

PMS: FROM PUBERTY TO MENOPAUSE

Premenstrual syndrome (PMS) is a monthly condition that afflicts women of all ages, ranging from young girls (sometimes even before menses) to women approaching menopause.

There is always a new generation experiencing the monthly puzzle of PMS-related symptoms for the first time. Previous generations struggle with changing symptoms as their reproductive systems evolve with their life stages.

For example, mothers and their adolescent daughters—both possibly subject to monthly mood swings and irritability, although perhaps for different reasons—may even end up on the same cycle, which can cause considerable hardship for everyone in the household.

Young and old alike, women (and their loved ones) are frequently befuddled by the varied and changing monthly symptoms, and often confused about where to go for help. They seek explanations and guidance from any source that will take their concerns seriously. Yet, even now, there are more questions than answers regarding PMS.

As the *Women's Health Connections* logo suggests, we are dedicated to helping women solve the monthly puzzle of PMS, so that women of any age can minimize their symptoms and the debilitating

effects those symptoms may have on their daily lives.

What are the Symptoms?

The symptoms of PMS are varied, with over 150 identified. It is not unusual to find that, within any set of women, no two women share the exact same set of symptoms; and, furthermore, that their symptoms may change over time. It is also true that PMS symptoms are not specific to PMS; most are also associated with other conditions.

However, the symptoms truly related to PMS typically occur after ovulation, during the luteal phase of the menstrual cycle (beginning approximately 14 days before menstruation), and cease at menstruation or shortly thereafter.

While a wide range of PMS symptoms are reported, the most common ones cluster as follows:

- **Physical symptoms:** headaches, acne, breast tenderness, weight gain, appetite changes, fatigue, dizziness, hot flashes, nausea, vomiting, muscle aches, abdominal bloating, pelvic pressure, constipation, palpitations and changes in vision.
- **Mood-related symptoms:** depression, sadness, irritability, tension, anxiety, tearfulness, restlessness, anger,

loneliness, food cravings and change in libido.

- **Cognitive symptoms:** mood swings, difficulty concentrating, decreased efficiency, confusion, forgetfulness, being accident-prone, social avoidance and angry outbursts.

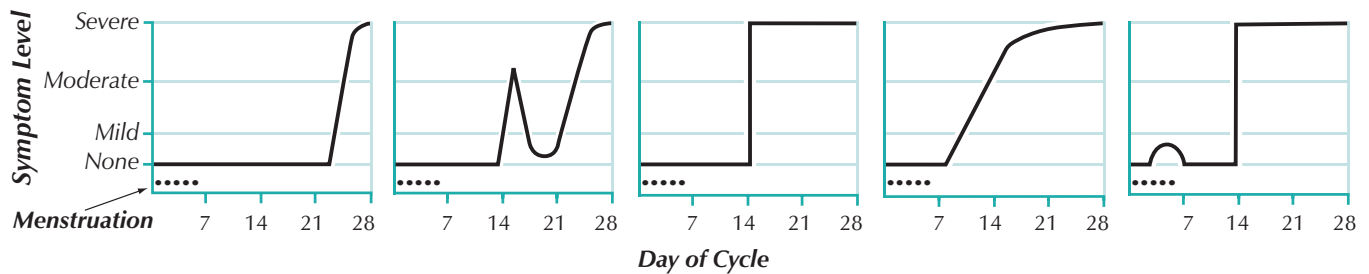
In fact, practitioners find that most women's symptoms tend to fall into one of four typical sub-groups: PMT-A (anxiety), PMT-C (cravings), PMT-D (depression), or PMT-H (hyperhydration, such as bloating and weight gain).

The most consistent characteristic of PMS symptoms is that they reoccur on a regular basis, coinciding with a woman's menstrual cycle. However, while PMS symptoms tend to be cyclical in nature, even the patterns of that cycle may vary among women.

In *PMS: Solving the Puzzle*, Linaya Hahn identifies five patterns of symptoms, all occurring primarily within the luteal phase, but varying in timing and intensity (see figure on page 2). Some women experience symptoms throughout the luteal phase, some only during the few days immediately preceding menstruation, and some have more than one peak period of severe symptoms.

