

Premenstrual asthma and atopy markers

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Background: The frequency of atopy in women with premenstrual asthma (PMA) and its possible effect on the premenstrual exacerbation of asthma are unknown.

Objective: To analyze the relation between atopy markers (total IgE, Phadiatop, and specific IgE) and PMA.

Methods: Asthmatic women of reproductive age completed a questionnaire about respiratory symptoms and recorded peak flow during an entire menstrual cycle to be classified as asthmatic patients with or without PMA. Their asthma severity was graded according to the 2005 Global Initiative for Asthma scale. PMA was defined as a clinical or functional exacerbation ($\geq 20\%$) in the premenstrual phase compared with the preovulatory phase. Blood tests for several atopy markers were conducted for: total IgE and screening for aeroallergens (Phadiatop) and specific IgE.

Results: Blood determinations were performed in 59 asthmatic women, of whom 31 (53%) had PMA. Twenty-six patients with PMA (84%) and 12 without PMA (43%) had total IgE values greater than 100 kU/L ($P = .001$). Twenty-one patients with PMA (68%) and 14 without PMA (50%) tested positive for Phadiatop ($P = .17$). Those who were positive for Phadiatop were also tested for specific IgE. No relation was found between specific IgE and PMA; values for ryegrass (63%), olive (60%), and *Dermatophagoides pteronyssinus* (54%) exceeded 0.35 kU/L.

Conclusions: PMA seems to be closely linked to total IgE levels but not to specific allergens. The atopy affects the clinical manifestations of PMA in women of reproductive age.

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INTRODUCTION

Atopy is clearly related to bronchial asthma,^{1–3} especially in early life and midlife. Atopy can be measured by means of skin testing or by determining values of total IgE or IgE specific to certain aeroallergens. Atopy screening, which includes a mix of specific aeroallergens (Phadiatop; Phadia AB, Uppsala, Sweden),^{4,5} can be used to select patients for detailed specific IgE analysis.

At the same time, many asthmatic women of reproductive age present with a clinical or functional exacerbation in the premenstrual phase, which is defined as premenstrual asthma (PMA).⁶ The literature tends to define PMA by more or less objective criteria based on patient perception, the increase in

respiratory symptoms, or the presence of functional alterations in the premenstrual phase.⁷

The causes of this exacerbation of asthma in the perimenstrual phase are unclear. The most common causes are hormonal factors,⁸ variations during the menstrual cycle in certain substances (catecholamines, leukotriene C4,⁹ prostaglandin F2 α ,¹⁰ and, more recently, cytokines¹¹), psychological factors, a lower resistance to infections, and an increase in bronchial hyperreactivity.¹² But these do not sufficiently clarify the pathogenesis of PMA.

Few studies have analyzed the effect of atopy on PMA. Shibasaki et al¹³ discussed the case of a patient with asthmatic symptoms in the premenstrual phase but subject to evident seasonal variability between April and October. They referred to a possible relation between allergy and PMA, although their data did not seem to confirm this hypothesis. Martínez-Moragón et al¹⁴ found that asthmatic women who experience a near-fatal asthma attack on the first day of menstruation, as opposed to those who fall ill on the other days of the cycle, had double the amount of total IgE (1,071 IU/L vs 538 IU/L). Although the differences are not significant owing to data variability, these figures suggest a possible relation between total IgE and perimenstrual exacerbation of asthma.

Roby et al¹⁵ proposed a relation between symptoms linked to hormonal changes, as occurs in PMA, and the production of antibodies (IgG, IgM, and IgE) against progesterone and estrogen. They found higher levels of these antibodies in patients with symptoms related to hormone

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variations than in controls. The objectives of the present study were to analyze the possible relation between atopy markers and PMA and to determine whether the atopy is a pathogenic factor in PMA.

METHODS

The general methods and partial results of this study that refer to the prevalence of PMA according to the definition applied have been published previously.⁷ A daily register of respiratory symptoms and peak flow was kept during the menstrual cycle in a consecutive sample of asthmatic women of reproductive age at outpatient clinics in 5 hospitals across Andalusia, Spain. The exclusion criteria were pregnancy and lactation. After informed consent was obtained, data were collected on asthma severity and oral contraceptive use. Patients were asked to record their respiratory symptoms (cough, shortness of breath, wheezing, and thoracic pressure) and peak flow in the morning and evening. We define PMA from a semiojective viewpoint based partially on the methods of Eliasson et al⁶ and Ensom et al.¹⁶ We propose a scale of 0 to 3 to measure each respiratory symptom, averaged across two 6-day phases: preovulatory (days 5–10 after menstruation) and premenstrual (the last 5 days of the cycle plus the first day of menstruation).

