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‘Circa Menstrual’ Rhythmcity and Asthma

Premenstrual asthma (PMA) is a recognized clinical entity. The question of whether PMA is an under- or over-recognized condition has not been adequately addressed. Large-scale longitudinal studies have just not been undertaken. Smaller studies, however, seem to suggest that 30 to 40% of female asthmatics experience a premenstrual worsening of symptoms. Rees et al.1 studied an unselected series of 81 female patients of reproductive age with asthma and found that 27 (33%) showed a “clear tendency for attacks during the week or ten days prior to the onset of menses with a peak incidence” during the two to three days before the menses.” Gibbs and colleagues2 reported the results of a questionnaire returned by 91 women with asthma. Thirty-six (40%) answered “Yes” when asked: “Does your asthma ever seem worse before the menstrual period?” Eliasson et al.3 found that 19 (33%) of 57 women with asthma reported significant worsening of total pulmonary symptom scores during the premenstrual period, the menstrual period, or both.

These and similar questionnaire studies rely on patient impressions and recollection. As a result, they suffer from a number of inherent biases. Several studies have attempted to use objective data to study the problem. Hanley4 noted statistically significant reduction of peak flow rate at the time of menstruation in those women whose asthma flared up compared to subjects who were unaffected. A similar finding was noted in the study of Gibbs and coworkers.2 In both studies, however, clinically significant deterioration was infrequent. Gibbs noted that the “falls in peak inspiratory flow were usually modest and of a degree that would not be expected to result in increased breathlessness.” Gibbs suggested that a heightened awareness of symptoms during the premenstrual period, rather than a demonstrable reduction in pulmonary function, may play a role. In a similar vein, Juniper et al.5 discussed altered perception of asthma symptoms as a possible explanation for PMA.

Several investigators have looked at the influence of the menstrual cycle on airway responsiveness. Juniper et al.5 examined changes in airway respon-
siveness to methacholine in 17 well-controlled asthmatics at 1 week prior to and 1 week after start of menses. They found no significant difference in responsiveness, FEV₁, or medication use, but reported that symptoms deteriorated just prior to and during menses. In a similar study, Weinmann and colleagues found no significant difference in FVC, FEV₁, or airway responsiveness to histamine when measured early and again late in the menstrual cycle of nine women with asthma. Pauli and coworkers studied 11 asthmatic women, who had not previously complained of a relationship between symptoms and their cycle, and 29 normal control subjects. They found no changes in airway function over the menstrual cycle in normal women. In the asthmatic subjects, a significant worsening of asthma symptoms and a slight decline in morning peak expiratory flow rates was observed, but no deterioration in spirometry or airway responsiveness to methacholine was detected. The results of these three studies seem to suggest that although reported symptoms increase in the premenstrual period, no clinically significant accompanying physiologic changes can be demonstrated. It has been noted, however, that these investigators studied an unselected sample of asthmatic women and that the results might be different in a symptomatic population.

Whatever the true prevalence and true significance of PMA, most experienced clinicians will recall one, several, or many female patients whose asthma would significantly worsen on a monthly basis. The literature would support such an impression. Beynon and colleagues reported three patients with severe, life-threatening premenstrual asthma. In all cases, there was a striking fall in peak flow rate premenstrually. None of the patients responded to conventional treatment, including high-dose corticosteroids. Interestingly, the addition of intramuscular progesterone to the regimen eliminated the premenstrual dip in peak flow and allowed daily doses of oral corticosteroids to be reduced. Eriasson et al reported three patients who were hospitalized repeatedly for worsening of asthma in relation to menstruation, two of whom had recurrent respiratory failure without evidence of other precipitating factors. Skobeloff and colleagues reported that 75% of adult patients admitted to the hospital for treatment of asthma are women. Moreover, these patients encountered longer hospital stays than age-identical men. In a subsequent study, this same group reported an analysis of data from 182 nonpregnant, adult women who presented to the emergency department for asthma treatment. They found that nearly half of all exacerbations requiring an emergency department visit occurred during the period from 2 days before until 4 days after the onset of menses. The weight of the evidence would seem to suggest that there is at least a subset of female patients with asthma who develop significant morbidity in conjunction with their menstrual cycle.

