

2006 CE Series — Lesson Two

An Overview of The Premenstrual Syndrome

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Goals and Objectives

Goals: To provide the pharmacist with information regarding the definition, etiology, symptoms, and treatment of the premenstrual syndrome.

Objectives: After completing this article, the pharmacist should be able to:

1. Define the premenstrual syndrome and its cyclic relationships.
2. List the major symptoms associated with the premenstrual syndrome.
3. Discuss the postulated etiologies associated with premenstrual syndrome.
4. Describe the patient assessment techniques associated with PMS.
5. Discuss the various treatments for PMS.

Premenstrual syndrome or PMS is a diagnosis that, depending on the population studied, may affect as many as half the women in some form. There are many descriptions of the relationships between the phase of the menstrual cycle and mood and behavior disorders dating back to the time of Hippocrates. During the 1800's in the United States, women in middle and upper socioeconomic classes were expected to be genteel. It was considered both stylish and intelligent to retire to bed with unmentionable female problems. In general, women were considered sicker than men and this sickness was related to their sexual organs.

Early in the 1900s, many of these problems became associated with the female psyche as the role of psychiatry expanded. As laboratory techniques improved, there was a slow merging between alterations in hormones and other physiologic parameters and the psychological components encountered throughout the menstrual cycle.

Today, PMS is recognized as a disease characterized by the cyclic recurrence of certain physical, psychological and/or behavioral symptoms usually beginning during the two weeks before menses and disappearing within a few days of onset of menses.

The Menstrual Cycle

The menstrual cycle is a complex and rapidly changing series of biological events that involve the CNS and reproductive organs and results in regulating many of the physiologic and social aspects of a woman's life.

The menstrual cycle is composed of three stages known as the menstrual, proliferative and secretory phases. The proliferative and secretory phases are separated by ovulation.

The menstrual phase begins with the onset of menses and usually lasts about 5 days. During this phase estrogen and progesterone levels are low and sloughing of the endometrial tissue from the uterus occurs.

The proliferative phase follows the menstrual phase and has increased estrogen and a thickening of the endometrium. This prepares the uterus for implantation of a fertilized ovum. There are

changes in the ovary and the initial low levels of estrogen stimulate the production of follicle stimulating hormone. This causes maturation of follicles containing ova in the ovaries. As these changes occur, the anterior pituitary gradually secretes luteinizing hormone which stimulates follicular cells to synthesize estrogen. These processes lead to ovulation.

The secretory phase of the menstrual cycle begins with ovulation and is characterized by the formation of the corpus luteum. This leads to increased synthesis of estrogen and significant amounts of progesterone and alterations in the endometrium. These changes result in an environment that supports zygote implantation. If the ovum is not fertilized, the corpus luteum degenerates and there is a decrease in estrogen and progesterone concentrations. This leads to a decrease in nutrient delivery to endometrial tissue which results in sloughing and entry into the menstrual phase.

Another approach to reviewing the menstrual cycle is as follows. The menstrual cycle can be conveniently separated into two distinct phases: the follicular phase and the luteal phase. The follicular phase begins at the onset of menses and is associated with a rise in estrogen levels under the influence of follicle stimulating hormones. During the follicular phase, progesterone plasma levels are low in relation to estrogen levels. At approximately day 14 of the menstrual cycle, luteinizing hormone peaks in concurrence with a sharp drop in estrogen levels and ovulation occurs.

The luteal phase is heralded by the occurrence of ovulation and is associated with rising levels of progesterone under the influence of luteinizing hormone. During the luteal phase, estrogen levels are low in relation to progesterone, although there is a minor peak of estrogen during this phase between days 18 and 22. This rise in estrogen is not nearly of the magnitude of elevation seen in the follicular phase of the cycle. At approximately day 28 of the menstrual cycle, progesterone and estrogen levels decline sharply. This event marks the onset of menses. Premenstrual syndrome is associated with the luteal phase of the menstrual cycle where progesterone levels are normally high and estrogen levels are low in relation to progesterone. It is during this phase of the cycle that the symptomatology of premenstrual syndrome occurs.

