Rostrum

Perimenstrual asthma: A syndrome without known cause or cure

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Perimenstrual worsening of asthma has been documented in 30% to 40% of asthmatic women. This increase in symptoms has been backed up by increased health care use perimenstrually, as well as by cyclic variation in peak expiratory flows. The cause of perimenstrual asthma (PMA) remains unclear. Fluctuations in hormone levels, their ratios, or both are a plausible explanation but have not been demonstrated with any consistency. Influences of sex hormones on inflammation is an area of future research, as are hormone-induced changes in smooth muscle function and β-adrenergic receptors, prostaglandin levels, and fluid retention in the bronchial mucosa. In the light of the high prevalence of PMA, it is difficult to understand why there has been no randomized controlled trial of hormone therapy. Nevertheless, several case reports have suggested beneficial effects of estrogens, progestins, and their combination. In light of these positive case reports, well-designed, double-blind studies of sufficient sample size should now be performed to give treatment of PMA an evidence base. (J Allergy Clin Immunol 2003;112:271-82.)

Key words: *Asthma, perimenstrual asthma, severe asthma, sex differences, inflammation*

Abbreviations used
β_2-AR: β_2-Adrenoceptor
DHEA: Dehydroepiandrosterone
ERT: Estrogen replacement therapy
OCP: Oral contraceptive pill
PEF: Peak expiratory flow
PG: Prostaglandin
PMA: Perimenstrual asthma
PMS: Premenstrual syndrome

It has been known for a long time that some female asthmatic patients experience an aggravation of asthma symptoms during the premenstrual or menstrual phase of their cycle. This has been described by terms such as (pre-) menstrual, circamenstrual, or perimenstrual asthma (PMA). In this article we will combine the menstruation-related increases in asthma symptoms in the term PMA. Around 30% to 40% of the women with asthma who visit outpatient clinics report perimenstrual worsening of symptoms (Table I).[1-11]

One of the first studies to mention PMA was that of Frank in 1931.[12] As an example to illustrate the relationship between ovarian function and manifestations of organ dysfunctions, Frank reported on a woman with severe asthma attacks, which generally occurred just before the menstrual period. Amenorrhea was induced with a sterilizing dose of roentgen rays at the ovaries, and the asthma attacks disappeared. The patient had a severe asthma attack again 2½ years later, and the menstruation returned subsequently. Only a few more studies highlighting the association between menstruation and asthma attacks were published in the ensuing years.[1,2,13,14] In the 1980s, newer reports appeared, which documented peak expiratory flow (PEF) abnormalities in addition to increases of symptoms during the perimenstrual phase in PMA. Premenstrual PEF decreases of 35% to 40% and up to 80% from baseline were reported. Additionally, in this time period, PMA symptoms were also studied prospectively, and it appeared that many female asthmatic patients who had never been aware of menstruation-related symptoms in fact experienced them. Finally, further studies linked the existence of PMA to more severe asthma, and several case reports documented life-threatening morbidity to be associated with PMA.

More recent studies have focused on the cause and treatment of PMA. The suggestion that female sex hormones play an important role in the cause of PMA seems obvious. The underlying mechanisms through which these hormones influence asthma symptoms, however, remain unclear. The results of hormone replacement therapy or other treatment options have been reported in case reports and small series and have yielded contradictory results.

In this review we will first try to define PMA and then describe the results of objective measurements of PMA and other patient characteristics associated with PMA. We will focus on the suggested causes of PMA and then finally discuss treatments assessed for PMA and future areas of research.

DEFINITION OF PMA

There is no generally accepted definition of PMA, and most authors are not very explicit about quantitative criteria they have used to define PMA. Investigators have

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TABLE I. Prevalence of PMA symptoms in asthmatic patients

Reference	Year of publication	No. of patients	With PMA symptoms (%)	Source of patients
Rees[1]	1963	81	33	Outpatient
Wulfsohn and Politzer[2]	1964	27	74	?
Hanley[4]	1981	102	35	Outpatient/clinic
Gibbs et al[3]	1984	91	40	Outpatient
Eliasson et al[8]	1986	57	33	Outpatient
Weinmann et al[10]	1987	9	0 ?	
Juniper et al[7]	1987	30	6 (self-reported), 77 (symptom score)	?
Agarwal and Shah[6]	1997	100	23	Outpatient
Chandler et al[9]	1997	14	36 (self-reported), 71 (PEF), 100 (symptom score)	Advertisement/former participants in studies
Mirdal et al[11]	1998	10	40	Outpatient
Shames et al[5]	1998	32	28	Outpatient/advertisement

generally relied on self-reported worsening of asthma symptoms in the perimenstrual phase to distinguish between women with and without PMA, yet without specifying the exact questions used.[1,3-8,15] A decrease in PEF just before or during menstruation has been used also by several authors. Unfortunately, explicit criteria were either not given[16] or varied between 20% and 40% decreases.[9,17,18]

We have operationally defined PMA as an increase in asthma symptoms or a decrease in lung function immediately preceding or during the menstrual phase of the female cycle.

