Allergol Immunopathol (Madr). 2012;40(6):368–373

Allergologia et immunopathologia

www.elsevier.es/ai

ORIGINAL ARTICLE

Premenstrual asthma and leukotriene variations in the menstrual cycle

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Received 28 July 2011; accepted 6 September 2011
Available online 23 November 2011

KEYWORDS
Asthma;
Menstruation;
Leukotriene;
Premenstrual asthma

Summary
Background: Several authors have reported an increase in leukotriene C4 in the premenstrual phase in women with severe premenstrual asthma, indicating that antileukotrienes could be used in treatment.
Objective: To analyse the role of leukotrienes in premenstrual asthma.
Methods: A questionnaire on respiratory symptoms and peak flow during one complete menstrual cycle was given to women of fertile age to define them as asthmatics who suffered from premenstrual asthma or not. Premenstrual asthma (PMA) was defined as a clinical or functional deterioration ($\geq$20%) in the premenstrual phase compared with the preovulatory phase. Blood samples to measure leukotriene C4 were taken during the preovulatory and premenstrual phases.

Abbreviations: 95%CI, 95% confidence interval; GINA, global Initiative for Asthma; IL, interleukin; LT, leukotriene; LTC4, leukotriene C4; NO, nitric oxide; PMA, premenstrual asthma.

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doi:10.1016/j.aller.2011.09.007

Results: Blood samples were taken in 62 asthmatic women, 34 of whom (54.3%) presented PMA criteria, all with a premenstrual deterioration of between 20 and 40%. There was no difference in leukotriene C4 levels between the preovulatory and premenstrual phases in the women who suffered from PMA (1.50 ng/mL vs. 1.31 ng/mL; $p = 0.32$) and those who did not (1.40 ng/mL vs. 1.29 ng/mL; $p = 0.62$). Neither were there any differences in leukotriene levels between women with or without PMA. The results were similar for each category of asthma severity.
Conclusions: Our data show that leukotriene C4 does not appear to be involved in the pathogenesis of premenstrual asthma, or support the use of anti-leukotrienes in the specific treatment of premenstrual asthma, at least in women with a moderate premenstrual deterioration. No differences appeared in any of the categories of asthma severity.

Introduction

Some asthmatic women suffer an exacerbation of their illness in the premenstrual phase, with worsening respiratory symptoms and/or peak flow levels – a condition known as premenstrual asthma (PMA). According to some studies, this deterioration could affect as many as 30% of asthmatic women.[1–5]

The factors associated to this deterioration in asthma during the perimenstrual phase are unclear. They have been related to psychological factors such as reduced resistance to stress and infections or an increase in bronchial hyperreactivity.[6,7]

Certain substances that increase or decrease during the premenstrual or luteal phase have been linked to PMA, in particular the female sex hormones, although the results are not uniform. Rubio et al.[8] noted a fall in progesterone in the luteal phase in women with PMA, while other authors found the opposite, a premenstrual deterioration due to higher levels of the same hormone.[9,10] Oestrogens have been linked to PMA both for the sharp premenstrual fall in oestradiol[11,12] and for the rise in oestrogens and progesterone in the luteal phase.[13] Other authors[14] found no differences in oestrogen and progesterone levels in the luteal phase among asthmatic women with or without PMA.

Variations in other substances during the menstrual cycle have also been related to PMA, perhaps secondary to hormonal factors: catecholamines, leukotriene C4 (LTC4),[15] prostaglandin F2a[16] and cytokines.[17]

Nakasato et al.[15] posed that leukotriene LTC4 plays a significant role in PMA aetiopathogenesis and suggest the possible use of antileukotrienes (pranlukast) for PMA to improve premenstrual asthma symptoms and peak flow values in women with PMA. Pasaoglu et al.[14] noticed that the use of another antileukotriene (montelukast) improved the premenstrual symptoms and peak flow values in 11 women with PMA, although they did not measure the leukotriene levels.

We have analysed leukotriene behaviour during the menstrual cycle in a group of asthmatic women who met PMA criteria and another group that did not, with the aim of discovering the potential role of the LTC4 in the aetiopathogenesis of premenstrual asthma as the possible basis for specific treatment with antileukotrienes.