Epidemiology

The exact incidence of PMS is unclear. Many of the symptoms associated with PMS have been known from the time of Hippocrates, so the broad definition used today also affects estimates of incidence. However, women with a 28 day cycle usually do not have symptoms for the first 18 to 21 days of the cycle. Then, there is an increase in symptoms during the week before the onset of menses and a rapid decline in symptoms during the first 4 days after the onset of menses.

Investigations indicate that virtually all women who menstruate have some symptoms associated with PMS. However, when very strict definitions for PMS are used, the incidence of PMS may be as low as five percent. It is estimated that between 20 and 50 percent of women of reproductive age have recurrent symptoms that often alter lifestyle.

The onset of PMS is insidious. However, women in their middle to late twenties usually realize a need to seek medical attention. Symptoms often begin to disappear in women in their early forties. Factors which appear to be associated with PMS include multiparity, a history of preeclampsia, alcohol abuse, drug abuse, and affective disorders. However, several of these problems produce symptoms related to PMS.

PMS has become more clearly defined and recognized in the last two decades. Today, women often experience their first menstrual periods at age 11 or 12 and reach menopause in their early fifties, while in the early 1900's menarche was uncommon before 14 and menopause occurred

between ages 35 and 40. In addition, there are fewer pregnancies today than during the early 1900's. Consequently, menstrual disorders are more prevalent and of more concern than during the previous generation.

Etiology of PMS

There have been a variety of theories regarding the exact etiology of premenstrual syndrome. Hormonal imbalance is a primary theory associated with PMS. This may be a reduction in progesterone in the luteal phase of the cycle. Another theory supporting a hormonal imbalance supports an increase in estrogen which causes an imbalance between the estrogen and progesterone levels. This results in a reduction of progesterone level in relationship to other ovarian hormones. Therefore, it is a relationship between estrogen and progesterone which is significant in the occurrence of PMS. Investigations conducted in patients with PMS have provided variable results, when attempting to correlate the occurrence of symptoms with measured levels of these hormones. There are, however, physiological effects associated with estrogen excess and progesterone deficiency which are similar to those occurring with PMS.

PMS has been associated with vitamin B-6 or pyridoxine deficiency. Vitamin B-6 is involved in the hepatic metabolism and clearance of estrogens as well as being a necessary coenzyme in the biosynthesis of tryptophan and serotonin. Diminished serotonin synthesis has been implicated in depression, while a reduction in the metabolism of estrogen would result in an abnormal hormonal balance precipitated by excess estrogen.

Prolactin levels fluctuate throughout the menstrual cycle with peaks occurring at ovulation and during the luteal phase. Prolactin is also known to produce behavioral changes in animals. Therefore, it is possible that altered effects of prolactin may influence the occurrence of PMS.

Endorphins are endogenous opiate peptides which have a wide variety of physiological effects. When normal amounts of endorphins are altered, some of the physiological effects encountered with premenstrual syndrome occur. Changes in the amounts of endorphins appear similar to the cyclic changes associated with PMS.

Since there are similarities between individuals with thyroid dysfunction and those with PMS, thyroid hormone has been suggested as a possible cause of PMS. In some investigations, women with PMS have demonstrated alterations in the thyroid hormone processes. There are also similarities between certain symptoms associated with PMS and alterations in insulin and glucose metabolism. During phases of the menstrual cycle, glucose handling will differ. However, there is not clear evidence that women with PMS have hypoglycemia.

Neurotransmitters, such as serotonin, may have an effect on the occurrence of PMS. Since serotonin is associated with mood disorders, it is possible that changes in levels of it or other neurotransmitters may result in altered mood. Women with PMS have been shown to utilize serotonin somewhat differently than normal.

