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Premenstrual Syndrome and Anxiety Disorders: A Psychobiological Link

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Premenstrual Syndrome

The term premenstrual syndrome (PMS) has been used for many years to describe disturbances of mood or physical symptoms occurring regularly 7–10 days before menses and remitting during menses. The Diagnostic and Statistical Manual of Mental Disorders (DSM III-R) included PMS among the 'proposed Diagnostic Categories Needing Further Study' under the name of Late Luteal Phase Dysphoric Disorder (LLPDD), and established among its diagnostic criteria the need for daily prospective symptoms self-ratings during at least two cycles, for confirmation [1]. The more recent fourth edition of DSM maintained PMS among the categories needing further study, adding the new category of Premenstrual Dysphoric Disorder (PMDD) [2]. PMDD is distinguished from PMS in several respects: It requires at least one mood symptom; the symptoms must be severe enough to cause functional impairment, and they must not be a mere exacerbation of another psychiatric disorder. Since no other diagnostic criteria have been proposed, many studies have compared the scores from the premenstrual and follicular phases: a 30–50% increase found in prospectively administered diaries is now normally accepted as an indicator of the diagnosis of PMS [3], no attention being paid to the quality of symptoms.

On the other hand, no specific hormone changes or other biological markers are able to distinguish between PMS sufferers and normal women [4]. Therefore, the absence of both a universally accepted definition and an objective biological or clinical marker makes it impossible to study the etiology of PMS. Accordingly, the therapeutic approach is presently indefinite. Steinberg [5] correctly stated that the time-honored medical adage maintaining that 'in the absence of cure, treatments multiply' seems to be appropriate to PMS.

Nevertheless, it is well accepted that the severe form of PMS, i.e. the one characterized by psychosocial impairment and thus requiring medical treatment, is present in 5–8% of women during their 40s. This implies that we should multiply our efforts toward the understanding of the disorder.

Anxiety Rather Than Mood Disorder

The comorbidity of PMS with mood disorders was a matter of numerous studies conducted mainly by Halbreich and Endicott [6]. The aim of these studies was to establish whether or not women with PMS are more vulnerable to mood disorders. However, a comparison between these different studies is very difficult, firstly due to

the different methods used to assess PMS and secondly due to the different classification criteria of psychiatric disorders.

On the one hand it has been reported that women with a lifetime history of major depressive disorder (MDD) are more likely to report premenstrual mood changes than healthy women, or those who have experienced other types of mental illness [6, 7] and that women with premenstrual mood changes have greater prevalence of MDD than women without such a history [8]. Gaze and Endicott [9] documented that the assessment of premenstrual depression has validity in identifying women at risk for future MDD. Moreover a past history of depressive illness as defined in terms of treatment with antidepressants was found to be more common in women complaining of PMS [10].

In a study published by Fava et al. [11] the authors showed that current anxiety and mood disorders are very common among patients with prospectively confirmed LLPDD, and involve 66% of their population. Moreover, this percentage appears to be significantly higher than that observed among healthy, non-age-matched, female controls. In particular, anxiety disorders, either alone or with comorbid mood disorders, were present in 59% of the LLPDD patients, generalized anxiety disorder, panic disorder, and social phobia being the most common diagnostic groups. Neither marital status nor age was associated with such findings. These results partially concur with a previous study by Stout et al. [12] evaluating the lifetime prevalence rates of psychiatric diagnoses in clinic and community samples of PMS sufferers. It was found that 65% of women in the PMS Clinic met DSM-III criteria for phobia and 16% those for obsessive-compulsive disorder, with a greater frequency than in women from a community sample. Unexpectedly, none of the 223 women in that study was found to meet criteria for panic disorder. It should be noted that those subjects were simply seeking treatment for premenstrual symptoms, whereas PMS was prospectively confirmed in the study by Fava et al. [11]. Furthermore, in this paper LLPDD patients with anxiety and/or mood disorders displayed a Menstrual Distress Questionnaire profile almost identical to that of LLPDD patients without these disorders. Although the relatively low sensitivity of the tool used (with a small score range) may account for these findings, this supports the view that it is impossible to distinguish patients with LLPDD alone from those with comorbid anxiety or mood disorders purely on the basis of premenstrual symptomatology.

Lactate Test

It is well known that patients with panic disorder are highly sensitive to lactate infusion [13]. Thus, in view of the comorbidity with anxiety disorders described above, two different groups examined the effects of lactate in patients with PMS. Facchinetti et al. [14] demonstrated that 63% of 35 women with prospectively diagnosed PMS developed a panic attack in response to lactate infusion, while only 12% of the control subjects showed a similar response. The prevalence of panickers in control subjects was basically identical to that reported by other studies [15]. Therefore, a subgroup of PMS patients appears to be prone to lactate-induced panic attacks, and is likely to share some biological vulnerability factors with patients with panic disorder. In addition, a similar rate (58%) was found by Sandberg et al. [16], although in a relatively small number of patients (13 cases).