A database was designed that, after the entry of data for respiratory symptoms and peak flow for the specific days studied, indicated whether the patient had PMA according to clinical or functional criteria (an increase of $\geq 20\%$ in symptoms or a decrease of $\geq 20\%$ in peak flow in the premenstrual phase). When calculating the variation percentage between the 2 phases, the 0.01 constant was added to the denominator in all cases to prevent the 0 denominator from blocking the variability calculation. All the women in the 2 groups, with and without PMA, underwent blood testing for atopy markers: total IgE and aeroallergen (Phadiatop) screening. The allergens in the Phadiatop mix were *Dermatophagoides pteronyssinus* (d1), an epithelium mix (Ex1) of cat, dog, and horse dander (e1, e3, and e5, respectively), perennial ryegrass (*Lolium perenne*) (g5), *Alternaria alternata* (m6), olive (*Olea europea*) (t9), *Artemisia vulgaris* (w6), *Salsola kali* (w11), *Parietaria officinalis* (w19), and London plane (*Platanus acerifolia*) (t11). Those who were positive (≥ 35 kU/L) were also tested for specific IgE. Women who were positive for the

epithelium mix were then tested individually for cat, dog, and horse dander. All the samples were extracted according to the same protocol, frozen at -80°C , and analyzed in laboratories at the Juan Ramón Jiménez Hospital in Huelva. For total IgE, Phadiatop, and specific IgE, in vitro testing was performed using a fluoroenzyme sandwich immunoassay (ImmunoCap 250; Phadia AB).

The data on PMA prevalence and atopy are presented as percentages with their 95% confidence intervals (CIs). Comparisons of mean total IgE levels in patients with and without PMA were performed by means of the *t* test, after a logarithmic transformation, to improve the normal distribution condition. The relation between PMA and testing positive for the aeroallergens, high levels of IgE, and asthma severity classification according to the 2005 Global Initiative for Asthma scale (mild intermittent, mild persistent, moderate persistent, severe persistent) were analyzed using the χ^2 test. The statistical software package used was SPSS version 17.0 for Windows (SPSS Inc, Chicago, Illinois), with $P < .05$ considered significant.

RESULTS

The initial study sample consisted of 141 asthmatic women of reproductive age; 25 were excluded for not completing the questionnaire. Of the remaining 116 women who had registered their symptoms and peak flow during a complete cycle and who satisfied the inclusion criteria, 64 consented to blood testing. Five of the 64 women had taken oral contraceptives and were excluded, leaving a final total of 59 patients to be examined in this study. The baseline characteristics of these 59 patients are given in Table 1.

Of the 59 patients, 31 had PMA (53%; 95% CI, 39.8%–65.01%). Thirty-nine patients had total IgE levels greater than 100 kU/L (66%; 95% CI, 51.62%–75.81%). Thirty-five patients were positive for the Phadiatop aeroallergen mix (59%; 95% CI, 46.48%–71.27%).

The geometric mean total IgE values (Fig 1) were 206.31 kU/L in patients with PMA and 87.99 kU/L in those without PMA ($P = .01$). The total IgE level was greater than 100 kU/L in 26 of those with PMA (84%) and in 12 without PMA (43%) ($P = .001$). Twenty-one patients with PMA (68%) were positive for the Phadiatop aeroallergens vs 14 patients without PMA (50%) ($P = .17$).

Table 1. Baseline Patient Characteristics

	Global (N = 59)	Premenstrual asthma (n = 31)	No premenstrual asthma (n = 28)	P value
Age, y				
Mean (SD)	28.9 (9.6)	27.0 (6.8)	30.6 (11.4)	
Range	14–44	17–37	14–44	.33
Weight, mean (SD), kg	63.6 (12.9)	68.6 (15.9)	59.4 (8.3)	.04
FVC% of predicted, mean (SD)	96.4 (12.1)	90.3 (5.8)	101.5 (13.7)	.06
FEV ₁ of predicted, mean (SD)	92.1 (18.4)	86.3 (12.7)	97 (21.4)	.08
FEV ₁ /FVC% of predicted, mean (SD)	79.0 (12.1)	79.1 (10.9)	78.9 (13.5)	.91

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

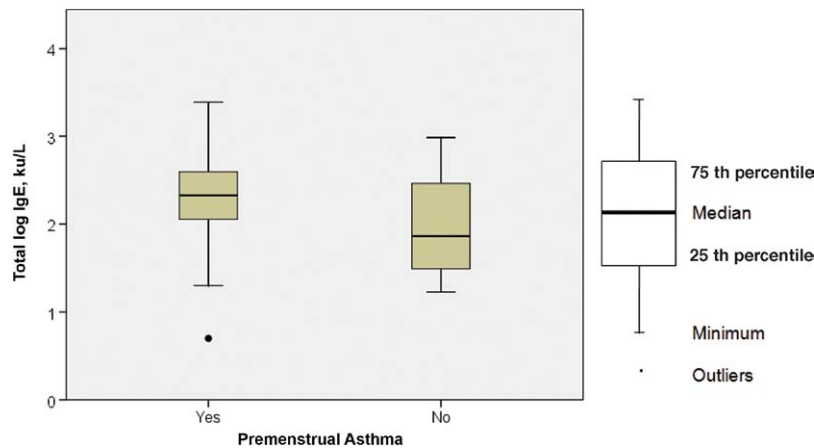


Figure 1. Total log IgE levels in women with and without premenstrual asthma.