FEMALE MENSTRUAL CYCLE

To indicate the time relative to the menstrual cycle, day 1 in this article refers to the first day of menstruation (Fig 1). The menstrual cycle consists of several phases. In the first (follicular) phase, one of the primordial follicles matures in about 10 days. The level of estrogen in the blood increases and induces the pituitary secretion of luteinizing hormone into the circulation. After this, ovulation takes place around the 13th day. The follicular phase can vary in duration as a result of differences in time for a follicle to start maturing. After the ovulation, the second (luteal) phase starts in which luteinized granulosa and theca cells form the corpus luteum and produce progesterone and estrogen. The duration of this phase is remarkably constant (12-14 days). If conception does not take place, luteolysis will occur, and progesterone and estrogen levels decrease sharply (Fig 1). This will be followed by menstruation.

DIAGNOSIS

Symptom scores and use of rescue medication

Changes in asthma symptoms can be measured by means of retrospective questioning or preferably by means of prospective notation of symptom scores in diaries (Table I). Only a few studies have reported detailed symptom scores and rescue medication use (Table II).[5,7,10,15,19] Most, but not all, studies found increased perimenstrual symptoms. The studies that did not show cyclic variation in symptoms were invariably small.[5,10,19] Agarwal and Shah[6] reported that breathlessness increased perimenstrually in 96% of their population, wheezing in 52%, chest tightness in 43%, coughing in 39%, and sputum production in 13%. It is a striking observation that a number of asthmatic patients not previously aware of PMA nevertheless appear to have a significant increase in symptoms or decrease in PEF around the time of menstruation.[7,9,15] Cyclic changes in rescue medication as a marker of symptoms were found in only 1 of 4 studies assessing medication use (Table II).

Peak expiratory flow

Several groups have measured PEF during the menstrual cycle in women with PMA, although usually in small groups (Table III).[3-6,9,15-17,19,20] Premenstrual PEF reductions of 35%,[21] more than 40%,[17,21] and even 80%[22] have been demonstrated in case reports. In most studies the nadir seems to be somewhere in the last week before menstruation, with low PEFs extending into the menstruation period. Two groups have additionally described individuals with a so-called "B-pattern" of PEF decreases during the menstrual cycle (ie, a short decrease around the ovulation and a more severe decrease in the week before the menstruation).[21,23]

FEV_1

Only 5 groups have described FEV_1 measurements during the menstrual cycle in women with PMA (Table IV).[5,7,10,15,20] All the study populations were small, and in most studies, one time point in the luteal phase was compared with one time point in the follicular phase. No significant cyclic changes were found, although Shames et al[5] observed women with PMA to have a lower overall FEV_1 than patients without PMA. In the study explicitly comparing women taking oral contraceptive pills (OCPs) with those with natural cycles, no significant differences in FEV_1 were found between the 2 groups.[7]

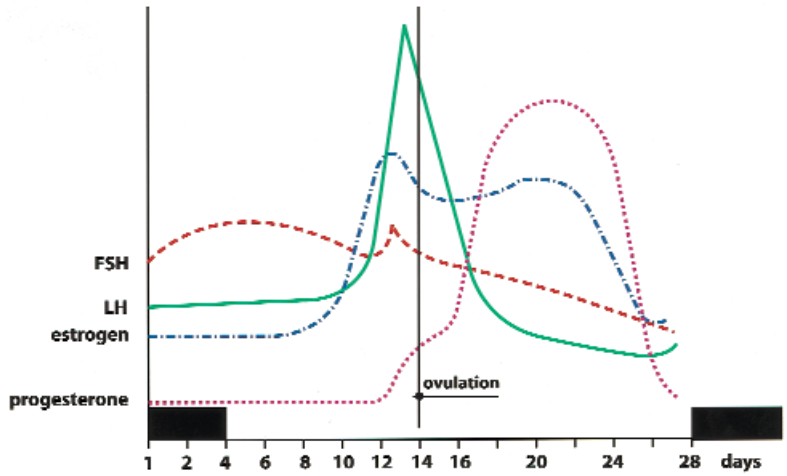

FIG 1. Course of female sex hormones during the follicular and luteal phases of the menstrual cycle. *FSH,* Follicle-stimulating hormone; *LH,* luteinizing hormone.

TABLE II. Symptoms and rescue medication use during the menstrual cycle in female asthmatic patients

Reference	Patients (n, category)	Period	Significant increase of symptoms	Increase in rescue medication
Weinmann et al[10]	9, mild disease	Whole cycle	—	—
Juniper et al[7]	10 NC, 7 OCP	A: Day +7 vs day –7;	+ (Wh+Co+Dy+Sp);	
		B: week without OCP vs last week with OCP	+ (Wh+Co+Dy+Sp)	–; –
Pauli et al[15]	10	Luteal peak (day 24-25) vs day 14-16	+ (Wh,Co,Ct,Dy)	
Chandler et al[9]	14	Day 26 vs day 13	+ (Wh,Co,Ct,Dy)	?
Tan et al[19]	9 NC/9 OCP	Day 21 to 24 vs day 1 to 4/week without OCP vs end of 21-day course of OCP	– (Wh), – (nocturnal asthma)	–
Shames et al[5]	9 PMA/20 NPMA*	Day –5 to day +5	– (Wh,Co,Ct,Dy)	+

Only studies with prospective data gathering are included.
NC, Natural cycle; *Wh,* wheeze; *Co,* cough; *Ct,* chest tightness; *Dy,* dyspnea; *Sp,* sputum production; *NPMA,* women with asthma but without PMA; *PMP,* premenstrual period.
*Comparison between groups.

