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Premenstrual Asthma
Epidemiology, Pathogenesis and Treatment

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Contents

Abstract

The exacerbation of asthma in the premenstrual period has long been of interest. Premenstrual asthma has been estimated to affect up to 40% of females with asthma, although the exact prevalence of this phenomenon is unclear as studies have involved small numbers in hospital clinics. Large-scale community-based studies are required to estimate its true prevalence.

Researchers are slowly piecing together clues as to the aetiology and pathogenesis of the disorder. Female sex-steroid hormones play an important role but the exact mechanism is still unknown. Recent evidence suggests that increased airway hyperresponsiveness, an indicator of underlying airway inflammation, during the luteal phase of the menstrual cycle may account for premenstrual exacerbations. In addition, there is now evidence of impaired or altered β_2-adrenoceptor function and regulation in females with asthma, which may have a part to play.

Accurate diagnosis is dependent on a detailed history and the demonstration of premenstrual dip in peak expiratory flow. Exacerbations in the majority of women will respond to the usual treatment of bronchial asthma. However, a few women will experience significant morbidity or treatment-related adverse effects. Case reports suggest that the combined oral contraceptive pill or gonadotrophin-releasing hormone analogues may be effective in these patients. This requires substantiation by randomised controlled trials.

It has long been recognised that some women experience an exacerbation of their asthma in the days prior to and during menstruation. The phenomenon was initially described by Frank[1] 70 years ago in one of the original accounts of premenstrual tension. Although awareness of premenstrual asthma is increasing, there is surprisingly little research into the condition.

The aim of this article is to review the literature describing the epidemiology, pathogenesis and treatment of premenstrual asthma. To do this, a Medline search of all English language reports of premenstrual asthma from 1966 to 2000 was undertaken using the keywords 'premenstrual asthma', 'asthma', 'menstruation' and 'menstrual cycles'. All relevant clinical studies were reviewed.

1. Epidemiology

A number of studies have investigated the prevalence of premenstrual asthma (table I). Most research has been questionnaire-based and, therefore, limited by recall bias and the use of leading questions, which may result in false positive reporting. The first study of this kind was undertaken in 1963 by Rees[2] who concluded that 33% of a group of 81 women with asthma attending a hospital chest clinic had premenstrual asthma. The study was limited by lack of objective data such as peak expiratory flow (PEF) measurements or spirometry. Two decades later, three questionnaire-based studies found a prevalence of 33 to 40%.[3-5] Hanley[3] and Gibbs et al.[4] also asked symptomatic patients to keep daily PEF diaries. Although statistically significantly lower PEF occurred premenstrually, the amplitude of the changes (16% in Hanley's, 5.3% in Gibbs' groups, respectively) was small enough to be of doubtful significance.

Recent research has found the prevalence of premenstrual asthma to be slightly lower at 23 to 28%.[6,7] Shames et al.[7] carried out a detailed prospective study of 32 women with asthma over six consecutive menstrual cycles. Self-reported worsening of symptoms premenstrually were associated with significantly reduced PEF readings and increased β-agonist requirements. Patients with premenstrual asthma were found to be significantly older and had had a longer duration of asthma compared with the other women. Agarwal and Shar[6] carried out a retrospective questionnaire evaluation of 100 Indian women with asthma of whom 23 reported premenstrual asthma exacerbations. Twenty patients, ten each with and without premenstrual exacerbations were asked to keep a PEF diary. Mean PEF was lower, with greater diurnal variability in the premenstrual group compared with those with stable asthma. PEF improved during the midcycle, giving objective evidence of poorly controlled asthma in the premenstrual phase. A recent report using self-completed questionnaires among women with asthma in primary care found a much lower prevalence of premenstrual asthma of only 8.2%[8] Whether this reflects a group with milder disease compared with the previous hospital-based studies is unclear.

