

REPLY

Menstrually Related Changes and Disorders: Conceptualization and Diagnostic Considerations

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Four decades ago, a distinguished panel of clinicians and academicians gathered "to establish the syndrome of premenstrual tension (PMT) as a clinical entity and to point the way to a better understanding of its etiology and treatment" (Morton 1953). They were concerned that "with an incidence of about 50% of all menstruating women, premenstrual tension must be regarded as the most common "nervous" disorder of women" and "the condition cannot be dismissed as being neurotic or primarily psychogenic." The panelists concluded:

It is obvious that disagreement exists concerning the specific pathogenesis of PMT. It is also apparent that one or more of the symptoms may predominate in any one patient and for that reason, the etiologic pattern is not necessarily identical in every instance. . . . It would appear therefore that the problem of the etiology of PMT requires further investigation.

It is disheartening that 40 years after the panel and 60 years after Frank's (1931) pioneering reports on PMT, literally dozens of papers include statements like "the etiology of Premenstrual syndrome (PMS) is still obscure" and "agreed upon definition and criteria are needed."

The report of the American College of Neuropsychopharmacology ACNP study group (Halbreich et al. 1993) is an attempt to delineate the points of consensus and disagreement in the field, which we believe is the first step toward the development of broadly accepted operational criteria and interdisciplinary cooperation. The main issues raised by the four commentators (who did not participate in the study group) are as follows.

- 1) Is the delineation of a list of points really productive?
- 2) Is an alternative to the DSM-III-R and DSM-IV "premenstrual dysphoric disorder" entity necessary?
- 3) Is suppression of ovulation effective as a treatment for PMS; is surgical menopause justified for that purpose?
- 4) What is the role of serotonin in the pathophysiology of PMS; what can we learn from the efficacy of serotonergic agonists as treatment for dysphoric PMS?
- 5) What are the roles of the environment and psychosocial factors in the formation or expression of PMS?

I strongly believe to achieve a substantial progress in this field that an attempt at integration should be made. Diagnostic as well as treatment issues cannot be separated from pathophysiology. The pathophysiology is multidimensional and symptoms cannot be attributed to a single factor. Indeed, the environmental and psychosocial aspects interact with the biological ones. Therefore, the points raised by the commentators will be addressed in an integrative solution-oriented way, instead of a point-to-point response that at least partially would be repetitious of the study group report.

During the last decade, a task force of the American Psychiatric Association (APA) has undertaken a commendable effort to examine PMS within the context of the APA's *Diagnostic and Statistical Manual, 3rd edition revised* (DSM-III-R, 1987), to accommodate "an urgent need for diagnostic criteria to differentiate cases

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of PMS in which disturbance of mood predominates, from cases of PMS with only physical symptoms" (Spitzer et al. 1989). An attempt to achieve a consensus on operational criteria for this prevalent state (Davis 1985; Williams et al. 1983) resulted in the definition of late luteal phase dysphoric disorder (LLPDD), which has been included in the appendix as a "Proposed diagnostic category needing further studies." The criteria for LLPDD represent a descriptive approach to allow for "research evidence to accumulate, that either validates or negates the utility of this diagnostic construct" (Spitzer et al. 1989). It appears that the task force for DSM-IV adheres to the descriptive phenomenologic approach and the emphasis on the premenstrual period. It is suggested here that cumulative research might be interpreted as questioning the utility of LLPDD or "premenstrual dysphoric disorder" as they are currently constructed, and the need to completely differentiate cases of dysphoric PMS from physical PMS can also be open for discussion.

One important prerequisite to the elucidation of the etiology of PMS, as well as to the development of appropriate treatment modalities, is the recognition that menstrually related changes (MRCs), including PMS, represent a multidimensional interdisciplinary issue which is best dealt with by an interdisciplinary collaborative effort (e.g., ISPOG 1989, 1992; Halbreich et al. 1988). The first step in a productive collaboration is the delineation of points of consensus as well as disagreements (as has been done by the 1991 study group), and then to agree upon a working conceptualization and a definition of the entity (or entities) in focus. Here a departure from the current phenomenology-descriptive thinking will not only provide a common denominator but might also be conceptually more productive. The biological and diagnostic data supporting the following suggestions were reviewed by us in great detail (Halbreich et al. 1988). To avoid redundancy and another lengthy review, only their relevant essence will be summarized here.