TABLE III. PEF decrease (absolute) in groups of female asthmatic patients with and without PMA symptoms

Reference	Patients (n, category)	Baseline FEV_1 (% predicted)	Period	Perimenstrual PEF decrease per group
Hanley[4]	8 PMA/8 NPMA	?	Day –3 to 4 vs day 5 to 19	+/–*
Gibbs et al[3]	21 PMA/12 NPMA	?	Day –7 to –1 vs day 10 to 16	+/–*
Eliasson et al[16]	17 PMA	97		Trend†
Pauli et al[15]	11 NPMA/29 healthy	87/108	Day 24 vs day 21	–/–
Agarwal and Shah[6]	10 PMA/10 NPMA	?	Day –7 to –1 vs day 1 to 7 vs day 10 to 16	+/–*
Chandler et al[9]	14, not selected	79	Day 26 vs day 13	+*
Tan et al[19]	9 NC/9 OCP	93/93	Day 21 to 24 vs day 1 to 4/week without OCP vs end of 21-day course of OCP	No trends†
Tan et al[20]	15, not selected	94		No changes
Shames et al[5]	9 PMA/20 NPMA	73/88	Day –5 to day 5	Significant decrease in PMA compared with NPMA (morning PEF)‡
Nakasato et al[17]	5 PMA/5 NPMA	91/95	Just before-during menstruation	PMA selected for PEF decrease ≥40%

NPMA, Women with asthma but without PMA; *NC,* natural cycle.
*Change within PMA group during cycle/change within NPMA group during cycle.
†On the basis of figures; no analysis is mentioned.
‡Compared between groups.

TABLE IV. Assessments of cyclic variation in FEV_1 decrease in female asthmatic patients with and without PMA symptoms

Reference	Patients (n, category)	Days of measurements	Perimenstrual FEV_1-decrease*
Juniper et al[7]	10 NC/7 OCP	Day +7, day –7 day/week without OCP, last week of 21-day course of OCP†	–/–
Weinmann et al[10]	9	Day 7, 24	–
Pauli et al[15]	11 NPMA/29 healthy	Day 6, 24, 28	–/–
Tan et al[20]	15	Day 1-6, day 21-24†	–
Shames et al[5]	9 PMA/20 NPMA	Day –7 , +7	–/–

NC, Natural cycle; *NPMA,* women with asthma but without PMA.
*Change within first group during cycle/change within second group during cycle.
†One measurement per phase.

TABLE V. Assessments of cyclic variation in bronchial hyperresponsiveness in female asthmatic patients with and without PMA symptoms

Reference	Agent	No.	Days of measurements	Perimenstrual BHR-increase*
Weinmann et al[10]	Histamine	9 with mild asthma	Day 7, 24	–
Juniper et al[7]	Methacholine	10 NC/7 OCP	Day +7, day –7 day/week without OCP, last week of 21-day course of OCP†	–/–
Pauli et al[15]	Methacholine	11 NPMA/29 healthy	Day 6, 24, 28	–/–†
Shames et al[5]	Methacholine	4 PMA/15 NPMA	Day –7,+7	–/–
Tan et al[19]	AMP	9 NC/8 OCP	Day 21-day 24, day 1-4/ week without OCP, end of 21-day course of OCP†	+/–
Tan et al[20]	AMP	15 with stable asthma	Day 1-6, day 21-24‡	+

NC, Natural cycle; *NPMA,* women with asthma but without PMA.
*Change within first group during cycle/change within second group during cycle.
†One measurement per phase.
‡Expressed as "reactivity score."

Other lung function parameters

Several investigators have studied changes in respiratory parameters other than spirometry during the menstrual cycle. Maximal exercise response, minute ventilation, respiratory drive, and respiratory muscle endurance are all affected by the menstrual cycle. Ventilatory responses to hypercapnia and hypoxia and exercise ventilation tend to be greater in the luteal phase than in the follicular phase.[24-26] Inspiratory muscle endurance is greater in the midluteal phase than in the follicular phase in healthy women, yet the respiratory muscle strength and resting pulmonary function remain the same.[27] Interestingly, the diffusing capacity in 14 healthy women (8 with and 6 without use of OCPs) showed an 8% to 10% decrease from the week before menses to a lowest point on the third day of menses.[28] The differences could not be explained by changes in hemoglobin levels.

Bronchial hyperresponsiveness

Six studies have presented results on measurements of bronchoprovocation tests with various constrictor agents (Table V).[5,7,10,15,19,20] Only the 2 studies by Tan et al[19,20] showed significant cyclic variations in PC_{20}. A 4- and 2.5-fold increase in PC_{20} to adenosine monophosphate was found in the luteal phase compared with in the follicular phase in the asthmatic patients with natural cycles. In the 9 women using OCPs in the same studies, no cyclic variation in PC_{20} was found.[19,20] The other studies did not find significant cyclic variation in PC_{20} by using either histamine[10] or methacholine,[5,7,15] although Pauli et al[15] did find a tendency toward decrease (from 165 to 109 mg/mL) in the luteal phase. Apart from differences in bronchoconstrictor agents used, the protocols also differed as to the days that were chosen to measure PC_{20} relative to the date of menstruation (Table V).

In summary, most authors have diagnosed PMA on the basis of increased symptoms. Perimenstrual worsening of PEFs has also been documented by several groups. Changes in other lung function parameters and hyperresponsiveness have been found by some, but not by other, authors.