Does premenstrual asthma influence hospital admissions? Skobeloff and colleagues[9] estimated that 75% of adults admitted to hospital for asthma were female, and that these patients required longer hospital stays than age-matched males. The authors concluded that hormonal changes might be responsible and went on to demonstrate, in a prospective study of 182 female patients with asthma, that presentation to the emergency department for acute asthma was greatest (46% of all admissions) during the perimenstrual period.[10] In contrast, a larger multicentre study of 288 women[11] found that the greatest number of emergency presentations (33%) occurred prior to ovulation. Only 21% of visits occurred in the perimenstrual period. In addition, only 13% of women with asthma reported that menstrual cycles influenced exacerbations. The discrepancy between these studies could be accounted for by differences in sample selection and methodology. However, it is important to clarify this issue and further investigation with larger numbers of patients is required.

Two case reports have highlighted that premenstrual asthma can be associated with serious morbidity and rarely mortality. Barkman[12] reported that two sisters, aged 13 and 14 years, died during

Table I. Prevalence of premenstrual asthma (PMA)

Reference	No. of pts	Study design	Prevalence of PMA (%)	Objective measures
Rees[2]	81	Questionnaire, retrospective	33	None
Hanley[3]	102	Questionnaire, retrospective	35	PEF in selected patients
Gibbs et al.[4]	91	Questionnaire, retrospective	40	PEF in selected patients
Eliasson et al.[5]	57	Questionnaire, retrospective	33	None
Agarwal & Shar[6]	100	Questionnaire, retrospective	23	PEF in selected patients
Shames et al.[7]	32	Questionnaire, prospective	28	PEF and methacholine challenge in all patients
Forbes et al.[8]	481	Questionnaire, retrospective	8	None

PEF = peak expiratory flow.

acute asthmatic attacks the day before the expected date of menstruation. Three women with severe acute asthma associated with menstruation required ventilatory support until the end of their periods.[13]

2. Pathogenesis

The aetiology and pathogenesis of premenstrual asthma are unknown. The cyclical nature of this phenomenon implies that female sex-steroid hormones have a pivotal role. The fact that the sex ratio of asthma incidence alters at puberty in females[14] and that asthma control may differ in pregnancy[15] provides further evidence for this. However, the exact mechanism by which these hormones exert their influence on asthma control is unclear.

Some of the earliest work centred on the erroneous hypothesis that those with premenstrual asthma may have been 'allergic' to endogenous hormones because of cutaneous reactions to steroid hormones.[16] As the combined oral contraceptive pill became widely available, a case report documented worsening of asthma with its use.[17] More recently, hormone replacement therapy has been implicated in a postmenopausal woman.[18] In each case, asthma improved following withdrawal of the exogenous sex steroid. Therefore, it would seem that female sex-steroid hormones have the potential to exacerbate asthma in certain susceptible individuals. In fact, the risk of developing new-onset adult asthma has been associated with the use of exogenous oestrogen therapy.[19] A prospective, questionnaire-based study was carried out in 36 094 postmenopausal nurses. The age-adjusted relative risk of developing asthma for women who reported ever using postmenopausal oestrogen was 1.49 [95% confidence interval (CI) 1.10 to 2.00] compared with women who reported never using these. This risk was dose dependent and related to duration of use.

With evidence linking sex-steroid hormones to premenstrual asthma, a number of studies investigating possible pathogenetic mechanisms have been undertaken. These are discussed in the following sections (2.1 to 2.5).

2.1 Premenstrual Syndrome

It has been suggested that premenstrual exacerbation of asthma is part of the premenstrual syndrome. Rees[2] found that more patients with premenstrual asthma had symptoms of premenstrual syndrome compared with those without. Another small study suggested that psychological factors might play an important role.[20] Eliasson et al.[5] also found an association between premenstrual asthma and symptom scores for premenstrual syndrome and dysmenorrhoea. Although neither study included an objective measurement of asthma control, they suggest that mood changes, which occur in some women premenstrually, may give rise to the subjective feeling that stable asthma is worse even though physiologically it is not altered. Alternatively, low mood may be a consequence of the morbidity associated with poor asthma control.