So, it is not only the type of symptom but also the intensity or severity that can vary dramatically

Patterns of PMS Symptoms



The timing and severity of PMS symptoms varies across women and throughout the menstrual cycle, but tends to represent one of these patterns.

from woman to woman, and even for the same woman throughout her cycle. For some women, PMS is merely an annoyance; for others, it is so severe that they cannot even get out of bed. About 5% of women suffer from Premenstrual Dysphoric Disorder (PMDD), a more severe form of PMS in which nearly totally disabling mood symptoms predominate.

What Causes PMS?

Researchers are still unraveling the cause of PMS but, because it occurs only in women who are still menstruating, most agree that hormones (particularly progesterone) play a significant role. The levels of the hormones associated with menstruation fluctuate widely during a woman's cycle.

In *Once a Month: Understanding and Treating PMS*, Dr. Dalton notes that estrogen hormone levels vary throughout the cycle, and that blood levels of progesterone are much smaller during the first half of the cycle and then suddenly rise at ovulation to levels that are far greater (see figure, page 3).

The Role of Progesterone

Our understanding of the association between progesterone and PMS has evolved, as has our

ability to measure hormone levels. Previously, many researchers and practitioners believed that it was the amount of progesterone in the blood stream that affected PMS symptoms. With more advanced analysis tools (such as radioimmunoassays), researchers discovered that PMS sufferers do not necessarily have low progesterone levels. More recent molecular biology advances have allowed researchers to dig deeper into how our body cells absorb progesterone into the nucleus of cells, leading to a greater understanding of progesterone receptors.

As it turns out, having a sufficient amount of the progesterone hormone does not guarantee that there is an adequate number of receptors, nor that those receptors are working properly. In fact, we now know that progesterone receptors do not transport progesterone molecules into the nucleus of cells if adrenaline is present, such as during times of stress or when our blood sugar level drops, times during which PMS symptoms are also exacerbated. We also know that progesterone receptors do not transport artificial progestogens (also called progestins) to the cell nucleus, which may help explain why they have not been effective in treating PMS-related symptoms.

Dr. Dalton observes that the locations of progesterone receptors are also the primary locations of the most common PMS symptoms (see figure on page 4). She thinks this is no coincidence, and that the cause of PMS may be linked to progesterone receptors. For example, Dr. Dalton notes that, in women, the largest concentration of progesterone receptors is in the limbic area of the brain, the area that controls emotions and has been identified as the center of rage and violence. Emotional outbursts, mood swings, violent urges, and uncontrolled rage are common PMS symptoms.

Other parts of the body that have concentrations of progesterone receptors include:

- the cells lining the brain, which are involved in headaches, a very common PMS symptom
- the breasts, which may explain why breast tenderness is also a common PMS symptom
- the womb, ovaries, and fallopian tubes, which obviously go through significant premenstrual changes
- the optic pathway, which may account for changes in ocular pressure during menstruation

Continued on Page 3

- the nose, nasal passages, and lungs, which may explain a tendency for premenstrual asthma, rhinitis, sinusitis, or laryngitis.

According to Dr. Dalton, “the widespread distribution of progesterone receptors in different target cells explains the numerous different symptoms of PMS.”

Neurotransmitters

Dr. Thomas Shiovitz and senior research scientist Edyta Frackiewicz, PharmD, report on a hypothesis that PMS may be related to neurotransmitter function. They contend that some women may have “an underlying neurological vulnerability to normal fluctuations” in menstrual hormones, such that their central nervous system reacts differently to those normal hormonal fluctuations, altering brain neurotransmitters, and leading to PMS symptoms.

Shiovitz and Frackiewicz found that women with PMS tend to have abnormal neurotransmitter function during the luteal phase of their menstrual cycle, particularly with respect to serotonin, a vital neurotransmitter that drops at ovulation and has been linked with depression, moodiness, irritability, anger, aggression, poor control of

impulses and increased craving for carbohydrates. Another indicator of this relationship is the observation that serotonin reuptake inhibitors (SSRIs) such as Prozac® have shown some effectiveness in reducing the symptoms of severe PMS-related mood disorders and PMDD.