PATIENT CHARACTERISTICS ASSOCIATED WITH PMA

The first person to systematically describe factors associated with the occurrence of PMA was Rees in 1963.[1] He investigated differences in personality traits; neurotic symptoms; allergic, infective, and psychologic factors; and the course of menstruation between women with and without premenstrual asthma. He found that women with PMA had a longer menstruation, more premenstrual tension, and a higher incidence of allergic, infective, and psychologic factors, as assessed by a panel of specialists. We describe a number of such characteristics and their relationship to PMA.

Severity and duration of asthma

Several studies have associated the occurrence of PMA with more severe asthma.[3,5,6,8,16,17,29,30] This increased severity of asthma was reflected by more asthma symptoms and use of rescue medication,[5] lower spirometry and home PEF values,[4,5] and more severe airway hyperresponsiveness[15] at baseline. Women also have up to 3 times more frequent visits to emergency departments for their asthma than men, and this was linked to the perimenstrual phase of their cycle.[30] In line with this, PMA attacks have also been associated with frequent hospitalizations and even mechanical ventilation.[22,23,31-35] Adult women have 2 to 3 times more frequent emergency department visits and hospitalizations compared with men.[36,37] Of the emergency visits for asthma exacerbations by women, 46% took place in the perimenstrual week.[30]

Whether the occurrence of PMA has a relationship with a longer duration of asthma remains unclear because it was observed by some authors[5,6] but could not be confirmed by others.[4,8]

Allergy

A few investigators have studied the relationship between allergy and PMA but with conflicting results.[1,4,29] Interestingly, a seasonal variation of PMA (increase from April to October) was detected in one study.[38] Kalogeromitros et al[39] found cyclic changes in skin reactions to histamine and allergen, with the responses being higher on days 12 to 16 than on days 1 to 4. This cyclic variation was similar in atopic and nonatopic women and irrespective of PMA complaints. These findings on cyclic variation of histamine responsiveness were not confirmed by others when they compared day 7 with day 24.[10]

Characteristics of the menstrual cycle

The perimenstrual aggravation of asthma symptoms varies in severity and timing per cycle both between and within individuals.[3,6,16,11] The peak incidence of PMA complaints is generally 2 to 3 days before the onset of menstruation, but these complaints can occur during both the premenstrual and menstrual interval[1-3,6,16,29] and in one case even 2 days after the menstruation was over.[6] Although most studies found no relationship between the length of the menstrual cycle and the occurrence of PMA,[1,3,5] shorter[4] and longer[1] and irregular[40] cycle lengths in women with PMA have been suggested. The duration of menstrual flow has been found to be longer in the PMA group,[1] but again, others could not reproduce this result.[4] Finally, differentiation of asthmatic patients with and without PMA could not be made on the basis of age of menarche[1,5] or the course of asthma when these patients were pregnant.[3]

Use of oral contraceptives

At first thought, one might perhaps expect PMA to occur solely in menstruating women not taking the contraceptive pill and certainly not in women taking monophasic pills who have no swings in sex hormone levels. Unfortunately, many studies do not provide details of pill use. In a study by Juniper et al,[7] changes in symptom scores (but not in FEV_1 and PC_{20}) occurred both in women with natural cycles and in women taking OCPs. Tan et al[19] reported that in their population significant diurnal variation of PEF was present in women with natural cycles, whereas this variation was absent in women taking OCPs. Two small studies of women with PMA taking the contraceptive pill were unable to find differences in asthma symptoms induced by starting or stopping the pill. These data were assessed on the basis of history taking and are perhaps imperfect.[3,4] A more extensive review of studies with the effects of OCP on PMA is given in the section on therapy.

Premenstrual syndrome

Premenstrual syndrome represents a marked aggravation of the normal minimal premenstrual distress. It usually develops 3 to 7 days but occasionally as long as 7 to 14 days before the period is due and reaches a peak 24 to 48 hours before the onset of the menses. Given the fact that perimenstrual syndrome (PMS) and PMA occur in the same period of the menstrual cycle, a link between these 2 manifestations has been suggested. In most,[1,6,18,29] but not all,[3,5] studies a higher incidence of PMS was found in women with PMA compared with a control asthma group. A correlation between both dysmenorrhea and increased premenstrual syndrome scores and poorer pulmonary symptom scores was found in one study.[8] On the other hand, in a study from New Zealand, women with PMS did not consult their physician more frequently for asthma than women without PMS.[41]

Psychology

In older studies, differences in psychologic characteristics between women with and without PMA have been suggested but were not well documented.[1] In more recent and detailed work, the frequency of self-reported depression was not different between groups with and without PMA.[5] A diminished resistance to stress might also contribute to PMA.[11]

In summary, several studies of generally rather few patients have examined many patient characteristics that are postulated to be associated with PMA. From the available literature, the information to date is, however, too fragmentary to reach firm conclusions on the value of any of these characteristics. Especially conflicting are the data relating characteristics of the menstrual cycle, such as age of menarche and length or regularity of cycle, to PMA.

