Women's Health: The Menstrual Cycle

Introductory Remarks

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Synopsis

These discussions will encompass important areas which relate to the pathophysiology of the menstrual cycle. Unfortunately, only a narrow window of the pathology that is associated with the menstrual cycle will be presented. For instance, areas not to be covered include menstrual dysfunction associated with drug abuse, environmental toxins, the effect of systemic illness on the menstrual cycle, the effects of weight and exercise on the menstrual cycle and, finally, genetic abnormalities that are associated with menstrual dysfunction. The menstrual cycle should be looked upon as an early warning system for signaling that something is wrong, intrinsically or exogenously, with the individual. Hence, it raises a "warning" for a woman during her reproductive lifespan to seek medical help, simply because she may have a systemic illness which is not evident, but from which subsequent problems may arise and for which therapy may be available.

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Premenstrual Syndrome

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Synopsis

Premenstrual syndrome (PMS) is a difficult disorder to study because there is no convincing evidence for a simple, basal, physiologic lesion associated with it. PMS is characterized by a cyclic recurrence of symptoms of varying severity and is temporally related to menstruation, with exacerbation of symptoms during the luteal phase. Some new models are being developed to aid in studying PMS.

UNTIL RECENTLY, premenstrual syndrome (PMS) research has been characterized by confusion as a result of the failure of investigators and clinicians to define carefully the entity under investigation and to ask relevant questions.

The first question that one should ask is, "What is it that you want to study or diagnose?" I have defined a menstrually related mood disorder as follows: a cyclic recurrence of symptoms that are of sufficient severity so as to interfere with some aspects of menstruation and that occur with a consistent and predictable relationship to onset of menses.

In order to break down this preliminary definition into workable units, we must address several questions that are inherent in the definition. Those questions are as follows: What are the symptoms about which we are talking? What is their intensity or severity? When do they occur in relation to menstruation? What is the symptomatic baseline upon which symptoms occur? By what methods can one

establish the menstrual linkage or entrainment of symptoms?

The answer to the first question, what symptoms are experienced, is that practically every symptom that has ever been described as experienced by anybody under any condition has at one time or another been attributed to PMS. The fact is that the symptoms are totally nonspecific, and one cannot make a diagnosis on the basis of such symptoms.

Several investigators have attempted to define certain meaningful symptom clusters and have described some subsyndromes, such as premenstrual anxiety syndrome, craving syndrome, or a variety of subtypes of depressive syndromes. These subsyndromes are descriptors, not diagnoses. One must keep in mind the fact that simply by naming something, one cannot impart reality or suggest that normal experience is a disorder.

Chris Boros has underscored this point by describing what he called CED and MDS. CED is catastrophic economic dysthymia, which describes how dysphoric you feel when you are broke, and MDS is the meteorological decompensation syndrome, which is what one experiences after spending August in Washington, DC.

The second question, to what degree are the symptoms experienced, or what is the severity, is frequently not even addressed. When addressed, there is, at times, statistical over-interpretation, that is, attribution of clinical significance to statistically significant, but clinically unsubstantial, changes. In other instances, the scales that are used are insufficiently sensitive to the degree of change that one can experience under normal conditions.

When do the symptoms occur in relation to menstruation? This is the deciding factor. This is what makes PMS or a menstrually related syndrome, in fact, menstrually related. Symptoms must occur to some extent proximate to the beginning of menstruation.

What is the symptomatic baseline? This addresses the need to differentiate between premenstrual appearance of symptoms, that is, those that occur *de novo,* having not existed throughout the rest of the menstrual cycle; premenstrual exacerbation, that is, the worsening of symptoms that have been present throughout the menstrual cycle but become worse in the luteal phase of the menstrual cycle; premenstrual clustering of symptoms, that is, the concentration of episodically experienced symptoms, such as panic attacks or bulimic episodes in the luteal phase, with more random occurrence during the rest of the menstrual cycle; or premenstrual recrudescence, demonstrated by the case of a patient who had an endogenomorphic depression that was adequately treated, but who experienced a characteristic depressive syndrome in the context of the luteal phase with complete elimination of symptoms with onset of menstruation.

Finally, how does one evaluate the symptoms and determine if they are menstrually linked? The answer is clearly that retrospective historical reports are not reliable. Since the early 1930s, people have demonstrated that prospective, longitudinal ratings do not confirm retrospective symptom assessment.