The study of specific IgE shows which allergens tested positive the most (specific IgE level >0.35 kU/L): perennial ryegrass (63%), olive (60%), and *D pteronyssinus* (54%) (Table 2). There are no statistically significant differences between the 2 groups for any of the aeroallergens analyzed.

In women with PMA, asthma severity was mild intermittent in 6/20 (30%), mild persistent in 9/12 (75%), moderate persistent in 6/10 (60%), and severe persistent in 10/17 (59%), without a linear association ($P = .12$). The geometric mean total IgE level for all patients with and without PMA was 136.5 kU/L for those with mild intermittent asthma, 115.1 kU/L for those with mild persistent asthma, 189 kU/L for those with moderate persistent asthma, and 130.9 kU/L for those with severe persistent asthma ($P = .85$). The mean total IgE level was somewhat higher in the PMA group for all grades of asthma severity, although there were no statistically significant differences (Fig 2).

DISCUSSION

We analyzed total IgE, Phadiatop, and specific IgE values in asthmatic women of reproductive age with and without PMA.

Shibasaki et al¹³ examined a 19-year-old woman with bronchial asthma from early infancy that improved with age, regular treatment, and immunotherapy for *D pteronyssinus* (d1). After menarche, she began to show asthmatic symptoms almost exclusively during the perimenstrual cycle between April and October. The researchers performed skin tests for total and specific IgE to try to find a possible link between the allergy data and the PMA symptoms. The results were surprising. The patient was clearly allergic to d1, which implied that the symptoms were constant throughout the year. On the other hand, the concentration levels of house mites in the area did not correspond to the phase when the patient presented typical PMA symptoms. All this suggests that there was no relation between PMA and d1 allergy data.

Martínez-Moragón et al,¹⁴ in a study of near-fatal asthma attacks in women of reproductive age and their relation to menstruation, showed that these attacks occur mainly on the first day of menstruation, resulting in the need for rescue medication in the days leading up to the event. These data suggest that PMA could be the cause of the near-fatal asthma, especially in unstable asthma. The authors separated patients

Table 2. Tested Positive for Specific IgE (Specific IgE Level >0.35 kU/L)

	Patients, No. (%)			P value
	Global (N = 35)	Premenstrual asthma (n = 21)	No premenstrual asthma (n = 14)	
<i>Artemisia vulgaris</i>	9 (26)	4 (19)	5 (38)	.27
<i>Dematophagoides pteronyssinus</i>	19 (54)	12 (57)	7 (50)	.68
<i>Lolium perenne</i>	22 (63)	13 (62)	9 (64)	.89
<i>Olea europea</i>	21 (60)	14 (67)	7 (50)	.32
<i>Parietaria officinalis</i>	12 (34)	7 (33)	5 (36)	.88
<i>Salsola kali</i>	14 (40)	10 (48)	4 (29)	.26
<i>Platanus acerifolia</i>	11 (31)	7 (33)	4 (29)	.77
<i>Alternaria alternata</i>	9 (26)	5 (24)	4 (29)	.75
Screening for epithelium (+/–)	15 (43)	9 (43)	6 (43)	$>.99$
Dog	14 (93)	8 (89)	6 (100)	.99
Cat	10 (67)	5 (56)	5 (83)	.58
Horse	7 (47)	5 (56)	2 (33)	.75

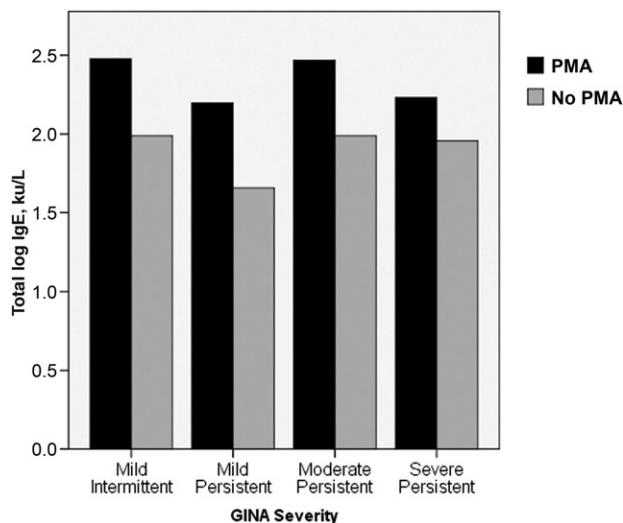


Figure 2. Mean total log IgE levels according to degree of asthma severity in women with and without premenstrual asthma (PMA). GINA indicates Global Initiative for Asthma.

who had experienced an attack on the first day of menstruation (possible relation to PMA) from the others and found that the mean total IgE level for the first group (1,071 IU/L) was almost double that of the second group (538 IU/L). Although these values show no significant differences due to data variability, they point to a possible atopic effect on the production of perimenstrual symptoms.

