Family Practice Grand Rounds

Premenstrual Syndrome

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DR. JAMES DUNLAY *(Second-year resident in Family Practice)*: The topic for today's Family Practice Grand Rounds is premenstrual syndrome, also known as PMS. PMS is an important topic for family physicians for several reasons. Because PMS is a source of significant morbidity in a large number of women, it is a disorder that family physicians will encounter frequently. In addition, because PMS is a relatively newly recognized syndrome, many physicians have not had formal training in its diagnosis or treatment. The objective of this Family Practice Grand Rounds is to make family physicians aware of the existence of PMS and its implications. PMS is an illness with prominent physical and behavioral symptoms, and as such is especially well suited for treatment by family physicians. We will begin by interviewing Mrs. Black, a patient with PMS.

Mrs. Black, could you describe your major premenstrual symptoms?

MRS. BLACK: My major premenstrual symptom is migraine headaches. The headaches consist of a severe throbbing sensation on one side of my head and are often accompanied by vomiting. They are so severe that I usually have to interrupt what I'm doing and lie down in a dark, quiet room. The headaches occur only during the one to three days preceding my period and go away once my period starts.

DR. DUNLAY: Do you have any other symptoms during this time?

MRS. BLACK: Yes. My breasts get tender and I feel bloated, although I'm not sure whether I actually gain any weight. I'm also very susceptible to mood swings and become extremely irritable. I notice a craving for salty foods, something that I don't have at other times during my cycle. It's also difficult for me to sleep, especially the night immediately preceding the start of my period. I wake up feeling very tense for no apparent reason. Sometimes I feel like I need to scream.

DR. DUNLAY: Could you tell us how you found out that you had PMS?

MRS. BLACK: I had seen physicians for several years for these complaints, especially the migraine headaches, without a diagnosis of PMS being made and without adequate therapy. Then, about six months ago, a friend saw a segment about PMS on the *Today Show* and mentioned it to me. I started to read about it and realized that I had it. Even with this information, I went to three doctors before I finally found one who confirmed the diagnosis of PMS and agreed to treat it.

DR. DUNLAY: What treatments were used?

MRS. BLACK: When I first discovered that I had PMS, I tried vitamin B_6 on my own without success. I was later given diuretics without effect. I am currently going to a biofeedback class and learning to relax my muscles during a headache, and this has helped a lot. However, I'm still bothered by fluid retention, appetite changes, and especially the feelings of extreme tension.

DR. JOHN O'BRIEN *(Instructor, Department of Family Practice)*: Have the more traditional therapies for migraine, such as ergotamine and propranolol, been prescribed for you?

MRS. BLACK: Yes, I've tried various analgesics, Cafergot, and propranolol without significant relief.

DR. DUNLAY: What about progesterone suppositories?

MRS. BLACK: I haven't used them yet, although I'm told that they're the next step if the current therapy doesn't work.

DR. THOMAS HUPPE *(First-year resident in*

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Family Practice): Do you have any children?

MRS. BLACK: Yes, two.

DR. HUPPE: Did you continue to have premenstrual symptoms during your pregnancies?

MRS. BLACK: I had mild symptoms during the first couple of months at about the time my period would have occurred, but no symptoms during the last six or seven months and none until my periods started again after my children were born.

LINDA WARREN *(Registered Nurse, Department of Family Practice)*: I'm sure this illness has affected your family a great deal. Could you tell us about that?

MRS. BLACK: It certainly has. During the days preceding my period my symptoms, especially the headaches, get so severe that my husband often has to take over caring for our two children and taking care of the house. Our children don't understand why mommy gets sick for a few days each month, and I'm sure this is hard on them. I also have a demanding job, and I often have to miss work for a few days before my period begins. This causes obvious professional difficulties, and I have to try to schedule my work so that I don't have any important deadlines during my premenstrual phase. Because this isn't always possible, I sometimes have to give up attractive projects. I can only guess at the effect PMS has had on my career, but I think that it's been a significant hindrance.

DR. DUNLAY: Thank you very much, Mrs. Black. As we will see, Mrs. Black's case illustrates several common features of PMS.

Premenstrual syndrome is best defined as any combination of emotional or physical symptoms that occur cyclically in a woman before menstruation and that regress or disappear during menstruation.[1] PMS includes symptoms that occur exclusively in the premenstruum, such as Mrs. Black's headaches, and symptoms that occur throughout the cycle and are exacerbated during the premenstruum.

DR. SARAH FOX *(Instructor, Department of Family Practice)*: What time frame are you referring to when you say "premenstruum"?

DR. DUNLAY: Although a few women experience symptoms from ovulation to the time of menstruation, most women have their most severe symptoms in the two to five days immediately preceding their period. The onset of menstruation rapidly relieves the symptoms in most women, but

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1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
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BRIEF SUMMARY
PROCARDIA®(nifedipine) CAPSULES For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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in some women these symptoms persist for the first day or two of the period.[2]

DR. SHIRLEY McCORMICK *(Instructor, Department of Family Practice)*: Does PMS include dysmenorrhea?

DR. DUNLAY: No, it does not. Dysmenorrhea is a separate disorder. Some women with PMS also have dysmenorrhea but some do not.