The phenomenon is partly explained by Diane Ruble's misattribution hypothesis, whereby people will misjudge the timing of symptom occurrence. The hypothesis states that events that occur in a temporaly related fashion, that is, occur in some proximity to one another, tend to mutually reinforce the recollection of them as occurring and as being related. When the events occur randomly, disassociated from one another, one tends not only to forget that they occur, but also tends to ignore the negative informational value of the random, separate occurrence of the symptoms.

The distillate of this concept is that as difficult as it is to remember what symptoms are experienced, it is even more difficult to remember when they occurred. Thus, when we began studying PMS, we had people rate themselves along a variety of dimensions, such as depression, anxiety, and irritability, over a 3-month period, and then we evaluated and graphed their changes with respect to menstruation before admitting them to the study.

In some people, we observed a worsening of mood until the onset of menses, a sudden, dramatic lessening of symptoms, and then a gradual symptom buildup again. In other people with similar histories, we observed no such changes. Of the first 300 people we screened, 57 percent did not appear to have a menstrually related mood disorder. Similar results have been found in studies in England and New York, suggesting that of people who apply to take part in studies and who are motivated enough to fill out rating forms for 3 months, over half do not have what they said they had when they first appeared. This is obviously not a function of people attempting to be deceitful, but rather it reflects something about the way we attribute symptoms to physiologic events. The two groups were clinically indistinguishable at the time of initial presentation in terms of types or severity of symptoms.

Given the fact that so many people who *say* they have PMS prove to have no evidence of a menstrually related syndrome, one should not be surprised that there is so much controversy about what

causes PMS. In fact, the data suggest that more than half the people who have been studied for a biological cause of PMS do not have it in the first place. The biological studies, then, can be summed in the following way.

There is no convincing evidence that there is any simple, basal, hormonal lesion in PMS. There may be a more complicated endocrine abnormality, but there is no evidence that there is too little progesterone or too much estradiol.

Unfortunately, the same methodological problems, as well as a variety of others, apply to the treatment of PMS. People have seized upon particular treatments and then have proceeded to promote these treatments, almost in an ideological way. The data that have accumulated to date suggest, for example, that in 9 out of 10 studies that are double-blind and placebo-controlled, progesterone is not superior to placebo in the treatment of PMS. Again, one should keep in mind that many of the earlier studies had some severe methodologic problems, but in the recent studies, many of which have not been published yet, progesterone is not superior to placebo.

That does not mean that progesterone does not work. It does mean that progesterone as a panacea is an antiquated and erroneous concept, and we must understand PMS a great deal more than we presently do.

Two additional points deserve mention: first, everything that cycles is not PMS; and second, there is an advantage to looking at a process longitudinally. Do not look only at the symptomatic episode—look at the whole process. How does it evolve? How does it change?

In an attempt to clarify the pattern of symptom change with respect to menses, we derived a mean of each person's rating values in relation to the onset of menses. We then derived means from those individual means to obtain group data. We found a group of patients who met our criteria for PMS, who not only shared a gradual but significant deterioration of mood before the onset of menses, but also experienced a dramatic postmenstrual mood elevation. These patients "felt great," and I submit that this postmenstrual euphoria or sense of well-being is at least as interesting as the premenstrual dysphoria and in some cases is actually in excess of the premenstrual dysphoria that is experienced.

The group that said that they had PMS but did not meet our criteria were indistinguishable from the normal controls who said that their moods never changed. In fact, the worst day of the month for the former group was the first day of menses, in contrast to the PMS group.

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The main point here is that when you are selecting a control group, it is important to control for the relevant variable, and the relevant variable is the presence or absence of menstrually related changes in mood.

Finally, I would like to provide three models for considering PMS that I think are superior to the current monolithic, medical, and psychological models. First, the sensitization model. By repetitively administering small doses of electrical current to a rat's brain, you can change the way the brain responds to what was initially perceived as an innocuous stimulus. One has to wonder if a similar kind of sensitization process might be at work in patients with a major affective disorder whereby the occurrence of menstrually related dysphoria, month after month, might influence the course or expression of depression. One also might wonder whether this sensitization process accounts for the anecdotal observation that most people who present with PMS are in their thirties.

The learned helplessness model suggests that the perception of mastery can influence biology and can influence subsequent symptom development, that is, mastery can protect against subsequent symptom development.

Finally, the state-related model suggests that PMS may represent a biologically facilitated transition to a predictable, recurrent behavior state.

We are now in a position to build upon the knowledge that has accumulated. We have concepts and neurobiological techniques that may allow us to learn about PMS and apply what we learn to other disorders as well as to the normal human condition.