In this study, we found that patients with PMA had higher total IgE levels than did those without PMA (Fig 1), which suggests possible total IgE involvement in the pathogenesis of PMA. Measuring patients according to the Global Initiative for Asthma severity scale (Fig 2), those with PMA had higher total IgE values than patients without PMA at all levels of severity, although there were no statistically significant differences.

Roby et al¹⁵ highlighted the production of IgG, IgM, and IgE antibodies to estrogen and progesterone and their metabolites. According to the authors, these substances, which interacted with human tissue proteins such as albumin and globulin, may act as antigens to foment type 2 helper cells, regulating the production of antibodies and allergy. They found high levels of these antibodies in women with problems related to hormone swings, such as PMA, and put forward the possibility of future desensitization treatments. In this case, it seems that the increase in antibodies such as specific IgE against the sexual hormones might be the cause of possible PMA. In this present study, no measurement of specific IgE against the sexual hormones was taken, and although the possible effect of these specific IgE antibodies on total IgE is unknown, it is difficult to attribute the increase in total IgE levels in the present study to this mechanism.

The relation between total and specific IgE levels has been studied by various researchers and is not fully clarified.

Matricardi et al¹⁷ found similarities between total and specific IgE levels. However, Redding et al¹⁸ found that high total IgE levels in native children in Alaska were not associated with high specific IgE levels to the aeroallergens that they studied. On the other hand, Gergen et al¹⁹ found that total IgE was related to bronchial asthma only in people who had high specific IgE levels. Recently, Weinmayr et al²⁰ showed that increased total IgE levels in children with no evidence of sensitization to common aeroallergens contributed little to the risk of wheeze and rhinitis in the general population but may play a role in eczema. In short, total IgE could have a high degree of sensitivity as an atopy marker but less specificity than atopy markers based on specific IgE.

Another interesting aspect is the possible relation between hormone levels and total IgE level. Perry et al²¹ analyzed total IgE in the final 3 months of pregnancy, post partum, and 1 year after birth. They found that total IgE values increased after birth and that specific IgE values varied according to the aeroallergen involved. These data suggest certain hormonal effects on total IgE values.

If an allergic etiology was active in the genesis of PMA and was related to any of the aeroallergens tested, more women with PMA would test positive for Phadiatop. Although these results show that patients with PMA are more likely to test positive, we found no statistically significant relationship between PMA and testing positive for Phadiatop. In terms of specific IgE, none of the allergens studied seem to be present in the origins of PMA. In a sample of 17 women with asthma, there were increases in nitric oxide levels and prick test wheal sizes related to the increase in progesterone that occurs in the premenstrual phase.²² Moreover, Scott et al²³ considered that the increased levels of nitric oxide behave as a biomarker of atopy and the allergic asthma phenotype rather than of the asthma itself. In this sense, one could consider that the worsening PMA in women with PMA may have some relation to atopy.

The relation between total IgE level and asthma severity is contradictory according to data. Whereas Ozol et al²⁴ found no link between total IgE level and asthma severity in asthmatic women, Borish et al²⁵ stated that total IgE level was associated with asthma severity in young women. The present study found no direct link between asthma severity and total IgE level.

The limitations of this study include the effect of seasonal variability on blood sampling and symptoms according to the allergen involved. The study was not conducted at a specific time of year. As a result, the effect on patients' symptoms of their peak allergy susceptibility time and its coincidence with the study is unknown. However, the successive addition of asthmatic women to the study and its long duration reduce the possible effect of a specific allergen on the results. We determined specific IgE levels only to common aeroallergens (house mites, pollen, fungus, and animal dander) and not IgE against sexual hormones, as did Roby et al,¹⁵ which prevents us from making any comparison of results. An additional limitation could be in the low number of total IgE determi-

nations, specific IgE in particular, which reduces the comparability value. Bigger sample sizes would also be expected to detect greater reactivity to Phadiatop, which would be statistically significant in women with PMA.

This study finds that atopy seems to have an etiopathogenic link to PMA. This link is indicated by the total IgE marker, whereas the same link is not established by the specific IgE markers, either in the screening or with any other aeroallergen studied. The atopy does not seem to be related to asthma severity.

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