Materials and methods

The general methodology and partial results of this work have been published previously.[18,19] In short, asthmatic women of fertile age who attended outpatients' clinics at five hospitals in Andalusia, Spain were asked to keep a daily register of respiratory symptoms and peak flow during one complete menstrual cycle. The study was approved by the hospital's ethical committee and informed consent was sought from all patients. Exclusion criteria were pregnancy and lactation, and women who took oral contraceptives were excluded from the analysis.

We used a scale of 0–3 to measure the intensity of each respiratory symptom (cough, shortness of breath, wheezing and tightness across the chest). The average points score was calculated for two six-day phases: preovulatory (Day 5–Day 10 after menstruation); and premenstrual (the five days before menstruation and the first day directly after). We defined premenstrual asthma according to a semi-objective criterion[18] based partially on Ensom[20] and Eliasson[4], in which exacerbation in the premenstrual phase is equal to or more than 20% in the scores for respiratory symptoms and/or peak flow with respect to the preovulatory phase. Asthma severity was recorded according to the GINA[21] classification. Two blood tests were taken to measure leukotriene C4 levels in the preovulatory and premenstrual phases. All the samples were extracted according to the same protocol: frozen to −80 °C and analysed at the Balagué laboratory (Barcelona, Spain) using the competitive enzyme immunoassay between the enzyme conjugate and leukotriene C4 of the sample against a limited number of union points with the antibody that covered the microtiter plates. A final reading was taken by spectrophotometry at 450 nm. Reagents (EA38) from Oxford Biomedical Research were used. With the technique applied in the determination of LTC4, cross-reactions with other leukotrienes such as LTD4 and LTE4 are only 14.04 and 7.8% respectively. The sensitivity at 80% B/Bo is 0.15 ng/ml with an assay range of 0.04–4.0 ng/ml. The inter and intra variabilities (CVs) are both less than 10%.

Non-parametric methods were used in the data analysis, given the sample size and the relatively wide dispersion of values for the leukotrienes. The changes that occurred in the leukotriene levels throughout the cycle were checked via matched analyses (Wilcoxon signed-rank test). The non-parametric Mann–Whitney test was used to compare

Table 1 Baseline patient characteristics.

	Global	Premenstrual asthma	No premenstrual asthma	*p*
Age: mean (standard deviation)	28.4 (9.3)	27.2 (6.3)	29.6 (11.7)	0.504
Range	14–44	17–37	14–44	
Weight: mean (standard deviation)	64.5 (13.9)	66.7 (15.4)	62.3 (12.3)	0.269
FVC%: mean (standard deviation)	97.5 (13.8)	93.8 (12.9)	101.3 (14.1)	0.199
FEV1%: mean (standard deviation)	92.3 (19.3)	88.4 (16.1)	96.2 (22)	0.166
FEV1/FVC % mean (standard deviation)	78.8 (12.2)	78.8 (11.3)	78.8 (13.5)	0.939

changes between the groups with and without PMA for quantitative variables. The statistical package used was the SPSS system version 19.0 for Windows.

Results

The study initially consisted of 141 asthmatic women of fertile age. The questionnaire on respiratory symptoms and peak flow was completed by 116, and of these, 67 consented to blood tests. Five women who were taking oral contraceptives were excluded from the analysis. The results are based on blood samples from 62 women to measure LTC4 levels in the preovulatory phase, leukotriene premenstrual obtained in 58 of them. Table 1 shows the baseline patient characteristics (age, weight and spirometry readings) of the cases studied.

The results reveal that 34 women with asthma (53.4%; 95%CI: 42.4–66.9%) suffered a premenstrual deterioration in symptoms and/or peak flow of ≥20%, although none reached serious levels of more than 40% (severe PMA).[15]