The most common premenstrual symptoms are headache, breast swelling and tenderness, abdominal bloating, edema of the extremities, fatigue, mood changes including depression and irritability, increased appetite with a craving for sweet or salty foods, and acneiform skin eruptions.[3] As you can see, Mrs. Black had several of these symptoms. Other more unusual symptoms include constipation, backache, premenstrual epilepsy, and premenstrual asthmatic attacks.[4]

It is important to realize that PMS represents a broad spectrum of morbidity. At one end of this spectrum is the large group of women with mild symptoms. Surveys have shown that 80 to 95 percent of women have at least one premenstrual symptom. At the other end of the spectrum is a smaller number of women, such as Mrs. Black, who experience severe, debilitating symptoms. It is estimated that 10 to 40 percent of women have symptoms during the premenstruum that are severe enough to disrupt their lifestyle.[3]

DR. FOX: Are certain women at particular risk for developing PMS?

DR. DUNLAY: Although the epidemiology of PMS is not well documented, there is some suggestion that the incidence of PMS increases with age[5] and parity. As expected, PMS does not occur in postmenopausal women and usually does not occur during pregnancy.

DR. MARGARET DAVIES *(Assistant Professor, Department of Family Practice)*: Could you talk about the relationship between premenstrual syndrome and what used to be called premenstrual tension?

DR. DUNLAY: Premenstrual tension was the term applied to the mood changes women sometimes experienced before menstruation. Premenstrual tension was considered to be a psychiatric disorder, and women who complained of mood changes were often labeled as having neurotic personalities. However, studies have not shown any greater degree of psychopathology in women with premenstrual mood changes than in women without them.[5,6] Many authors now recommend that the term *premenstrual tension* be dropped and that these mood changes be included in the broad term *premenstrual syndrome*.

The diagnosis of premenstrual syndrome is made by history alone, focusing on the cyclic nature of the symptoms. No objective laboratory tests are helpful. The family physician has to be an astute diagnostician because many women will not relate their symptoms to their periods. PMS should be placed in the differential diagnosis of any female patient who presents with intermittent symptoms, especially headache, abdominal pain or bloating, and depression, anxiety or other psychiatric symptoms. A health diary, which the patient uses to record the occurrence of her symptoms and her periods, can be extremely useful in making the diagnosis of PMS and in monitoring the effectiveness of therapy. While such a method can be used to document the existence of PMS, much more needs to be learned about its etiology and treatment.

The cause of PMS is unknown. One theory, especially popular in Britain, is that PMS is caused by a deficiency of progesterone.[2] This theory developed because the symptoms of PMS occur during the time in the menstrual cycle when involution of the corpus luteum causes the levels of progesterone to fall. However, studies have failed to show a consistent difference in the levels of progesterone between women with PMS and women without PMS who are used as controls.[7] Thus, the progesterone theory remains unproven. Other theories suggest that PMS is the result of estrogen excess, vitamin B_6 deficiency, hypoglycemia,[3] prolactin excess,[8] fluid retention, or a disorder of the neurotransmitters in the central nervous system, such as the β-endorphins and α-melanocyte-stimulating hormone.[3] Again, none of these factors has been established as the cause of PMS.

As for most illnesses of unknown etiology, the therapy for PMS is empiric. While all of the proposed treatments have worked in some women, none has been proved consistently effective in placebo-controlled, double-blind studies. The family physician must be cautious when recommending any treatment because of the potentially serious side effects. Because the use of nonphar-

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macologic and vitamin therapies minimizes possible complications, they are especially attractive as first-line therapy for PMS.

There are many nonpharmacologic therapies recommended for use in PMS. Simply explaining the diagnosis of PMS to the patient and her family can be considered a form of nonpharmacologic therapy. Knowing that she suffers from an identifiable illness can be helpful to the woman who has been told repeatedly that her problems are "all in her head." Armed with this knowledge, the woman can try to minimize stress during the premenstruum. It is important to realize that this lifestyle change is often impractical, however, and further treatment will be required. General health measures such as increased exercise, reduction of alcohol and smoking, loss of excess weight, and regular meals with less refined sugar have been proposed to help alleviate premenstrual symptoms.[4] As in Mrs. Black's case, biofeedback and relaxation techniques can be used for premenstrual headaches, tension, and irritability. There is little objective evidence in the literature to support the use of these nonpharmacologic therapies. Many physicians who treat PMS, however, have had success using them. Some of these therapies, such as biofeedback, may work by providing symptomatic relief, while others, such as dietary change or exercise, may work by changing the body's metabolism. One of the research priorities in the field of PMS should be the objective measurement of the effectiveness of these nonpharmacologic therapies and the explanation of their mechanism of action. Until then they should be considered a safe, but only possibly effective, therapy for PMS.