In the formulation of a framework for MRCs, some observations might be widely accepted and might serve as common denominators and a foundation for a factually based conceptualization. 1) The phenomenology of menstrually related changes is diversified and reflects involvement of many body systems including changes in mood and behavior, water retention, mastalgia, pain in various organs, migraine, changes in circulatory and autonomous systems, skin disorders, allergies and asthma, epilepsy, and numerous other changes (over 200 symptoms have been reported) (Halbreich et al. 1982; Dalton 1985). 2) Many times clusters of symptoms (syndromes) can be identified, but sometimes a woman has only a single dominant symptom (e.g., asthma, temporal lobe epilepsy, a skin disorder) that appears cyclically and is usually entrained to the menstrual cy-

cle. 3) Some women experience positive changes during the late luteal phase (e.g., increased energy and productivity, increased affection). 4) None of the symptoms per se is exclusively related to the menstrual cycle; similar symptoms might appear during other periods of life and most of them (excluding mastalgia and other gender specific symptoms) are also experienced by men. 5) A statistical association between dysphoric luteal symptoms and lifetime history of Major Depressive Disorder (MDD) has been reported, and women diagnosed as having dysphoric PMS might be more vulnerable to develop MDD in the future. 6) Cyclical symptoms tend to appear mostly during the late luteal phase, but many women report symptoms during longer periods and even the entire luteal phase. In some women the symptoms continue well into the menstrual period (they are distinguished from dysmenorrhea) (Bancroft 1989) and are *perimenstrual*. Some women report periovulatory symptoms. Although symptoms appear during or shortly after periods of hormonal fluctuations, they usually do not appear during the more stable midfollicular phase. 7) Chronic disorders (including MDD, epilepsy) may exacerbate or worsen during the luteal phase. Sometimes their exacerbation can be prevented by adjustment of dosing of maintenance drugs according to phase of the menstrual cycle (Halbreich and Carson 1989). 8) Treatment-response reports demonstrated that suppression of ovulation with gonadotropin-releasing hormone agonists or danazol have been beneficial for elimination of menstrually related phenomena as diverse as severe dysphoria, porphyria, lupus erythematosus, epilepsy, and skin disorders (Muse et al. 1984; Watts et al. 1985; Magos et al. 1986; Bancroft et al. 1987; Anderson et al. 1984). Similar results were also reported following surgical menopause by ovariectomy, but as Dr. Steege commented such a radical approach is hardly justified when similar therapeutic benefits can be achieved pharmacologically. 9) Many symptoms similar to MRC might be aggravated by, or are side effects of, contraceptive pills (Cullberg 1972; Kane et al. 1967). 10) Women with MRC are probably also more vulnerable to symptoms during other periods of instability or change, such as, postpartum, following abrupt hormonal withdrawal, and during menopause. There is probably an association between having MRC and Seasonal Affective Disorder. 11) The cyclicity of symptoms is usually eliminated during spontaneous anovulatory cycles (Backstrom et al. 1989), during pregnancy, and following menopause. 12) Cyclic PMS-like symptoms can be simulated in postmenopausal women by treatment with sequential contraceptive pills (Hammerback et al. 1985). 13) Symptoms were reported to appear with a time lag of 5 to 6 days after changes in levels of gonadal hormones (Halbreich et al. 1986; T. Backstrom, personal communication). 14) Absolute levels of gonadal hormones do not

necessarily distinguish between women with and without PMS (Rubinow et al. 1988). 15) Curtailment of the late luteal phase does not eliminate symptoms (Schmidt et al. 1991). 16) Appropriate symptomatic treatment is sometimes but not always beneficial. Its efficacy is limited to subgroups of women with specific Premenstrual syndromes (Magos 1989). For example, as was emphasized by Dr. Brown, some serotonergic agonists have been reported to be very effective as treatment of dysphoric PMS. 17) As was emphasized by Dr. Severino, environmental influences, responses to stressors, coping styles, and attribution play an important role in the expression of MRC.

The above data can be conceptualized as follows. 1) Most, if not all, menstrually related changes might be related to the same generalized underlying mechanism that is probably at least partially related to events preceding, associated with, or following ovulation. 2) Cyclic changes in the hypothalamo-pituitary-gonadal (HPG) system, its regulation and relationship with other systems, are putatively playing an important role in the underlying mechanisms of MRC. 3) These changes might trigger changes in other systems. Even if the activity and changes of the HPG system are "normal," in some individuals, affected systems might be more vulnerable to dysregulation. 4) The changes in the HPG system are probably part of a destabilizing process that might cause impaired homeostasis and a decrease in threshold for surfacing or expression of symptoms. 5) The nature and constellation of symptoms depend on individual proneness and vulnerability. (The diversity of symptoms might be explained by the individual vulnerability traits as well as the multiple systems that are involved in the impaired homeostasis.) 6) Treatment might be aimed at the generalized underlying mechanism (e.g., fluctuation in the regulation and

interactions of the HPG system) or at a symptomatic relief of the individual's vulnerability and determined subtype of MRC (e.g., serotonergic reuptake inhibitors).