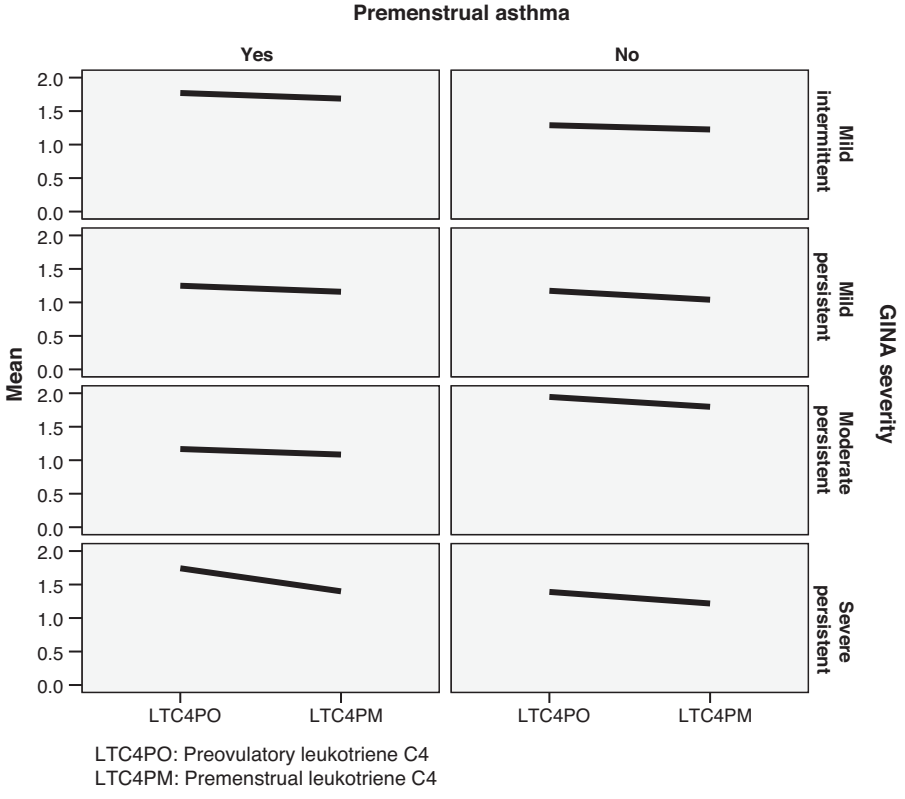

Figure 1 Evolution of leukotriene C4 between the preovulatory and premenstrual phases according to asthma severity.

The frequency of PMA did not increase with the severity of asthma: six women with PMA were mild intermittent (6/20: 30%), 12 mild persistent (12/15: 80%), seven moderate persistent (7/11: 63.6%) and nine severe persistent (9/16: 56.3%), with no linear association ($p = 0.171$), and where denominators represent the total sample at each level of severity.

LTC4 preovulatory values in the PMA group were 1.50 ng/mL (standard deviation 0.69), vs. 1.31 ng/mL (0.53) in the premenstrual phase. These differences were not statistically significant ($p = 0.32$). In the non-PMA group, LTC4 preovulatory values were 1.40 ng/mL (0.85), vs. 1.29 ng/mL (0.52) in the premenstrual phase, with the differences not being significant ($p = 0.62$).

The comparison of LTC4 preovulatory levels in PMA and non-PMA women was not statistically significant (Mann–Whitney *U* test: $p = 0.369$). Likewise, the LTC4 figures did not differ for women with or without PMA in the premenstrual phase ($p = 0.932$). The results were similar for all categories of asthma severity (Fig. 1).

Discussion

The aetiopathogenesis of premenstrual asthma is unclear. The causal mechanism of asthma deterioration in the perimenstrual phase has been related to psychological and immune factors, and particularly to sex hormone variations throughout the menstrual cycle.[6–9]

Other factors include inflammatory mediators such as leukotrienes or cytokines resulting from mast cell degranulation. Jeziorska et al.,[22] studying 107 healthy women, reported that there is a degranulation of mast cells in the endometrium in the days before and during menstruation. According to Vliagoftis et al.,[23] this is probably secondary to the variation of the female sex hormones. This suggests that the inflammatory mediators liberated by these cells could influence the aetiopathogenesis of premenstrual asthma.

Leukotrienes are inflammatory mediators that have been linked to bronchial asthma and early-phase bronchoconstriction as well as to chronic inflammation and bronchial remodelling,[24–27] although in this latter respect, authors such as Liebhart et al.[28] fail to support this hypothesis.

