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THE PREMENSTRUAL SYNDROME AND ITS TREATMENT

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Summary—The premenstrual syndrome has been described briefly and the literature relating to its pathophysiology and treatment have been reviewed. The great number of theories as to etiology and many different kinds of treatments attest to our ignorance of the exact nature of this problem. Although it is obvious that the hypothalamo–pituitary–ovarian axis must be involved, the exact mechanism whereby the symptoms come about remains elusive. Progestin in the presence of estrogen appears to be essential. Excess estrogen may aggravate the condition. The popular theory of progesterone deficiency has not been supported by double blind trials of progesterone in various forms versus placebo. Because of the important placebo effect in this condition, double blind trials are essential in the assessment of any form of treatment.

The premenstrual syndrome (PMS) can be defined as recurrent luteal phase distress, with complete remission in the follicular phase. It must be distinguished from dysmenorrhea, endogenous depression, anxiety neurosis, fibrocystic breast disease and idiopathic edema. Most women (70–90%) are aware of changes in mood in relationship to the cycle, realizing that when they are irritable they are about to start a menstrual period. In 20–40% there is some form of temporary disability and about 5% become seriously incapacitated during the premenstrual week or even two weeks.

PMS was first described by Frank in 1931 [1], who wrote "The group of women to whom I refer especially complain of a feeling of indescribable tension from ten to seven days preceding menstruation which, in most instances, continues until the time that the menstrual flow occurs. These patients complain of unrest, irritability, 'like jumping out of their skin' and a desire to find relief by foolish and ill considered actions. Their personal suffering is intense and manifests itself in many reckless and sometimes reprehensible actions. Not only do they realize their own suffering, but they feel conscience-stricken toward their husbands and families, knowing well that they are unbearable in their attitude and reactions. Within an hour or two after the onset of the menstrual flow, complete relief from both physical and mental tension occurs." This vivid description is comprehensive and accurate for many patients.

However PMS continued to be ignored for decades and it was only in 1987 that the American Psychiatric Association included "late luteal phase dysphoric disorder" as a "proposed diagnostic category needing further study" [2].

At times the picture may be bizarre—one case report describes a young woman who went to sleep for several days during each premenstrual phase and got up only to evacuate or when her parents woke her to eat [4]. This was relieved by inhibiting ovulation. Another patient presented with an acute periodic psychosis [5] a few days before each period; this was characterized by incoherent speech, insomnia, hallucinations, agitation and emotional lability. This behaviour had continued for a period of three years and she had received trials of chlorpromazine, thioridazine, haloperidol, tricyclic antidepressants, lithium and psychotherapy with no improvement. Finally she was given medroxyprogesterone acetate, which prevented ovulation and relieved the symptoms.

The symptoms are numerous—more than a hundred have been reported—and fall into two groups: mental and physical. The mental symptoms are usually the more disabling; they often include tension, irritability, depression, anxiety, a feeling of loss of control, insomnia or hypersomnia, violence (often leading to child

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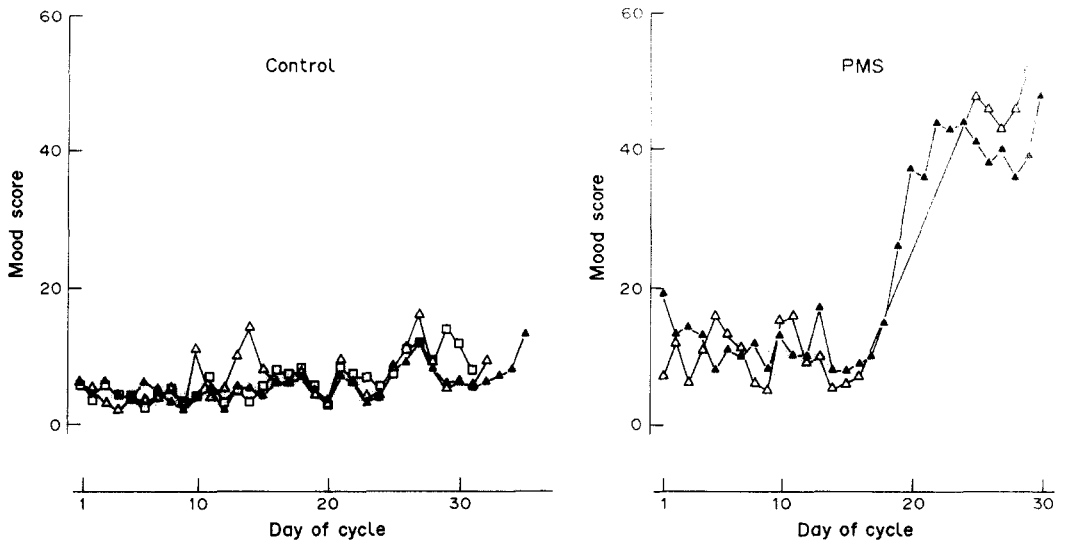

Fig. 1. Comparison of the symptom patterns for 3 cycles in a control subject (left) and for 2 cycles in a woman with PMS (right).

battering, assault, and even murder and suicide), fatigue and a craving for sweets. The commonest physical symptoms are bloating, breast tenderness, acne and headache. The diagnosis is made on the basis of the relationship of the symptoms to the timing of the menstrual cycle; there must be a period which is entirely free of symptoms during the follicular phase.