In our previous study, lactate infusion induced panic attacks in all but 1 PMS patient with associated panic disorder, as expected. However, a similar response to lactate was observed in another 14 patients, 50% with PMS alone and 50% suffering from PMS with other anxiety/mood disorders. The PMS population without anxiety/mood disorders is similar to that described by Sandberg et al. [16]. In both studies, the rate of panic attacks during lactate infusion was higher than in controls. Moreover, when the behavioral, cardiovascular and neuroendocrine changes evoked by lactate were examined in patients with PMS alone, heart rate, panic and mood responses were still of higher magnitude than those observed in controls. This suggests that increased sensitivity to lactate is a peculiar feature of this population, even in the absence of comorbid psychiatric disorders.

This concept is further endorsed by the observations of Harrison et al. [17] that women with LLPDD responded to a 35% CO₂ inhalation with panic symptoms, while no panic attack was observed in controls.

Lactate Test and the Menstrual Cycle

Lactate infusion (as previously described) was administered in both the mid/late luteal phase and the follicular phase of the cycle to 8 women meeting criteria for LLPDD. Retrospectively, lactate infusion was administered on day -5.4 (mean), in relation to the following menses and on day +6.3 (mean) in relation to the onset of previous menses. In 4 cases, the infusion occurred first during the premenstrual period. A panic attack was trig-

gered in 2 and 5 cases, in the follicular and premenstrual periods, respectively. Given the small number of the sample, there was no significant difference in the frequency of the panic attacks in the follicular and premenstrual periods [18]. However the responses of vital parameters and affective symptoms to lactate changed according to the phase of the menstrual cycle (fig. 1). With the exception of heart rate, all measures investigated showed a significantly higher response in the premenstrual than in the follicular phase. These findings confirm that patients with PMS are characterized by sensitivity to lactate, since they develop a panic attack during the infusion. Interestingly, however, this sensitivity is differently expressed in relation to the menstrual cycle. Indeed, the lactate-induced activation of sympathetic nervous system is of higher magnitude during the premenstrual period than in the follicular phase. Similarly, the psychological/affective reactions to such arousal are increased during the premenstrual period.

Conclusions

These data support the view that the premenstrual period may predispose individuals to a generally poor adaptation to stressors. This conclusion is closely linked to the 'coping – ineffectiveness of coping' concept derived from the theory elaborated by Lazarus [19]. The menstrual cycle is a source of variation in the activity of several systems (neuroendocrine, metabolic, behavioral, etc). Hence, women adopt their usual coping style in order to attenuate and/or prevent effects. Thus, a physiological arousal toward such potentially detrimental changes occurs. The ineffectiveness of coping strategies results in the development of distress. Therefore, when considering lactate infusion as a laboratory stressor mimicking those of everyday life, we may conclude that the PMS patients are unable to cope with stressors only in the premenstrual period. It may also be that tachycardia induced by lactate in two phases of the menstrual cycle results in a catastrophic interpretation only during the premenstrual period, allowing the onset of a panic attack.

In a therapeutic perspective, it is worth nothing that a low-dose alprazolam treatment was found to be more effective than placebo in reducing nervous tension, mood swings and irritability in women with PMS without previous or current psychiatric illness [20]. Similar results have been obtained with the nonsedating, non-benzodiazepine anxiolytic drug buspirone [21]. It is possible that buspirone could act through the serotonin system. In both

Fig. 1. Mean $\pm$ SD of the area under the curve (AUC) of heart rate (HR; beats/min), systolic blood pressure (SBP; mm Hg), diastolic blood pressure (DBP; mm Hg) as well as mood and panic scores in response to lactate infusion performed both in follicular (shaded bars) and premenstrual (black bars) periods in patients with PMS.

studies, physical symptoms like pain, cramps and aches were also relieved by the anxiolytic treatments, suggesting the existence of a domino between the conditions.

In conclusion, we believe that PMS is a psychobiological disorder sharing several clinical features with currently diagnosed anxiety disorders. This view is supported by: (1) the lifetime presence of panic attacks, as well as the comorbidity with panic disorder, which suggest the existence of common 'traits'; (2) the reaction to both lactate infusion and CO₂ breathing, which confirms that the negative interpretation of the somatic symptoms induced by these challenges, and typical of patients with panic disorders, are also present in patients with PMS apparently free from any other anxiety disorder; (3) the reported responsiveness of PMS patients to treatments with anxiolytic drugs. However, such conclusions require further investigations since similar biochemical changes could be related to apparently different clinical conditions, like in the case of anxiety and depression disorders.

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