CAUSE

Given the well-known large swings in female sex hormones throughout the menstrual cycle, one should consider a relationship of these swings to perimenstrual aggravation of asthma. Progesterone, estrogens, or both are the

most frequently implicated hormones but other metabolites of the steroid pathway, such as dehydroepiandrosterone (DHEA), a potent androgen, might be important as well. The relationship between the hormonal swings and asthma worsening could theoretically be due to increases or decreases in hormone levels[12,42] or a change in hormone ratio.[1] Moreover, there might be a lag time between these hormonal changes and worsening of asthma.

Many authors have linked deviations in levels of specific female sex hormones, in their amplitudes or ratios, to PMA. To date, no consistent picture arises from these studies. Rubio et al[43] measured serum levels of progesterone, estradiol, and cortisol on the 5th and 21st day of the menstrual cycle in women with asthma and in healthy control subjects. In 80% of the women with asthma, at least one of the hormones was out of range. The most frequent abnormality was a decreased progesterone level during the luteal phase; asthmatic women who reported PMA were found foremost in this group. However, in 55% of them, no relationship between decreased progesterone levels and PMA could be demonstrated, and severity of asthma symptoms was not associated with the abnormal hormone concentrations. By contrast, Tan et al[20] found normal luteal increases in serum estradiol and progesterone levels in patients with PMA.

Inflammation

Female sex hormones have effects on several cells and cytokines involved in inflammation. Most, if not all, of these effects have not been tested specifically in relation to asthma or perimenstrual worsening of asthma but could nevertheless be of relevance.

It has long been recognized that peripheral blood total white blood cells counts are increased during the luteal phase of menstruation.[44,45] This is true for neutrophils, monocytes, and lymphocytes, with a reciprocal trough for eosinophils.[44-46] It seems likely that these neutrophils are released from the bone marrow[47] rather than from the marginated pool and that estrogen is the major hormone involved.[44] The increase in lymphocytes is mainly due to an increase in cytotoxic T cells and natural killer cells.[46] Of particular interest is a marked deviation of the T_H1/T_H2 balance toward T_H2 in the luteal phase in peripheral blood, as reflected by an increased IL-4 production from lymphocytes with unchanged production of IFN-γ.[46] Because this increase coincides with an increase in both estradiol and progesterone, it is unclear from this study whether the shift is due to an estrogen or progesterone effect.[46] In vitro studies focusing on T lymphocytes have thus far not helped to elucidate this: progesterone was found to increase IL-4 and IL-5 production after activation of T_H1 clones.[48] However, in other in vitro experiments, estradiol increased IFN-γ production in activated T_H cells.[49] Inflammatory cells can have positive estrogen and progesterone receptors expressed on their surface. There has been remarkably little work done in this field in the airways. In the upper airways mast cells have been found to express estrogen and progesterone receptors, but this could not be demonstrated for lymphocytes, eosinophils, neutrophils, or macrophages.[50] The decrease in serum level of progesterone just before menstruation might facilitate mast cell degranulation, although an increase in histamine levels in patients with PMA could not be demonstrated in one study.[17] Extensive mast cell activation-degranulation, as judged on the basis of extracellular tryptase, in the functionalis layer of endometrial specimens has been demonstrated just before and during menstruation.[51]

It is not always clear which sex hormones elicit the changes in inflammatory cells and activity. Specifically attributed to estrogens are increases in B-cell differentiation, decreases in T-cell suppressor activity and numbers, and increases in antibody production (IgG).[52,53] β-Estradiol augments IgE-independent secretion of histamine and serotonin in purified rat peritoneal mast cells.[54] β-Estradiol treatment of eosinophils significantly enhances eosinophil adhesion to human mucosa microvascular endothelial cells, and a combination of β-estradiol and progesterone leads to a significant increase in eosinophil degranulation.[55] Finally, Bodel et al[56] have demonstrated that estradiol and progesterone can reduce the oxidative burst after a phagocytic stimulus.

There is less documentation of the effects of progesterone on inflammation in general. In addition to the abovementioned effects on the T_H2 shift in vitro, progesterone can act as a partial glucocorticoid agonist[57,58] and, for instance, suppresses histamine release from basophils.[59]

At least one of the other corticoid hormones, DHEA, is known to have immunomodulating effects in animals and human subjects; that is, a suppressive effect of DHEA on house dust mite–induced allergic airway responses in sensitized mice has been found that was associated with a downregulation of T_H2 response.[60]

The influence of sex hormones on inflammatory cell numbers is corroborated by the cyclic variability in blood levels of cytokines and mediators involved in inflammation. Leukotriene C4 levels in serum significantly increase premenstrually at the nadir of PEF compared with the level in the midcycle week in women with PMA.[17] This did not occur in women with asthma yet without PMA complaints. No cyclic variation in levels of histamine, IL-1β, IL-6, or leukotriene B4 was demonstrated. In another study 8 women with unexplained infertility (and no asthma) showed cyclic fluctuations in TNF-α levels measured from day –4 to day 14, with a peak on day 7 to 9.[61] In 15 patients with stable asthma, serum eosinophilic cationic protein levels did not differ between the 2 phases, but all levels measured were low.[20]