The most satisfactory way to establish the timing of the symptoms is to have the patient fill out a list of questions each evening for two cycles or more. There are many questionnaires available and we used one which is short, easy to fill out and to score, but which assesses both mental and physical symptoms and possible external factors as well [3]. Our questionnaire includes 28 questions: 12 describing mood, 9 describing physical symptoms and 7 which document other features. Those describing the symptoms are graded as 0, 1, 2 or 3 corresponding to nil, mild, moderate and severe. The score is the sum of the grades for the symptoms.

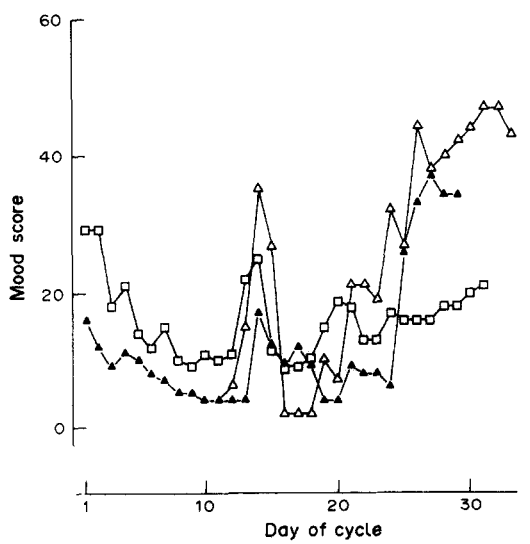

Fig. 2. Symptom patterns for 3 cycles in a woman with an ovulatory as well as a premenstrual peak.

The patterns vary from one individual to another but are remarkably reproducible in the same patient (Fig. 1). Some have symptoms at the time of ovulation (Fig. 2) with improvement in the early luteal phase and worsening in the late luteal phase. Although in many women the onset of the period is associated with a rapid improvement in symptoms, in a few the premenstrual distress extends through most of the period.

Although the effect of the menstrual cycle on the health of women was largely ignored until recently, Mackinnon and Mackinnon in 1956 [6] described its effect on the mortality of women in their reproductive years. Establishing the phase of the menstrual cycle from the histology, they showed that of 47 cases, only two died in the follicular phase and almost all died in the mid- and late luteal phase. The commonest cause was suicide, followed by accidents. Even death from various diseases occurred much more commonly in the luteal phase. Thus women appear to be much more vulnerable during the luteal than the follicular phase.

The pathophysiology of PMS is still poorly understood. It only occurs in the presence of functioning ovaries, ceasing after medical or

surgical menopause but unaffected by hysterectomy alone. There seems to be little doubt that it is related to cyclic fluctuations of the hypothalamic–pituitary–adrenal axis but the details remain obscure.

There are many theories as to the etiology of PMS [7]. For many years it was felt to be psychogenic, a subconscious rejection of femininity and reproduction. Generalized fluid retention, hypoglycemia, vitamin B6 or vitamin E or other nutritional deficiency, and hyperprolactinemia have all been considered, but no clear-cut abnormalities have been shown. Vasopressin excess, progesterone deficiency or alteration in metabolism, estrogen excess, and opioid withdrawal are currently under scrutiny.

The most popular theory has been that of progesterone deficiency postulated by Dalton [8]. Many anecdotal reports claimed dramatic improvement but a series of double-blind trials [9–12] have failed to confirm the efficacy of this treatment. Despite this, progesterone or progestin therapy is used widely but can only be considered a placebo.

The placebo effect in PMS is particularly prominent, up to 60% reporting improvement on placebo alone. This is probably because many affected women are concerned that they are "going crazy", so that the reassurance and support that come with any form of treatment are very important.