Regardless of whether premenstrual deterioration of function is a universal finding in asthmatic women or an ominous feature of a subset of this population, the immediate question is then, “why and how does this occur?” A number of mechanisms have been postulated and investigated, such as “allergy to endogenous hormones,” psychological changes associated with the premenstrual syndrome, progesterone-induced hyperventilation, low progesterone levels at the onset of menses leading to bronchial smooth muscle constriction, progesterone potentiation of an unidentified bronchodilator, progesterone-mediated loss of microvascular integrity with subsequent edema leak, dynamic fluctuations of estrogen levels after sustained but static elevation, increase in mucous secretions, and variation in prostaglandin synthesis.

The final answer(s) are not yet available. Clarification of the mechanisms behind premenstrual asthma, however, will provide another insight into the pathogenesis of asthma.

In this issue of CHEST, Tan and colleagues report a study that represents the next step in what appears to be a promising line of investigation. In a previous report, this group demonstrated that lymphocyte β₂-adrenoreceptors in normal women are under the cyclical influence of ovarian sex hormones. Greater receptor density and cyclic adenosine monophosphate response to isoprenaline occurred during the luteal phase, in association with increased postovulatory levels of progesterone and estrogen, as compared with the follicular phase of the menstrual cycle (11). In contrast, asthmatic women fail to show a similar cyclical pattern in that there is no luteal phase rise in β₂-adrenoreceptor density despite an appropriate postovulatory hormone response (12).

Building on their prior work, Tan and colleagues administered exogenous sex-steroid hormones to healthy women during the follicular phase of their cycle. The investigators were able to demonstrate that progesterone, but not estrogen, produced up-regulation of lymphocyte β₂-adrenoreceptor density (13). It should be noted that during the follicular phase of the menstrual cycle, endogenous hormone levels normally are low. By administering exogenous hormone, the investigators hoped to mimic what happens in the luteal phase of the cycle when endogenous hormone levels are high.

In the present study, exogenous estrogen and progesterone were separately administered to asthmatic women during the follicular phase of their
cycle. Not only did progesterone fail to increase receptor density, exogenous progesterone paradoxically decreased both receptor density and response in women asthmatics. Exogenous estrogen produced no significant effect.

Based on the results of these reports, Tan and coinvestigators concluded that the paradoxical effect of progesterone in female asthmatics suggests that abnormal cyclical β2-adrenoreceptor regulation may be a possible mechanism for premenstrual exacerbation of asthma. Similarly, I would conclude that, although a number of questions remain and significant further study is needed, they may just have something here.

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Presenting Results of Studies Evaluating Diagnostic Tests

Clinicians face daily decisions regarding diagnostic testing. The appropriate selection of tests affects not only the patient’s clinical outcome, but also the economic viability of a practice. How is the busy clinician to determine the true value of newer tests, or to interpret articles that compare two well-known tests? Such a question arises from the article by Colice in this issue of CHEST (see page 877), which compares bronchoscopy with CT scan in the diagnostic work-up of hemoptysis in patients with negative chest radiographs.

Traditionally, diagnostic tests are described in terms of their “operating characteristics,” including the sensitivity and specificity as determined in a defined population. By convention, an assumption underlying these measures is that they will hold true when applied to any population; that is, regardless of where or when an antinuclear antibody test is performed, or what the characteristics of the tested population are, a certain consistent percentage of patients with systemic lupus erythematosus will be detected by the test (sensitivity), and a certain consistent percentage of normal individuals will have a negative test (specificity).

Unfortunately for clinicians, knowing the sensitivity and specificity of a test might make it easier to decide which test to order, but these characteristics are not helpful when faced with the result of a test. What the patient and clinician most want to know in that situation is the predictive value of the test: if positive, how likely is the patient to have the disease; and if negative, how likely is the patient to not have the disease? The predictive values can be calculated from the two-by-two table that should be a part of each article addressing the utility of a diagnostic test. Because of the method by which they are calculated, the predictive values of a test are directly dependent upon the prevalence of disease in the studied population, the so-called “pre-test likelihood.” A positive antinuclear antibody test in a geriatric population will have a much lower positive predictive value than a positive test in a population of young women because systemic lupus erythematosus is more prevalent in young women.

One traditional use of the sensitivity and specificity in the comparison of two tests is to determine a receiver operating characteristic (ROC) curve for each test by plotting the sensitivity vs 1-specificity for each possible cutoff value. The resultant curves can be easily compared both visually and statistically, and the test with the greater area under the curve is