Smooth muscle function and β_2-adrenoceptor receptor function

Several steroid hormones, such as progesterone, 17 β-estradiol, and cortisol, potentiate the relaxing effect of the β-agonist isoprenaline on porcine bronchial smooth muscle in vitro.[62] In rabbits, β_2-adrenoceptor (β_2-AR) density can be increased by estrogen and decreased by progesterone.[63] Lipworth et al[64] have studied human β_2-AR function in relation to sex hormones. The expected increase in sex-steroid hormones in nonasthmatic female

patients during the luteal phase was mirrored by an increase in lymphocyte β_2-AR density and in maximal cyclic AMP response to isoprenaline.[65] This upregulation is most probably the result of progesterone rather than estrogen.[66] Estrogens do not seem to have these effects on β_2-AR function and density in human subjects.[9,66] Paradoxically, this cyclic variation of β_2-AR function seems to be lost in women with asthma,[20] who instead appear to show a downregulation of β_2-AR density and cyclic AMP response when exposed to progesterone.[67] This might have implications for the bronchodilator effects of β-agonists during the menstrual cycle. β_2-AR regulation and function did not differ between the periods compared with the period without the contraceptive pill in female asthmatic patients.[68]

Fluid retention

Increased perimenstrual hydration gives rise to swelling of subcutaneous tissue of extremities and other parts or organs of the body, such as the bronchial mucosa. This might lead to edema and airway narrowing. In 1963, Rees[1] suggested that fluid retention was a possible pathophysiologic factor in PMA. In a study on factors influencing PMS-like symptoms in 134 people, women with cyclic symptoms had a greater increase in body weight in the last 5 days of the cycle than women with absent or continuous symptoms.[69] The marked cyclic decrease in diffusing capacity during the menstruation could well be due to mucosal swelling.[28] Progesterone is important in the regulation of microvascular leakage.

Autonomic disequilibrium

The parasympathetic pathway is an important determinant of bronchial tone. Estradiol has been shown to increase acetylcholine and cholinesterase activity, which lead to changes in constriction of bronchial muscle and swelling of bronchial mucosa.[1,70,71] Similarly, female hormones are suggested to influence the autonomic nervous receptors of the nasal mucosa, which might lead to increased nasal discharge and nasal mucous swelling.[72]

Prostaglandin metabolism

Several prostaglandins have putative roles in asthma, both as bronchodilators (prostaglandin [PG] E_2) and as bronchoconstrictors (PGD_2 and $PGF_{2\alpha}$). Increased inactivation of PGE_2 both during pregnancy and progesterone treatment has been found in the rabbit lung.[73] $PGF_{2\alpha}$ levels have been found to correlate with estrogen levels.

Hyperventilation

Progesterone is known to have a stimulating effect on respiration, and it enhances hyperventilation.[74]

Psychologic factors

Psychologic status is known to influence respiratory symptoms.[75] Given the fact that some women experience an increase in irritability, symptoms of depression, or general discomfort preceding menstruation,[1] this could contribute to the self-reported worsening of asthma symptoms perimenstrually.[7] Women with PMA might have a changed perception of symptoms in this period, but alternatively, emotional changes might actually influence lung function, and in extreme cases there can be emotional precipitation of attacks.

Mirdal et al[11] have found a relationship between lowered resistance to stress, lowered resistance to infection, and increased bronchial hyperresponsiveness in 10 women with moderate asthma. The release of stress hormones (catecholamines and glucocorticosteroids) is known to be influenced by emotional states. This release can induce changes in the autonomic nervous system, neuroendocrine, and/or visceral organ functions and thereby influence lung function.

Changes in medication metabolism

Estrogens have been shown to significantly alter cortisol production, clearance, and metabolism.[76,77] Progesterone has a competitive action with cortisol for the binding site of the corticosteroid-binding globulins, and estradiol enhances corticosteroid-binding globulins production. Changes in sex hormones should influence the total cortisol/free cortisol ratio. Whether estrogen, progesterone, or both also influence the effects of exogenous inhaled corticosteroids has, to our knowledge, not been investigated. Significant variation in theophylline levels caused by higher clearance during the menstrual phase compared with that during the follicular phase has been demonstrated.[78]

In summary, thus far, no clear picture has emerged regarding possible abnormalities in sex hormone levels in women with PMA, but there is a paucity of rigorous data during the full cycle of women with PMA compared with those without PMA, limiting any conclusion. Collecting these data will be an arduous task, but good data should shed important new light. The changes in inflammatory cells and especially the T_H1/T_H2 shifts accompanying the menstrual cycle are also extremely interesting. Almost all these inflammation data have been collected not from the lung but usually from blood, and data from the lung are eagerly awaited. This could be from biopsy specimens or sputum.

THERAPY

Several therapies have been tried for the treatment of PMA on the basis of different putative causative mechanisms. Given the close association of PMA with sex hormone changes, hormonal interventions have been explored more extensively, be it in case reports or small studies only. Although at least 15 studies of interventions with female steroid hormones have been reported (Table VI),[9,22,32-35,79-87] we could not find a single randomized controlled trial. Several other treatments modalities have been reported, but only the treatment with meclofenamate, a prostaglandin synthesis inhibitor, has been tested in a controlled clinical trial (vide infra).