It was suggested by Halbreich and Endicott in 1981 [13] that PMS symptoms may be due to withdrawal of natural opiates in the luteal phase of the cycle. This is difficult to study because peripheral levels may not reflect brain levels of endorphin. Wehrenberg *et al.* [14] showed that levels of β-endorphin in hypophyseal portal blood of monkeys were high during the mid- to late follicular phase and the luteal phase but were undetectable at menstruation. Levels were undetectable after ovariectomy. Veith *et al.* in 1983 [15] found that plasma β-endorphin levels were relatively stable through the cycle except at the time of ovulation when they varied widely. Pain thresholds did not fluctuate in a consistent pattern; anxiety seemed to correlate with endorphin levels only during menses. Laatikainen *et al.* in 1985 [16] found that plasma β-endorphin peaked one day after ovulation but that levels at the first day of menstruation were slightly higher than in the follicular phase. Chuong *et al.* [17] showed that at the 7th day of the cycle, levels were similar in controls and PMS patients, but on the 25th day of the cycle, the levels in the PMS patients were significantly lower ($P \leqslant 0.0001$), although there was much overlap. This theory was also supported by the work of Peck in 1982 [18] who found that the opiate antagonist, naloxone, aggravated symptoms of PMS and by that of Cohen *et al.* [19] who induced withdrawal symptoms in normal volunteers with naloxone. Facchinetti *et al.* [20] studied the response of various hormones to clonidine in 9 women suffering from menstrual migraine and 6 healthy volunteers. In the patients, β-endorphin and growth hormone plasma levels were stimulated by clonidine only in the early luteal phase but not in the premenstrual phase. They felt that this might reflect a postsynaptic α-adrenoreceptor hyposensitivity during the premenstrual period in the patients. Nilssen *et al.* [20] reported improvement in a single case of PMS by clonidine in 15 consecutive cycles. Giannini *et al.* in 1984 [22] confirmed Chuong *et al.*'s observations [17] of lower β-endorphin levels in PMS patients but found them to be higher in more severe PMS than in less severe cases. They postulated a compensatory rise in the severe cases. In 1988 this same group carried out a double-blind crossover trial in women with evidence of decreased levels, but the results were of only borderline significance [23].

Estrogens are generally considered to increase energy while progesterone is known to have sedative properties. Backstrom has shown that administration of progesterone to an epileptic patient decreased the frequency of epileptic discharges [24], and he has observed that epileptic women have fewer seizures during the luteal phase [25]. On the other hand, Frank [1] reported a case of epilepsy which occurred almost exclusively during the luteal phase. Backstrom *et al.* [26] also found that estrogen peaked later and higher in PMS patients than in controls while progesterone levels were lower; while the same tendency was found by Munday *et al.* [27], Rubinow *et al.* [28] and others have been unable to confirm these findings.

One possibility we have considered is that the amount of progesterone metabolites may be more important than the amount of progesterone itself. Several metabolites of progesterone are known to be powerful anesthetics [29] and we have shown that the pregnanediones affect motor activity in rats [30]. When two isomers of pregnanedione (5α and 5β-pregnanedione) were given to ovariectomized rats in low doses over several weeks, changes in motor activity

Table 1. Steroids in serum

	n	5α-DHP	3α5β-THP	Progesterone
Control Follicular	3	99 ± 67	24 ± 2	154 ± 20
Control Luteal	5	631 ± 190	981 ± 236	6237 ± 538
PMS Luteal	4	525 ± 207	505 ± 215	4219 ± 1377

5α-DHP = 5α-dihydroprogesterone; 3α,5β-THP = 3α,5β-tetrahydroprogesterone. Mean ± SE pg/ml.

occurred. Since both compounds are powerful anesthetics in pharmacological doses we expected that both would decrease motor activity. However while the 5β isomer behaved as expected, the 5α isomer *increased* motor activity. We have measured some of these metabolites, which are difficult to assay, using a combination of high performance liquid chromatography and radioimmunoassay (Table 1), but have not yet established significant differences between patients with and without PMS (Murphy *et al.* in preparation).

Hammarback *et al.* [31] have shown that giving estrogens plus progestin to menopausal women could reproduce the symptoms of PMS. No symptoms occurred if no progestin was given. Estrogens act by increasing the bioavailability of norepinephrine in the CNS, and induce changes in dopaminergic, noradrenergic and serotonergic receptors. What differences arise by adding progestin are not known. Hammarback *et al.* in 1989 [32] postulated that the ratio of estrogen to progesterone is of importance so that relative estrogen excess might be more important than progesterone deficiency. Estrogens in the absence of progestin have been considered to have a beneficial effect on mood; however the results of administering estrogens in mood disorders have had mixed