2.2 Menarche, Menstruation, Pregnancy and the Menopause

The sex ratio of asthma incidence appears to alter during puberty. At the age of 10 years, the ratio of asthma in girls : boys was found to be 1 : 3, whereas at 14 years, the ratio became 1 : 1.[14] However, no consistent associations have been found between premenstrual asthma and characteristics of the menstrual period.[3-5] During pregnancy, when female hormone levels are greatly elevated, no consistent pattern in asthma control can de discerned. About one-third of women improve, one-third deteriorate and the remainder have stable control.[15] However, the more severe the asthma the more likely it is to worsen during pregnancy.[21] There are at present no prospective longitudinal studies to provide information on what happens to women with asthma after natural or surgical menopause.

2.3 Prostaglandins

Prostaglandins are mediators of airway inflammation in asthma.[22] A metabolite of prostaglandin (PG)$F_{2\alpha}$, 13-14-diOH-15-keto-prostaglandin $F_{2\alpha}$, has been found to peak at ovulation and premenstrually (570 pmol/L premenstrually *vs* 192 pmol/L at ovulation; $p < 0.001$).[23] As $PGF_{2\alpha}$ is a potent bronchoconstrictor, this could conceivably trigger premenstrual asthma. This hypothesis has not been borne out by Eliasson et al.[24] who, in contrast, found a dip in premenstrual values of this metabolite (68.4pg/0.1ml follicular phase *vs* 14.4pg/0.1ml luteal phase; $p < 0.001$).

2.4 Bronchial Hyperresponsiveness

Airway inflammation is central to the pathogenesis of asthma.[25] Bronchial hyperresponsiveness (BHR) is a manifestation of this inflammatory process and is best described as an exaggerated bronchoconstrictor response to a wide variety of exogenous and endogenous stimuli. It underlies much of the symptomatology of asthma and has been recognised in the description of the disease by the American Thoracic Society.[26] BHR is expressed as PC_{20}, the concentration of bronchoconstrictor producing a 20% fall in forced expiratory volume in one second (FEV_1). As BHR correlates closely with underlying airway inflammation,[27,28] it is also a marker of the need for treatment.[29] In premenstrual exacerbations of asthma it would, therefore, be logical to expect heightened BHR and other evidence of airway inflammation. However, because the condition tends to be under-recognised and under-reported most studies have been performed in women who do not experience premenstrual exacerbations.

Tan and colleagues[30] found increased BHR to adenosine monophosphate (AMP) during the luteal phase compared to the follicular phase in 15 women with asthma. Geometric mean PC_{20} to AMP was 19.0 mg/ml during the follicular phase and 7.6 mg/ml during the luteal phase; a 2.51-fold difference (95% CI 1.19 to 5.30). As these patients had stable asthma, it is difficult to extrapolate the findings to those with premenstrual exacerbations, who might conceivably have greater changes in BHR. Other small studies found no cyclical change in spirometry or BHR to histamine[31] and methacholine.[32,33]

What could explain the differences in outcomes? One possibility is that by acting indirectly on mast cells and airway sensory nerves,[34] AMP challenge is a more sensitive discriminator of airway inflammation than histamine or methacholine, which act directly on smooth muscle. A much larger study of 107 women with asthma did demonstrate increased BHR to methacholine during the luteal phase.[35] The findings of Tan and colleagues[30] would therefore reflect up-regulation of either or both processes as a measure of increased inflammation. Another possibility is that female sex-steroid hormones may modulate adenosine receptors on mast cells through which AMP acts. Against this is the lack of correlation between changes in PC_{20} AMP and alterations in hormone levels ($r^2 = 0.17$ with oestradiol and $r^2 = 0.08$ with progesterone).[30] Other possible reasons include the differences in timing of measurements between

studies and the inclusion of women who do not have premenstrual asthma.

Interestingly, in women without asthma, exhaled nitric oxide, which is a marker of asthmatic airway inflammation,[36] shows a cyclical change with a luteal phase peak.[37] This may provide a clue to putative airway inflammatory changes in premenstrual asthma. This research needs to be repeated in women with asthma, ideally in those with objective evidence of premenstrual worsening. Interestingly, skin prick tests also show cyclical changes in weal-and-flare reaction[38] demonstrating that the effects of sex-steroid hormones are not confined to the airway.