Vitamin B_6 has been used to treat PMS based on the theory that supplemental doses of this vitamin relieve PMS either by altering estrogen and progesterone production or by changing the levels of dopamine and seratonin in the central nervous system.[3] A daily dose of 50 to 200 mg is often recommended and is safe and nontoxic. Because the role of vitamin B_6 deficiency in PMS is unproven, many experts contend that any improvement seen during vitamin B_6 therapy is actually due to a placebo effect. Despite this criticism, vitamin B_6 remains a popular and sometimes effective therapy.[9]

Progesterone therapy for PMS is popular in Great Britain and has been used recently in the United States. The proponents of progesterone therapy argue that supplemental progesterone corrects the underlying pathophysiology of PMS and therefore will result in the relief of all symptoms of PMS.[2] This is in contrast to agents that treat individual symptoms, such as diuretics for fluid retention.

Because naturally occurring progesterone is not absorbed orally, it must be given intramuscularly or by rectal or vaginal suppository. The recommended starting dose is 400 mg each day by rectal suppository from day 14 to day 28 of the menstrual cycle.[2] The long-term side effects of this therapy are unknown. A small group of women on progesterone therapy has been followed in Britain for 10 to 20 years. These women have shown a slight decrease in glucose tolerance but have exhibited no other adverse side effects.[2] Although many physicians support the use of progesterone suppositories, double-blind, placebo-controlled studies have not shown that progesterone is consistently effective in the treatment of PMS.[7] Progesterone has not been approved by the Food and Drug Administration for the treatment of PMS and any use of progesterone for PMS should be considered experimental.

DR. JENNIFER FRANK *(Instructor, Department of Family Practice)*: What about the synthetic oral progesterones, such as Provera?

DR. DUNLAY: The use of the synthetic progesterones, called progestins, is controversial in the treatment of PMS. Proponents of natural progesterone therapy maintain that the synthetic progestins do not alleviate PMS and often worsen it.[2] They attribute this to the chemical differences between the synthetic progestins and natural progesterone, which result in different physiologic effects. For example, natural progesterone causes a decrease in sodium and total body water, while synthetic progestins lead to fluid retention.[2] On the other hand, some studies have found synthetic progestins, such as dydrogesterone, to be helpful in alleviating premenstrual symptoms.[10] The synthetic progestins should also be used with caution, and the patient should be informed of the experimental nature of this therapy.

DR. CAROLE TSOU *(Second-year resident in Family Practice)*: What about oral contraceptives?

DR. DUNLAY: These are generally not recommended. Because oral contraceptives contain synthetic progestins rather than natural progester-

one, the arguments against the synthetic progestins apply to oral contraceptives. In addition, many of the side effects of the pill, such as headache and fluid retention, are similar to the symptoms of PMS and therefore can result in a worsening of symptoms.[2,3]

Two other medications used to treat PMS are bromocriptine and spironolactone. Bromocriptine, a prolactin antagonist, is given orally in a dose of 2.5 mg twice a day from day 14 to the onset of menses. It is especially effective for the relief of breast symptoms in PMS.[8] Spironolactone, a diuretic, is given in a dose of 25 mg twice to four times a day and is especially useful for the relief of symptoms due to fluid retention, such as edema of the extremities and abdominal bloating.[11,12] In addition to providing relief for these specific symptoms, both medications are sometimes effective in relieving other manifestations of PMS as well.

DR. JAMES PEGGS *(Assistant Professor, Department of Family Practice)*: Can you give us some idea of a "flow chart" for the treatment of PMS? In other words, in what order should these therapies be used?

DR. DUNLAY: Most experts start with nonpharmacologic therapies or vitamin B_6 or both to avoid the possible side effects of the drug therapies. If these are not effective after two to three months, many will begin administering progesterone suppositories or the synthetic progestins. Spironolactone and bromocriptine can be used instead of or in addition to progesterone, especially if more specific relief of fluid retention or breast symptoms is desired.

As you can see from the issues we've covered, it is impossible to present the final word on PMS. However, there are several key points the family physician can be aware of in practice. First, PMS is a cyclic disorder that includes psychological as well physical symptoms. Second, PMS represents a spectrum of morbidity that ranges from mild to disabling. Third, the diagnosis of PMS can be difficult in women who have intermittent symptoms that they do not relate to their periods. In this situation a health diary is especially useful to establish the diagnosis of PMS and to evaluate treatment. Fourth, nonpharmacologic therapies, such as insight into illness, general health measures, relaxation techniques, biofeedback, and vitamin B_6, may be helpful in alleviating some of the symptoms of PMS. Finally, the use of drug therapy for PMS, especially progesterone and the synthetic progestins, is still an area of controversy. Bromocriptine and spironolactone seem to be especially useful in relieving breast soreness and fluid retention, respectively. The patient needs to be informed of the potential side effects of drug therapy as well as its unproven efficacy, however.

In conclusion, although some authors still question whether the current evidence supports the designation of PMS as a separate disease entity,[13] the view that PMS is a definable syndrome with both physical and psychological symptoms is becoming increasingly popular in the medical literature. PMS is a disease that can readily be managed by the family physician, with gynecologic consultation as necessary. As for any chronic illness in which therapy is symptomatic rather than curative, the importance of knowing the patient, her family, and her social environment cannot be overemphasized. By using these factors to individualize therapy while maintaining an open dialogue with the patient about what we know and don't know about PMS, the family physician can successfully manage this difficult problem.

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