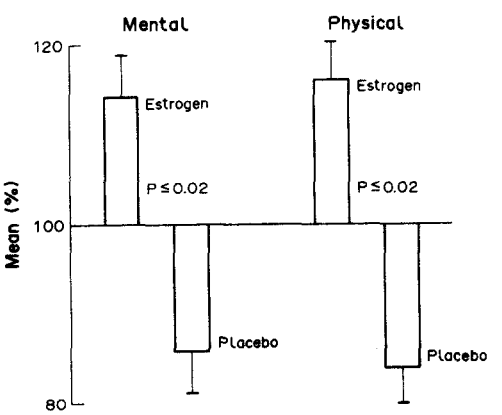

Fig. 3. Mean values (±SD) for mental and physical symptoms in 11 patients with PMS on placebo or Premarin. (Data from Ref. [3].)

results [33–37]. Oral contraceptives may induce PMS or make it better or worse [38–41] but unfortunately no good analysis of just which do what has appeared.

Because of anecdotal evidence that taking Premarin (a mixture of conjugated equine estrogens) during the luteal phase of the cycle improved PMS, we undertook a double blind, placebo-controlled crossover trial in patients with PMS [3]. Eleven subjects completed at least two cycles on Premarin and two cycles on placebo. The results are shown in Fig. 3. The symptoms were actually increased during the cycles on Premarin compared to those on placebo. Thus it would appear from these observations that estrogen makes PMS worse, supporting the theory of estrogen excess.

A recent paper by Messinis and Lolis [42], who gave the estrogen antagonist tamoxifen to subjects complaining particularly of premenstrual mastalgia, found in a double blind trial that tamoxifen decreased the breast symptoms but they did not study mood changes.

Although hyperprolactinemia has been postulated as a cause of PMS, no clear difference in prolactin levels between control and PMS subjects has been demonstrated. However bromocriptine has been shown to relieve the mastalgia [43, 44].

While hypoglycemic-like attacks may occur during PMS, these have been shown to be unrelated to true hypoglycemia or any abnormality in insulin or glucose metabolism [45].

Nutritional deficiencies of various kinds have been considered as possible causes of PMS [46]. Claims of success have been made for vitamin B6 (pyridoxine) [47], α-tocopherol [48], and prostaglandin synthesis precursors (linoleic acid and γ-linolenic acid, contained in evening primrose oil, Efamol) [49], but so far the efficacy of any of these has not been confirmed in a double blind trial. Recently, in fact, a double blind trial of evening primrose oil [50] indicated that the effects were due entirely to placebo.

Antibiotic therapy, on the basis that PMS might be caused by low-grade pelvic infection, has also been tried with claims of good results [51] but again the evidence is only anecdotal.

Various kinds of antidepressant and anxiolytic agents have been used, the most effective of which is alprazolam [52], which significantly improved symptoms in a double blind trial, although it did not afford complete relief. Lithium carbonate was tried but not recommended [53].

Light therapy has been used to treat men and women with seasonal affective disorder, a condition in which depression occurs only seasonally, usually in the winter. Treatment with bright light in the evening for 2 h has also been used in PMS with claims of some success [54].

Spironolactone [55] has been shown in a double blind placebo-controlled trial to relieve bloating but not other symptoms of PMS.

Abnormalities of thyroid function have been suggested as a cause of PMS [56]; but have not been confirmed by further studies [57].

Danazol, a gonadotrophin inhibitor which also has some effects at receptor levels, has been used with limited success [58, 59] but has some disagreeable side effects.

The one treatment which appears to be unequivocally effective in preventing PMS is to eliminate menstrual periods altogether. Frank [1] treated his patients successfully with ovarian x-radiation, a treatment we would not consider today; surgical and medical [60] oophorectomy are also successful but involve the long-term effects of castration, sterility and osteoporosis, which make them far from ideal.

It is only in the past ten to twenty years that PMS has been taken seriously, largely through the efforts of Katherina Dalton in England [8, 61]. She has provided evidence that PMS may lead to criminal acts. Thus a diagnosis of PMS has been used successfully as a defence for assault and even murder in France and the U.K. It is now being brought up as a defence in North America and may thus be important from a legal point of view in the future.

One cannot help feeling that there must be a more satisfactory way of dealing with PMS than any of those outlined here. When more is understood about the mechanism involved, a better treatment will surely be forthcoming. Is underlying chronic stress a factor which alters the hormonal environment in such a way as to affect the brain? Many of the women with PMS seem to have a difficult environmental situation to deal with. Are they able to cope until they become more vulnerable premenstrually?

At present an explanation of the hormonal changes involved in the menstrual cycle, emphasis on a healthy lifestyle with moderate exercise and a nutritious diet, and plenty of emotional support are the first steps to take in treatment; sometimes they are all that is required. Except in extreme cases, where temporary termination of menses is desirable, any further treatment should be one which has been validated by double blind, placebo-controlled clinical trial.

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