those scores at the time of ovulation. The authors conclude: "The menstrual cycles exercise gross influences on female behavior. That females may cope or not cope, test anxious, hostile or depressive, appear healthy or neurotic on physiological tests is due as much to the menstrual cycle phase as to the core psychological characteristics."

Golub55 evaluated the magnitude of anxiety and depression in the premenstrual phase of 50 volunteers aged between 30 and 45 years. She found that for most women, premenstrual anxiety levels were equivalent to the stress of "being in an unfamiliar situation or taking some tests." Active, unimpaired, normally functioning women showed a high incidence of premenstrual anxiety and depression. but women who suffered from chronic anxiety states were no worse during their premenstruum.

Management

Since the 1950s, progesterone has been used extensively, based on the hypothesis that diminished progesterone levels in the late luteal phase with unopposed estrogen are responsible for breast dysplasia, fluid retention, abnormal carbohydrate metabolism, and mood changes associated with PMS. Well-controlled double-blind studies.31,33,56 however, have failed to demonstrate a therapeutic effect. The use of birth control pills likewise produces inconstant effects, although a decrease in depression has been noted with their use.³¹ The sequential pills, however, seem to induce or aggravate mood changes.⁵⁷ Bromocriptine can reduce prolactin levels, but appears no more effective than placebo in reducing PMS symptoms.58-60 Pyridoxine is an essential coenzyme in monamine synthesis by neurons, and estrogens can suppress the availability of pyridoxine. Thus, a pyridoxine deficiency has been postulated as a factor in the etiology of PMS. Administration of pyridoxine, however, has not been shown to relieve the symptoms of PMS. 33,57,61

Minor tranquilizers and anxiolytic agents appear to be widely used in the treatment of PMS, but there are few well-controlled studies on their use.⁶² Lithium,³³ monamine oxidase inhibitors,³¹ tricyclic antidepressants, and major tranquilizers⁵ give variable results in psychotic patients who also have PMS. Psychotherapy alone is rarely effective,57 although several investigators feel that acceptance of a purely biological etiology of PMS might cause women to suffer guilt, anxiety, and feelings of inferiority.38,63,64

Diuretics are also widely used, although fluid retention is an inconstant finding in the syndrome, and the relationship between fluid retention and mood alteration has not been demonstrated.31,59,60 There is, however, a strong placebo effect from all

medications that have been used, 9,33,60,65

Any improvement that occurs should be interpreted with caution regardless of the therapeutic modality. Reassurance as to the benign nature of the problem is essential because no single drug therapy has been demonstrated to be consistently effective. Several community premenstrual clinics have been organized in the United States. Their success is primarily based on the reassurance provided.

Family physicians can contribute to the understanding of PMS by studies that better define the symptom manifestations, its relationship to other coexistent diseases, and its effect on other family members. Additional studies are needed to demonstrate the effect of such variables as age, work status, sexual preference, physical activity, and underlying beliefs and prejudices.⁶⁶ There is little knowledge of the frequency and variety of use of self-medication and alcohol for relief of negative affect.35,67

At present, currently available therapeutic choices will prove unsatisfactory for a significant portion of affected women.

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