Hahn states that PMS is caused by “correctable irregularities in the normal brain chemistry changes that accompany ovulation.” She notes that our bodies produce serotonin from tryptophan, an essential amino acid. (“Essential” meaning it must be replaced daily in our diet since our bodies do not produce it. Fortunately, it is available in many foods, such as turkey, milk, eggs, fish, and soybeans.)

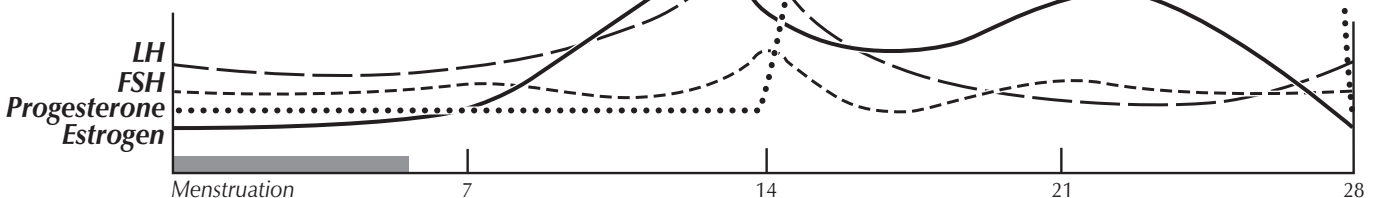
During menstruation, when serotonin levels are low, the body may trigger an insulin surge to get tryptophan to the brain. This may be noticed as a craving for sweets, pasta, bread, or alcohol, which are quickly converted to blood sugar. The presence of tryptophan generally increases serotonin levels, but there are many factors related to the efficiency of that conversion. For example, while many women crave sweets, if they choose a snack that contains aspartame (an artificial sweetener such as NutraSweet®

or Equal®), the phenylalanine in that component will compete with the tryptophan. Another factor involved is Vitamin B6, which is necessary for converting tryptophan to serotonin, and which may explain why B6 helps suppress some women’s PMS symptoms. Sodium is also necessary to keep serotonin active, which may be why salt cravings are also common during PMS. Hahn suggests that light, a switch that triggers the conversion of melatonin to serotonin, is also linked to PMS, and she sees a connection between Seasonal Affective Disorder (SAD) and PMS, especially among those women whose symptoms are primarily mood-related.

Lifestyle Factors

Lifestyle factors such as diet, exercise, and the amount of stress in your daily life also influence PMS symptoms. Shiovitz and Frackiewicz observed that women who eat a high-sugar diet have an increased risk of PMS. They also found that women who consume large amounts of caffeinated beverages or alcohol tend to have more severe symptoms. Deficiencies in calcium, magnesium, manganese, vitamin B6 and vitamin E were also associated with more severe premenstrual discomfort.

Estrogen levels are measured in picograms, whereas progesterone levels are measured in nanograms, a unit 1000 times greater than a picogram.



Researchers also note that day-to-day stress is more strongly associated with PMS than a major life event. The build-up of daily stressors such as caring for children, being in a difficult marriage, or dealing with a divorce may help explain why women in their 30s and 40s tend to have more severe symptoms than their younger counterparts. The stress-related symptoms build to the point that women can no longer tolerate the symptoms presented.

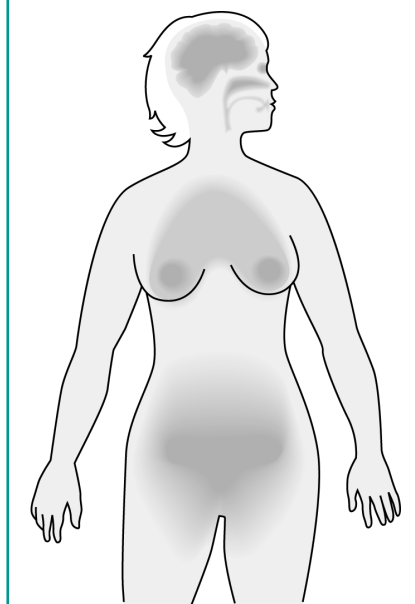
How is PMS Diagnosed?

