

Premenstrual asthma: still poorly understood

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Although a premenstrual increase in symptoms can occur in up to 40% of women with asthma, the mechanisms underlying this phenomenon are poorly understood and have not been frequently evaluated.^{1,2} This deterioration may represent an exaggeration of the normal cyclical variation in airway function in patients with asthma since a fall in peak respiratory flow rates occurs even in those patients without significant change in premenstrual symptoms.³ Premenstrual worsening of lung function begins 7-10 days before the onset of menses and peaks 2-3 days before their onset. This change in asthma in the latter half of the luteal phase of the menstrual cycle would appear, on the face of it, to be related to changes in female hormone activity. In particular, the observed improvement in severe premenstrual asthma seen with intramuscular progesterone would imply an abnormal level of this hormone during the late luteal phase of menstruation in this group of patients.⁴

Although the underlying mechanisms are unclear, it seems logical to expect that patients with premenstrual exacerbations of asthma would exhibit increased airway responsiveness and evidence of airway inflammation. Surprisingly, the study by Tan *et al* reported in this issue of *Thorax* is the first to establish clearly an increase in airway responsiveness during the luteal phase of the menstrual cycle.⁵ In a group of 15 stable asthmatic women without premenstrual symptoms, 10 of whom were taking inhaled corticosteroids, a 2.5 fold increase in airway responsiveness to adenosine 5'-monophosphate (AMP), an indirect bronchoconstrictor acting predominantly through mast cells,⁶ was seen. These data contrast with two other studies in similar groups of mild asthmatic patients, neither of which demonstrated changes in airway responsiveness to methacholine or histamine, direct smooth muscle stimuli.^{7,8}

This new finding using the indirect stimulus AMP requires explanation. The authors postulate that the increased response to AMP may be due to regulation of adenosine receptors on airway mast cells under the influence of circulating sex hormones. However, they failed to find a correlation between circulating hormone levels and changes in PC₂₀ AMP which makes this unlikely. On a simple level it seems plausible to believe that, during the menstrual cycle, there are changes in asthmatic inflammation within female airways. AMP challenge may be a more discriminatory tool than the smooth muscle stimuli methacholine or histamine as adenosine acts indirectly on both airway mast cells and airway sensory nerves.⁶ The observations of Tan and colleagues may therefore reflect upregulation of either or both processes as a measure of increased inflammation. Against this, serum levels of eosinophil cationic protein (ECP), a surrogate marker of airway inflammation, albeit poor, was unchanged between the follicular and luteal phases. This study prompts further research in menstruating females using other established markers of airway inflammation.

There are now several non-invasive tools to evaluate airway inflammation in asthma that may be applicable in premenstrual asthma. Nitric oxide (NO), a gas present in exhaled air, is increased in patients with asthma.⁹ Exhaled NO is thought to be a marker of airway inflammation as the abnormal levels recorded in patients with symptomatic asthma are reduced by inhaled corticosteroid treatment.¹⁰

Furthermore, the acute rise in NO levels observed during the late asthmatic response following allergen challenge correlates with the severity of bronchoconstriction.¹¹ A recent study in normal women which clearly showed higher levels of exhaled NO during the luteal phase of the menstrual cycle may provide a clue to possible airway inflammatory changes in premenstrual asthma.¹² This study needs to be repeated in women with asthma, ideally in those with objective evidence of premenstrual worsening of asthma control. The techniques used to process and analyse sputum samples obtained by induction with hypertonic saline have been refined to show changes in airway inflammation clearly, particularly eosinophil function measured by absolute counts and sputum levels of ECP.¹³ In combination with measurement of exhaled NO, assessment of sputum eosinophil activity could be readily and safely performed throughout both phases of the menstrual cycle of asthmatic patients.

Tan *et al* also reported a loss of normal cyclical changes in β_2 adrenoceptor regulation previously described in normal women by the same group.¹⁴ This occurred despite an appropriate rise in luteal phase sex hormones in the asthmatic patients studied. In a previous study from the same group exogenous progesterone upregulated follicular phase β_2 adrenoceptor function in normal women.¹⁵ Thus, as the authors suggest, the present findings may indicate a poor β_2 adrenoceptor response to increased luteal phase endogenous progesterone in asthmatic patients. Since female sex steroid hormones potentiate the bronchorelaxant effects of catecholamines,¹⁶ this blunted β_2 adrenoceptor response may contribute to the mechanisms underlying premenstrual asthma. It is not possible to draw any firm conclusions from this study as the patients assessed did not have overt premenstrual asthma. The lack of data on patients with objective premenstrual loss of asthma control hampers the development of insights into this problem.

Although as many as 40% of patients have premenstrual asthma,¹ most are likely to be controlled with standard treatment guidelines including increasing inhaled corticosteroids and possibly adding long acting β_2 adrenoceptor agonists during the second half of the menstrual cycle. Studies are needed to establish clear treatment protocols. As Tan *et al* suggest, these studies should include evaluation of theophylline, an adenosine antagonist,¹⁷ and the cromones which effectively attenuate adenosine-induced bronchoconstriction¹⁸ in view of the significant increase in AMP responsiveness during the luteal phase. Of particular note, the patients most prone to premenstrual exacerbations are those with severe asthma.⁴ In many cases even high dose oral steroids are of little benefit. In these difficult patients intramuscular progesterone has been advocated as an alternative treatment.⁴ Overall, there is a paucity of data on underlying mechanisms and possible treatment regimens for premenstrual asthma. It behoves respiratory physicians to develop a programme of research in this poorly understood subgroup of asthmatic patients.

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