TABLE VI. Intervention studies with female hormonal therapy in PMA

Reference	RCT	No.	Group	Therapy		Results
Waldbott and Bailey[79]	No	43	Allergic asthma	Estrogen	±	Symptoms + in a few cases
Horan and Lederman[81]	No	1	Asthma	Progestin + estrogen	↓	Suggestion of development of asthma because of pill use
Beynon et al[22]	No	3	PMA	Progestin	+	PEF +, prednisolone +
Morris[34]	No	1	PMA	Progestin + estrogen	+	Symptoms +, PEF +
Myers and Sherman[84]	No	1	Steroid- dependent asthma	Progestin + estrogen	+	Symptoms +
Gotthardt et al[32]	No	1	PMA	Progestin + estrogen	+	Symptoms +, FEV_1 +
Chandler et al[9]	No	14	PMA	Estrogen	+	Symptoms +, PEF/FEV_1 –
Ohrui et al[85]	No	1	PMA	Progestin + estrogen	+	Symptoms +, PEF +, exacerbations +
Derimanov and Oppenheimer[80]	No	1	PMA	Progestin + estrogen	↓	Symptoms ↓, PEF ↓
Lam and Huang[86]	No	1	NPMA	Progesterone	+	PEF +, prednisolone +
Matsuo et al[87]	No	1	PMA	Progestin + estrogen	+	Symptoms +, PEF +
Pride and Yuen[83]	No	2	Endometriosis and asthma	GnRH-analogue	+	Symptoms +
Blumenfeld et al[82]	No	1	PMA	GnRH-analogue	+	Symptoms +, PEF +, prednisolone +, exacerbations +
Perrin et al[33]	No	4	PMA	LH-RH agonist	+	Exacerbations +, PEF =
Murray et al[35]	No	1	PMA	GnRH-analogue	+	Symptoms +, PEF +, prednisolone +, exacerbations +

NPMA, Women with asthma but without PMA; *GnRH,* gonadotrophin-releasing hormone; *LH-RH,* luteinizing hormone releasing hormone.

Hormones

The first suggestion of an effect of hormone administration on premenstrual symptoms in allergic women was made by Waldbott et al.[79] Beynon et al[22] reported 3 patients with life-threatening PMA resistant to conventional therapy, including high-dose corticosteroids, who did respond very well to intramuscular progesterone injections. There are more case reports of large benefits from hormonal therapy, but invariably, the numbers are low. Many have reported favorable effects of progestins or progestins plus estrogens on symptoms of PMA (Table VI). Some have also documented improvements in PEF or FEV_1, but these could not be confirmed in all studies. Additionally, there have been reports of successful reductions in prednisolone dosages and exacerbation rates. However, there have been at least 2 case reports suggesting occurrence or deterioration of asthma caused by the introduction of the pill.[80,81] Although the majority of case reports show some benefit of hormonal therapy, hard evidence is lacking, as is a clear consensus on whether to use progestins alone or in combination with estrogens (Table VI).[84,88-90] The latter is perfectly in line with the absence of a unifying hypothesis on the mechanisms underlying PMA.

Some additional support of a possible advantageous effect of hormones in the treatment of PMA could theoretically be derived from case-control studies in which women taking the pill were compared with those not taking the pill.[7,19] Indeed, Tan et al[19] found that 9 asthmatic patients using OCPs compared with 9 asthmatic patients not using OCPs had attenuated cyclic change in airway responsiveness to AMP, as well as reduced diurnal PEF variability. By contrast, Juniper et al[7] found no difference in PC_{20} methacholine values according to pill use.

Four groups have described the effects of gonadotrophin-releasing hormone analogues or luteinizing hormone–releasing hormone agonists in case reports.[33,35,82,83] These drugs cause decreases in luteinizing hormone and follicle-stimulating hormone and induce hypoestrogenic amenorrhea. Three of the case reports (1-4 patients per report) suggested reductions of exacerbation rates and hospitalizations in patients with prior frequent premenstrual exacerbations.[33,35,82] The fourth report also suggested an improvement in one woman with asthma but without perimenstrual worsening of asthma.[83]

Given the association of estrogens with PMA, it is also interesting to evaluate the effects of estrogen replacement therapy (ERT) in postmenopausal women (Table VII).[84,88-90] Beneficial effects of ERT or combination therapy have been reported by 2 groups in smaller studies.[84,88] By contrast, severe exacerbations have also been reported after ERT was introduced.[89] Lieberman et al[88] demonstrated a small but significant improvement in bronchial hyperresponsiveness to histamine with ERT in 36 postmenopausal women who were otherwise healthy,

TABLE VII. Postmenopausal hormone replacement therapy

Reference	RCT	No.	Group	Therapy	Results*
Collins and Peiris[89]	No	1	Asthma +	ERT	↓ Symptoms ↓, PEF ↓
Myers and Sherman[84]	No	2	Steroid-dependent asthma	ERT	↑ Symptoms ↑
Lieberman et al[88]	No	36	Healthy women	ERT	↑ PC_{20} ↑
Lieberman et al[90]	No	15	Asthma +	ERT	↓ Symptoms =, PEF ↓

RCT, Randomized controlled trial.
*↓, Deterioration; ↑, improvement.

but they did demonstrate a small deterioration in hyperresponsiveness and β-mimetic use in a second study of asthmatic postmenopausal women.[90] Troisi et al[91] derived data from a large epidemiologic cohort study of 23,000 women with 2 years' prospective follow-up. They found that postmenopausal women who had never used ERT had a significantly reduced risk of development of asthma compared with that of postmenopausal women who were past or current users. Individuals who had used at least 10 years of ERT had twice the age-adjusted risk of asthma compared with women who had never used postmenopausal hormones. Moreover, there was a positive dose response between daily dose and asthma risk among current users of conjugated estrogens.[91]

Conventional asthma therapy

The vast majority of women with perimenstrual worsening of asthma are treated like all asthmatic patients. There is little literature as to whether conventional asthma therapy with inhaled corticosteroids and β_2-agonists is less effective in women with PMA complaints in general or during the perimenstrual phase in particular. Several case reports document incomplete response to systemic corticosteroids in the treatment of perimenstrual exacerbations.[33,34] It has to be kept in mind that selection of cases has probably been skewed to include patients refractory to conventional therapy.