Dr. Dalton defines PMS as “the recurrence of symptoms before menstruation with complete absence of symptoms after menstruation.” She claims that the most important criteria for an accurate diagnosis are the cyclical nature and timing of symptoms, relative to menstruation, rather than which specific symptoms occur. If symptoms are not restricted to the luteal phase, they may indicate another condition.

For this reason, most practitioners will ask you to keep a monthly symptom chart to track daily symptoms for three or more consecutive months. Because symptoms are so varied in type, timing, and severity, PMS is very difficult to pinpoint. Even with rigorous charting and notes, PMS may not be recognized as the predominant condition, or it may be misdiagnosed as another condition.

Before offering a diagnosis, most healthcare practitioners will probably try to rule out conditions such as anemia, thyroid imbalance, yeast infection, chronic fatigue syndrome, an autoimmune disorder, diabetes and endometriosis. One or more of these conditions is often pres-

Concentrations of Progesterone Receptors



ent in women suffering from PMS symptoms. For example, Hahn reports that early research on PMS indicated that one in six women with symptoms also had a thyroid imbalance.

If symptoms are severe and primarily mood-related, your healthcare practitioner might also explore other disorders, such as major depression, generalized anxiety, panic attacks, or bipolar disorder. Another factor he or she might consider is that some PMS symptoms, such as breast tenderness, headache, and sleep disturbances, are also associated with perimenopause.

Further confounding the diagnosis of PMS is a phenomenon called “menstrual magnification” whereby certain conditions such as migraine headaches, seizures, asthma, allergies, irritable bowel and chronic fatigue are exacerbated during the luteal phase.

Specific criteria for a diagnosis of PMDD are more rigorous,

including that the symptoms are primarily related to mood; must persist for at least one year; and serious enough to interfere with a woman’s work, social activities, and relationships. Indicators include marital discord, social isolation, parenting difficulties, and poor work performance. Although PMDD can be diagnosed by a psychiatrist, a biological basis may be missed. Another concern expressed by Hahn is that the label might be used against women in job qualifications or child custody cases.

How is PMS Treated?

When dealing with PMS, the primary treatment goals are typically to reduce or eliminate symptoms in order to restore daily function, while optimizing overall health. If there is only one severe symptom, it is best to try treating just that symptom. For example, if the worst symptoms are headaches or back aches, an over-the-counter pain reliever may be sufficient. If there is a collection of symptoms, a combination including lifestyle changes and other therapies may be needed.

Dr. Dalton suggests seeking out a sympathetic practitioner who will help you formulate a plan that focuses on relieving the specific symptoms that are most distressing to you. Because you will have to work closely with that practitioner for several months, perhaps years, it is important that you feel comfortable talking with him or her and asking questions. You may want to get a referral for a practitioner specializing in women’s health issues because his or her knowledge is likely to be more current regarding advances in treating PMS.

Lifestyle Modifications

Most practitioners will begin treatment with a two- to three-month trial of lifestyle modifications, including dietary changes such as reducing or eliminating sugar, salt, caffeine, chocolate, dairy products and alcohol. They might also recommend eating smaller, more frequent meals of a diet that is lower in trans fats (partially hydrogenated vegetable oils) and higher in fiber. It is very important to continue charting symptoms while undergoing these changes to see what effect, if any, they have on your PMS symptoms.

Other lifestyle-related recommendations might include stopping smoking, which is known to contribute to PMS symptoms, and getting regular moderate exercise, which has been proven to be quite effective in relieving PMS symptoms. Regulating sleeping and waking routines might also be suggested. Another suggestion might be to reduce stress, where possible, or to explore stress management techniques to better deal with the stresses that you cannot control. For example, yoga is a form of exercise and stress reduction that has proven to be beneficial for some women with PMS. Using gentle stretches, yoga helps release tension, ease lower back stiffness, regulate breathing, improve circulation and relieve stress.

Although these lifestyle changes will take time and perseverance, you are likely to recognize benefits above and beyond their effects on your PMS symptoms. For many women, these types of changes

tend to lead to improvements in overall physical and mental health, as well as relieving their PMS symptoms.