2.5 β_2-Adrenoceptor Function and Regulation

Female sex-steroid hormones have been shown to potentiate the vasorelaxant[39] and bronchorelaxant[40] effects of catecholamines. Studies show that, compared with men, women exhibit greater systemic β_2-adrenoceptor responses to inhaled and intravenous β_2-agonists.[41,42] This effect is independent of bodyweight. These studies suggest that female sex-steroid hormones may have a facilitatory effect on β_2-adrenoceptor function.

There are cyclical changes in lymphocyte β_2-adrenoceptor function during the menstrual cycle in normal women with greater β_2-adrenoceptor density and isoprenaline responsiveness in the luteal phase when sex-steroid levels are raised.[43] The up-regulating effect is most probably mediated by progesterone rather than oestrogen.[44] This cyclical change is lost in women with asthma[30] who appear to demonstrate a paradoxical down-regulating response in β_2-adrenoceptor function when exposed to progesterone.[45] It is conceivable that altered β_2-adrenoceptor function and regulation may reduce the response to endogenous and exogenous bronchodilators, and play a part in premenstrual worsening of asthma. These studies were again carried out in patients with stable asthma. Similarly, those with premenstrual asthma do not show significant differences in β_2-adrenoceptor density and isoprenaline responsiveness at follicular and luteal phases of the menstrual cycle.[46]

3. Treatment

In order to properly manage premenstrual asthma, an accurate diagnosis is necessary. A detailed history of timing of exacerbations is essential to this end, and a diary of symptoms and PEF recordings highlighting premenstrual worsening is often invaluable.

Although as many as 40% of female patients may have premenstrual asthma, most are likely to be controlled using standard treatment guidelines.[47] Some may require an increased dose of inhaled corticosteroid or the addition of a long-acting β_2-agonist during the second half of the menstrual cycle. However, there may be a subset of women who experience significant morbidity and treatment-related complications.[48] Evidence-based treatment for these individuals is scantily reported with only two randomised controlled trials published on the subject. Studies are largely observational and results anecdotal, making it difficult to draw firm conclusions. The experimental therapies that have been tried are discussed in this section and are summarised in table II.

A remarkable response to intramuscular progesterone was reported in three women with severe premenstrual exacerbations of asthma resistant to systemic corticosteroids.[49] Treatment with intramuscular progesterone eliminated premenstrual PEF dips and allowed a significant reduction in systemic corticosteroid dose. Dosages and frequency (100mg daily in two women and 600mg twice weekly in the other) were greater than those currently licensed. It is not known whether lower and less frequent doses would be as efficacious. Interestingly, two patients were treated previously with the combined oral contraceptive pill, which did not improve asthma control.

Estrogens have also been shown to be beneficial. In an uncontrolled study, 14 women with asthma, five of whom reported premenstrual asthma exacerbations, were given a single dose of oestradiol 2mg during the luteal phase.[46] Asthma symptom

Table II. Trials of treatment for premenstrual asthma (PMA)

Reference	No. of pts	Intervention	Study design	Outcome
Beynon et al.[49]	3	Intramuscular progesterone (100mg daily, 600mg twice weekly)	Uncontrolled	Improvement in PEF, reduction in oral corticosteroid dose
Chandler et al.[46]	14 (5 with PMA)	Oral estradiol 2mg	Uncontrolled	Improvement in symptoms
Myers & Sherman[50]	3 (2 postmenopausal)	Oral estrogens 0.625mg	Uncontrolled	Improvement in symptoms, discontinuation of oral corticosteroids
Tan et al.[51]	18 (not with PMA)	Combined oral contraceptive pill	Parallel group, uncontrolled	Improvement in BHR to AMP, reduction in PEF variability
Blumenfeld et al.[52]	1	Monthly intramuscular GnRH analogue	Uncontrolled	Improvement in symptoms and FEV_1; reduced oral corticosteroid dose
Murray et al.[53]	1	Monthly intramuscular GnRH analogue	Uncontrolled	Improvement in symptoms, PEF and reduction in oral corticosteroid dose
Ensom et al.[54]	14 (7 with PMA)	Oral estradiol 2mg	Uncontrolled	No improvement
Eliasson et al.[24]	24	Oral meclofenamic acid 100mg daily	Randomised, placebo- controlled, double-blind	No significant improvement in FEV_1 and symptoms
Eliasson et al.[55]	17	Oral meclofenamic acid 100mg twice daily	Randomised, placebo-controlled, double-blind	No significant improvement in PEF and symptoms