Since there are a wide variety of factors associated with PMS, all theories regarding a definite etiology are easily challenged. In addition to the physiological factors related to PMS, there are psychological factors, such as stress, the patient's attitude toward menstruation, and the response of family and friends to the effects of PMS.

Major Symptoms of PMS

There are many varied symptoms associated with premenstrual syndrome. Therefore, the symptoms are frequently divided into three categories. These are physical, psychological and motor symptoms.

The largest category consists of those which are physical and includes breast pain, abdominal bloating, headache, and backache as commonly occurring, while palpitations, chest pain, and shortness of breath are among those occurring less frequently.

Psychological symptoms are the next largest category. Tension, depression, anxiety and irritability are the common symptoms in this group, while aggressive behavior and hostility occur less frequently.

Motor symptoms occur much less frequently and are often recognized when the patient is questioned about events which occurred during their pre-menstrual phase. These symptoms are quite variable and include changes in coordination and an increased incidence of accidents during the daily routine.

Although there are a wide variety of symptoms listed as associated with pre-menstrual syndrome, one evaluation indicated that more than ten percent of the women with premenstrual syndrome questioned experienced more than ten of these symptoms each month.

Clinical Evaluation of PMS

A patient history is the initial process in establishing a diagnosis of PMS. The patient completes a questionnaire or self-rating scale which assesses the alterations that occur during the menstrual cycle. The questionnaire retrospectively reviews the week after and the week before the most recent menstrual period and is appropriately scored to determine whether the patient has symptoms related to PMS. If the ratings are sufficiently high to indicate the possible occurrence of PMS, the patient is told to complete a diary which is provided with a list of instructions. The diary is completed daily at bedtime for at least one and, if possible, two menstrual cycles. A similar process is used in which parameters are employed to evaluate the specific patient problems during the menstrual cycle.

In addition, a careful patient history is required to differentiate between gynecological and psychiatric disorders. Therefore, it is important to document the cyclicity of the symptoms and the types and severity of the psychological effects.

The clinical examination by the physician is important to determine the presence or absence of a medical or gynecological disease. In addition, it relieves the patient's anxiety and provides an opportunity to reassure the patient regarding her overall health and educate her regarding the symptoms of PMS.

General Treatment

Like the etiology, the treatment of PMS cannot be clearly defined. Treatment should begin with patient counseling and good nutrition. Then, the use of specific drugs to treat symptoms can be employed.

Patient counseling is an essential component of any treatment regimen. It is important that patients understand both the physiological and psychological components of PMS. This improved understanding assists the patient in recognizing the multiple symptoms and cyclic nature of the disorder.

Alteration of the patient's diet is the least invasive approach to alleviating the symptoms of PMS. A number of dietary alterations have produced various results in reducing the symptoms associated with PMS. These included decreasing or eliminating alcohol, tobacco and methylxanthine containing foods (i.e., coffee, tea, chocolate, soft drinks with caffeine). Dietary sodium should be restricted, refined sugars should be minimized and replaced with complex carbohydrates, green leafy vegetables should be increased, and fat intake should be reduced.

Moderate exercise, such as bicycling, may be beneficial in reducing fluid retention and some symptoms associated with PMS. The development of good sleep habits may be useful as some women with PMS have sleeping problems that further complicate the disorder. The use of stress reduction techniques, such as body massages, may be helpful in relieving some symptoms of PMS.

Drug Therapy

Since PMS is a complex disease with a wide variety of symptoms, appropriate drug therapy is difficult to initiate and assess. In most instances, drugs should be used to reduce specific symptoms rather than using many drugs that may be useful for a variety of potential symptoms. Frequently, drug therapy is initiated with multiple vitamins; then an assessment of which single agents should be used is made. Once a therapeutic program is employed, it should be maintained for at least two months. The complex cyclical nature associated with premenstrual syndrome requires that each therapeutic regimen have the opportunity to be used for a sufficient time to be evaluated.