Drug Therapies

If lifestyle changes do not provide enough symptom relief, especially for those women with symptoms that are predominantly mood-related, healthcare practitioners typically turn to antidepressants, primarily SSRIs such as Prozac[®], as the first line of treatment. Shiovitz and Frackiewicz claim that, for PMDD patients, response to SSRI therapy has been about 60% or better. Anti-anxiety medications such as alprazolam (Xanax[®]) are sometimes prescribed to treat irritability, anxiety, and milder forms of depression.

While the results of these drug therapies may sound encouraging, each woman should take into account the pros and cons of such treatments. Antidepressants and anti-anxiety medications also tend to have a wide array of potential side-effects, including nervousness, agitation, dizziness, difficulty concentrating, drowsiness, insomnia, loss of libido, and others, which may turn out to be just as troublesome as the PMS symptoms they are intended to treat. For example, we now know that the prolonged use of SSRIs is associated with diminished bone density, which can lead to osteoporosis and a higher propensity to falls.

Hormone Therapies

Oral contraceptives are frequently suggested as a possible PMS treatment because they suppress ovulation,

usually with a combination of estrogen and progestin (a synthetic progesterone replacement). However, many women report a worsening of their PMS symptoms when taking oral contraceptives, or they experience side-effects worse than the original PMS symptoms.

Dr. Dalton notes that severe PMS sufferers tend to have high levels of the estrogen hormones, and that they may benefit from natural progesterone therapy. (The good news is that women with high estrogen levels tend to have fewer symptoms as they approach menopause, when other women typically need estrogen therapy for menopausal symptom relief.)

Natural progesterone is fairly inexpensive, has very few (if any) side-effects, and has been effective in reducing or relieving many PMS symptoms.

The typical treatment protocol requires adjusting dosages throughout the cycle. However, Dr. Dalton emphasizes that clinicians must also take into account the behavior of progesterone receptors when determining the appropriate dosages. She recommends that, after the first dose, subsequent doses need to be much higher to achieve the same reaction in the progesterone receptor cells.

Supplements

There is also a wide variety of over-the-counter, PMS-specific supplements, which may offer symptom relief. These supplements typically include calcium, magnesium, manganese, vitamin B6 and vitamin E,

among other ingredients. Many women report broad symptom relief simply from taking vitamin B6.

Herbal supplements such as evening primrose oil, black cohosh, St. John's Wort, and garlic tablets may be beneficial for treating some symptoms, but they have not been fully evaluated for treating PMS.

As with all therapies, it is best to discuss any supplement you are taking with your healthcare practitioner to make sure it is not interfering with other medications or treatments.

Resources

- *Once a Month: Understanding and Treating PMS*, Sixth Edition by Katharina Dalton, MD; Hunter House, Inc.; Alameda, CA; 1999.
- *PMS: Solving the Puzzle, Sixteen Causes of Premenstrual Syndrome & What to Do About It* by Linaya Hahn; Chicago Spectrum Press; Evanston, IL; 1995.
- "Evaluation and Management of Premenstrual Syndrome and Premenstrual Dysphoric Disorder" by Edyta J. Frackiewicz, PharmD, and Thomas M. Shiovitz, MD, in the *Journal of American Pharmaceutical Association*, Vol. 41, No. 3, May/June 2001.

Connections is a publication of **Women's International Pharmacy**, which is dedicated to the education and management of PMS, menopause, infertility, postpartum depression, and other hormone-related conditions and therapies.

This publication is distributed with the understanding that it does not constitute medical advice for individual problems. Although material is intended to be accurate, proper medical advice should be sought from a competent healthcare professional.

Publisher: Constance Kindschi Hegerfeld, Executive VP, Women's International Pharmacy

Co-Editors: Michelle Davenport and Carol Petersen, RPh, CNP; Women's International Pharmacy

Writer: Kathleen McCormick, McCormick Communications, Inc.

Illustrator: Amelia Janes, Midwest Educational Graphics

Copyright © December 2003, Women's International Pharmacy. *This newsletter may not be reproduced or distributed without the permission of Women's International Pharmacy.*

For more information, please visit www.womensinternational.com or call (800) 279-5708.

Women's International Pharmacy | PO Box 6468 | Madison, WI 53716-0468