Leukotriene receptor antagonists

In one open study a leukotriene receptor antagonist (pranlukast) was administered to 5 patients with PMA, showing a 40% decrease of PEF from baseline premenstrually.[17] Symptom scores and PEF improved significantly in the perimenstrual period compared with status before treatment. The baseline PEF remained the same as before treatment, and therefore pranlukast appeared to act mainly on PMA symptoms. The lack of a control group in this report necessitates further evidence.

Prostaglandin synthesis inhibitors

The only randomized placebo-controlled trial of any medication for the treatment of PMA was performed by Eliasson et al[16] with the prostaglandin synthesis inhibitor meclofenamate, in which 17 women with PMA participated. During both treatment regimens, the same perimenstrual nadir of PEF occurred. The therapy resulted in an overall trend of PEF improvement. Further analysis by segments of the menstrual cycle revealed a significant PEF increase in the early premenstrual and late menstrual period. Because there was no treatment effect on PEF during the late premenstrual and early menstrual period, overall menstrual PEF variation increased. There was no effect on relief bronchodilator use, but treatment with meclofenamate did improve total asthma symptom scores at baseline and total menstrual symptom scores (no coincidence with PEF improvement in time). These results lend no support for the use of sodium meclofenamate in women with PMA.[16]

In short, it is fair to say that there is very little if any proof of effective treatment for PMA, and randomized controlled trials of proper size should be started.

DISCUSSION

Approximately 30% to 40% of women with asthma report perimenstrual aggravation of symptoms. This figure is derived from more than 10 studies and is relatively constant across these studies. This figure concerns patients seen mostly by pulmonologists and can represent a selection bias. There is a definite need for a consensus on the definition of PMA with defined criteria for changes in PEF values and a validated symptom score.

Most studies have used retrospective questioning for PMA, yet the available prospective studies[5,7,9,18] have found approximately the same prevalence in PMA, on average around 30%. The use of rescue medication is a reflection of symptom perception and, in this way, a subjective measure as well. Reports on rescue medication are too scarce to draw inferences.

Daily PEF measurements seem to be the ideal way to obtain objective data on the occurrence of PMA. It is currently quite unclear how variable the nadir of lung function (in timing and depth) during the menstrual cycle is between women. On average, it seems fair to say that PEF starts to decrease 1 week before the menstruation in some women and 3 to 4 days before menses in most women with PMA complaints. The PEF seems to recover early during menstruation. In a few women a pattern of biphasic PEF decreases has been seen, with dips both in the midcycle and in the luteal phase.[21,23] The PEF decreases coincide roughly with the estrogen peaks but could also be related to the 2 peaks of $PGF_{2\alpha}$ metabolite levels found by Koullapis and Collins.[92]

Cyclic variation in characteristics of asthma other than symptoms and lung function have been found by some authors. Only 2 of 6 studies were able to find cyclic varia-

tion in bronchial hyperresponsiveness (Table V). Most studies are very small, with a heterogeneous patient selection. None of the 6 studies selected on the basis of the presence of PMA complaints. Another problem is the inclusion of women with natural cycles versus those using OCPs. Finally, there is a problem of timing of the measurements. Most premenstrual measurements were performed around the peak progesterone (and estrogen) levels (day 22-24, Table V), although PMA complaints are reported to start generally around day 26. Timing the tests on the day of the hormone peak might be too early to demonstrate a deterioration in lung function or hyperresponsiveness.[5,7,20] We submit that there is a need for further, well-designed studies of cyclic changes in FEV_1 and PC_{20} in women with symptoms of PMA. These studies need thoughtful patient selection and timing of measurements in the menstrual cycle, as well as sufficient sample sizes.

Mechanisms worth considering include the effects of female hormones on bronchial mucosa inflammation. The group that revealed a cyclic variation in hyperresponsiveness used AMP,[19,20] and it has been demonstrated that AMP is more sensitive to detect changes in airway inflammation than methacholine.[93,94] The ability of AMP to demonstrate cyclic changes in the lower airways might also be due to cyclic variation in hormone receptors, especially on mast cells.[50] Female sex hormones exert important effects on several inflammatory mediators and processes. Neutrophils, IL-8, and monocyte chemotactic protein 1 are under the influence of female sex hormones.[95,96] It remains to be established whether mast cells in the lung (among others) are activated in the perimenstrual period as well and whether there is a relationship with hormone receptor expression on the mast cells. An intriguing possible explanation for cyclic changes in the severity of asthma is the knowledge that the T_H1/T_H2 balance varies with the menstrual phase, shifting more toward the T_H2 profile in peripheral blood perimenstrually.[97]

PMA has not been described solely in women with natural cycles, but several changes seem to be smaller in women taking OCPs. There is a total lack of placebo-controlled trials of hormone therapy, and such studies are eagerly awaited, including greater differentiation in hormones tested, improved timing of measurement, increased sample size, and more sensitive detection methods.

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