Multiple vitamin and mineral supplements have been used with variable results, but have been very useful in some patients. Pyridoxine (vitamin B-6) is one of the most frequently used drugs in the treatment of PMS. Pyridoxine is often used in large doses and is usually well tolerated. Results with pyridoxine therapy have been variable. Vitamin E and vitamin A have been used to treat PMS. Each vitamin relieved some symptoms in some patients.

Progesterone or medroxyprogesterone has been used to treat PMS. It is postulated that women with PMS have reduced progesterone during the luteal phase of the menstrual cycle. Progesterone rectal and parenteral dosage formulations have been utilized, but their absorption and/or acceptability has been undesirable in many instances. Oral micronized progesterone is used more often to treat PMS.

It decreases stress, anxiety, edema, depression, and hot flashes in some women with PMS. However, progesterone has not been consistently successful, is relatively expensive, and may induce symptoms associated with PMS. Oral contraceptives and estrogen preparations have also been used to treat PMS. As with other therapies, some symptoms have been relieved in some patients.

Tamoxifen is an oral nonsteroidal antiestrogen that acts by competing for estrogen binding sites on receptors in target organs such as the breast. Tamoxifen was useful in treating women who complained of premenstrual mastalgia (breast pain).

Danazol is a synthetic androgen used to suppress the hypothalamic-pituitary-ovarian axis by inhibiting the release of specific gonadotropins. Danazol is used to treat endometriosis and should not be used in pregnant women. Danazol has been used to treat PMS and appears to relieve breast pain. Other symptoms of PMS were not affected. Danazol produced multiple adverse effects and is expensive.

Bromocriptine is an ergot derivative and dopamine receptor agonist which is highly effective in decreasing plasma prolactin concentration. Bromocriptine appears to be beneficial in treating the breast symptoms associated with PMS, but does have adverse effects.

Diuretics are often employed for relief of bloating and edema, but should be used only if diet and exercise are not beneficial. Spironolactone has been used for severe bloating and edema.

Nonsteroidal anti-inflammatory drugs, such as ibuprofen and mefenamic acid, have been used in treating pain and headache. These prostaglandin inhibitors vary in their usefulness in treating PMS.

Alprazolam, fluoxetine and naltrexone have been used to treat irritability, depression, fatigue, anxiety, headache, cramps, and bloating in women with PMS. For example, alprazolam is used from day 20 through day two (based on a 28 day cycle with one being the onset of menses) while naltrexone was used from day nine through day 18. These treatment programs were successful. However, there are adverse effects associated with these drugs (i.e., drowsiness, tolerance/dependence, sedation, unsafe during pregnancy) and further evaluation is needed to determine their role in treating PMS.

The drugs used to treat PMS represent a wide variety from different pharmacologic families. Some therapies have been useful in relieving some symptoms associated with PMS. However, there are no specific treatments for PMS.

Summary

PMS has received increased amounts of attention and interest during recent years. Since there are a variety of symptoms, exact treatment regimens are difficult to develop. Patient counseling is an important component of the treatment program. The pharmacist can provide an important role in the treatment processes associated with PMS.

Bibliography

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Table 1
Major Drugs Used in PMS

GENERIC NAME	EXAMPLE OF BRAND NAME
Alprazolam	Xanax
Bromocriptine	Parlodel
Danazol	Danocrine
Fluoxetine	Prozac
Ibuprofen	Motrin
Medroxyprogesterone	Medrol
Mefenamic Acid	Ponstel
Naltrexone	Trexan
Progesterone	Marketed generically
Pyrodoxine	Marketed generically
Spironolactone	Aldactone
Tamoxifen	Nolvadex

Table 2
Common Symptoms Associated with PMS

SOMATIC Breast tenderness

Bloating
Edema of the ankles
Headache
Fatigue
Acne

EMOTIONAL

Anxiety
Depression
Anger
Desire for Solitude
Irritability
Aggressiveness
General loss of control