AMP = adenosine monophosphate; **BHR** = bronchial hyperresponsiveness; **FEV_1** = forced expiratory volume in 1 second; **GnRH** = gonadotrophin releasing hormone; **PEF** = peak expiratory flow.

scores improved compared with the previous natural cycle, although the 'before and after' design of the study made it difficult to rule out the possibility that improvements occurred for reasons other than hormone administration. Another uncontrolled study found no benefit with estradiol supplementation.[54] A report of three cases found that the addition of supplemental estrogens improved asthma control and allowed the withdrawal of oral corticosteroid therapy.[50] However, two of the women were postmenopausal and the results may not be directly applicable to premenstrual asthma.

There has been interest in the use of the combined oral contraceptive pill as a treatment of premenstrual asthma. Fluctuations in BHR and PEF variability during the menstrual cycle are eliminated by its use, possibly by suppressing endogenous hormone levels.[51] In those with natural cycles, geometric mean PC_{20} to AMP increased from 18.8 to 4.7 mg/ml, a 4-fold difference (95% CI 1.25 to 13.03). However, those receiving the combined pill showed no such fluctuation with geometric mean PC_{20} to AMP remaining at 23.5 and 21.4 mg/ml, a 1.06-fold difference (95% CI 0.41 to 2.78). There have been case reports of premenstrual asthma improving[56] and worsening[57] with the combined pill. Further investigation with larger numbers in a randomised, controlled study is needed to clarify the situation.

Two case reports have demonstrated a marked improvement in premenstrual asthma with a gonadotrophin-releasing hormone (GnRH) analogue.[52,53] Clinical improvement coincided with the amenorrhoea that resulted from endogenous ovarian hormone suppression. This mechanism may also explain the benefit seen with high-dose intramuscular progesterone.[49]

As levels of 13-14-diOH-15-keto-prostaglandin $F_{2\alpha}$ fluctuate during the menstrual cycle[23] it was thought that inhibition of prostaglandin synthesis might be efficacious in premenstrual asthma. This hypothesis has not been substantiated in randomised, double-blind studies with sodium meclofenamate (meclofenamic acid), a nonsteroidal anti-inflammatory that had no significant benefit compared with placebo in terms of symptom scores and lung function.[24,55]

Other potential therapeutic strategies have yet to be explored. In view of the significant increase in AMP responsiveness seen during the luteal phase,[30] it would be reasonable to investigate the effects of theophylline, an adenosine antagonist,[58] the cromones (for example sodium cromoglycate),[59] and nedocromil,[60] all of which attenuate adenosine-induced bronchoconstriction.

4. Conclusions

Premenstrual asthma may affect up to 40% of women with asthma, although it is difficult to be certain of the exact prevalence. The aetiology and pathogenesis of the condition are also unclear. It is known that female sex-steroid hormones play a pivotal role, and there is some evidence that they may exert their influence via changes in airway inflammation or through altered β_2-adrenoceptor regulation and responsiveness. It is likely that symptoms in the majority of affected women are controlled with conventional anti-asthma treatment. For the few who experience significant morbidity, advice on therapy is inadequate and can only be taken from anecdotal, uncontrolled studies. A trial of treatment to suppress endogenous hormone production with either the combined oral contraceptive pill or a GnRH analogue may be reasonable. Larger randomised controlled studies are required to glean further information on the pathogenesis and treatment of this intriguing condition.

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