The conceptualization of a putative underlying physiology of MRC is summarized in the upper part of the integrative Table 1. The possible relevant diagnostic phenomena and entities are summarized in the table under each physiologic stage, starting from generalized MRC and leading to the system-oriented symptomatic subtypes. According to this approach, the variety of dysphoric or physical premenstrual (or perimenstrual) syndromes and disorders might be considered as subtypes of MRC. The treatment implications of each stage are summarized in the lower part of the table. (In cases of system-oriented symptomatic subtypes, a targeted symptomatic treatment might be effective.)

Based on this conceptualization, it is suggested that the definition of premenstrual and other menstrually related changes should be based mostly on a temporal occurrence and not on phenomena: on the timing of the appearance and disappearance of changes and not on their description. The main diagnostic issue is "when" rather than "what." In the case of premenstrual changes (PMCs), any symptom may occur premenstrually, and as long as it is occurring cyclically and is essentially limited to the luteal phase, it is a premenstrual change. In most women PMCs consist of multiple symptoms; in others only a single change might be dominant. Because at present no difference in any underlying mechanism has been demonstrated between changes of different lengths or menstrual cycle timing (e.g., symptomatic period of 1 to 2 days versus entire luteal phase), although they all share the aforementioned common denominators, the overall term MRCs might be more accurate.

Table 1. Menstrually Related Changes: Summary of Mechanism, Diagnoses, and Treatment

Underlying Mechanisms:	Changes in HPG Regulation and Modulating Factors	Impaired Homeostasis and Lower Threshold Symptoms Surface According to Vulnerability	Nature of Symptoms Depends on Individual Traits
Changes and diagnosis:	Menstrually related changes (MRC)	Positive, productive, pleasant changes ^{1,2} Negative, unpleasant changes but no distress or impaired function (MRS) ² Negative changes with distress and/or impaired function (MRD) ³ MR exacerbations ⁴	MR dysphoric disorders MR skin disorders MR allergic disorders MR seizure disorders
Treatment:	Suppression of ovulation, elimination of hormonal fluctuations		Symptomatic treatment

¹ Normal.

² No treatment is warranted.

³ Abnormal, treatment is warranted.

⁴ Treated by adjustment of maintenance dosing or, in severe cases, suppression of ovulation.

This suggested conceptualization implies another departure from current concepts. If the main mechanism of MRC is a menstrually related dysregulation or a decrease in threshold, and specific symptoms appear or worsen according to individual vulnerability, then menstrually related exacerbations or a menstrual cycle-entrained worsening of a chronic disease might be considered under the same umbrella. (Indeed the main diagnosis should be according to the main underlying mechanism with a qualifier of MRD.) It might be a subject for future research to ascertain whether hormonal interventions are of benefit in reduction of these exacerbations. The significance of underlying mechanisms of the various subtypes of MRC in relation to the stimulus inducer of symptoms in a particular timing is still debatable and is also a subject for future research.

Apparently the suggestion that the same underlying mechanism might trigger diversified, sometimes nonoverlapping phenomena in different individuals, and therefore people with completely different signs and complaints (e.g. skin disorders and epilepsy) might carry the same diagnosis and be identically treated, is currently not widely accepted. However, this is also the case with disseminated disorders (e.g., Rheumatic disease, Systemic Lupus Erythematosus, Multiple Sclerosis). An integrative and cross disciplinary reading of the available literature can lead to the conclusion that this might also be the case with MRC.

Hopefully, the ideas presented here will stimulate conceptualization and research of multidimensional processes that are clinically manifested in diversified sets of signs and symptoms. But above all, they provide a common denominator for interdisciplinary cooperation. A multidisciplinary task force is needed to develop a generalized set of operational criteria that reflect input from psychiatry, gynecology, endocrinology, general medical practice, psychology, and epidemiology (among others). Only then should symptom-specific subtypes be developed by the relevant specialties. To enhance and promote the acceptance and use of diagnostic categories across medical specialties, such a task force should be under the aegis of a unifying organization such as the American Medical Association or the World Health Organization. Hopefully, such a timely interdisciplinary initiative will be pursued in the near future.

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