Nakasato et al.[15] studied the role of different cell mediators related to inflammation and premenstrual asthma in five women with ''severe'' PMA (a premenstrual deterioration of more than 40% in respiratory symptoms and/or peak flow values) and five women without PMA. Tests revealed that the levels of LTC4 in the serum in women with PMA were significantly higher in the premenstrual phase, with its exacerbation of asthmatic symptoms, than in the preovulatory. They analysed other markers (the platelet-activating factor LTB_4, histamine and the IL-1β, IL-4, IL-5, IL-6 cytokines, and GM-CSF) and found no differences between the two phases. In the five women who did not fulfil PMA criteria, no differences were found in the LTC4 levels or in any of the other parameters analysed for the two phases. The authors noted an improvement in the premenstrual asthma symptoms and peak flow of the five patients with PMA when treated with the antileukotriene pranlukast. Pasaoglu et al.[14] also saw an improvement in PMA when treating patients with another antileukotriene (montelukast).

These data led us to study LTC4 as a possible inflammatory mediator in PMA for the following reasons: this mediator, if its involvement in PMA is confirmed, can be readily and effectively treated with medication (antileukotrienes); the possibility of checking Nakasato et al.'s promising data against a larger number of patients.

Nakasato et al.[15] only selected patients with a premenstrual peak flow deterioration of >40% and a lack of clinical control over their illness with occasional hospitalisations in this period, a condition that suggests ''severe'' PMA. Our analysis did not include patients with such a high degree of premenstrual deterioration, only between 20% and 40%, so a strict comparison between the two studies cannot be made.

Regarding the latter, we would highlight the following: although PMA with the severity of those described by Nakasato et al.[15] might be most attractive to a specific treatment of PMA, the majority of them referred worsening asthma premenstrual, as we found in our study, do not reach this level of deterioration of baseline.

Another aspect to consider and which might explain the different results of our study with the study of Nakasato et al.[15] is the possibility that these asthmatics with symptomatic deterioration and worsening clear perimenstrual of peak flow values above 40% may have some pathogenic factors and/or behaviour therapy (or LTC4) different than the rest. We cannot investigate this last issue but we can indicate that the behaviour of LTC4 was similar in all levels of asthma severity.Among our patients, 57.1% were treated with anti-leukotrienes (montelukast). However, we believe that this does not change our results. Although treatment with montelukast can decrease the value of leukotrienes in blood[29] this effect should occur throughout the menstrual cycle and not only in the preovulatory or premenstrual period, specifically. We compare the preovulatory and premenstrual values in women with and without PMA.

Individual response of patients with asthma to treatment with leukotriene is highly variable, because in part, probably they are not yet well-known receptors for cysteinyl-leukotrienes LTC4, LTD4 and LTE4. Montuschi et al.,[30] reviewing the role of leukotriene in the treatment of asthma, indicated that there are at least two different receptor subtypes (CysLT 1 and CysLT2). These authors believe that LTB4 may be related to the pathogenesis of more severe asthma, with an important role in exacerbation and development of bronchial hyperreactivity. Nakasato's article and ours only analyse leukotrienes LTC4, so we cannot provide such data, but both consider that it might be a future line of research.

Although we could have looked at other types of leukotrienes (LTD4 in blood, urine or leukotriene LTE4 in sputum) in our study, we measured LTC4 to try to reproduce Nakasato's data in patients with moderate PMA (most frequent), and a larger number of patients.

Our study has analysed the variations of LTC4 in peripheral blood during the preovulatory and premenstrual phases in asthmatic women who match moderate PMA criteria and those who do not and found no clear differences between the values obtained in both groups. These data do not support the possible involvement of leukotrienes in the aetiopathogenesis of moderately intense premenstrual asthma.

Sources of funding

This study was financed in part by grants from Neumosur (7/2003) and the Health Ministry of the Regional Autonomous Government of Andalusia (0074/2005).

Conflict of interest

The authors have no conflict of interest to declare.

Author contribution

Antonio Pereira-Vega involved in the conception and design of the study and is a lead researcher, coordinator and writer of the manuscript. José L Sánchez Ramos involved in the analysis and interpretation of the data and is a supervisor of statistics and writer of the manuscript. Rosa Vázquez Oliva is a study coordinator at Hospital Infanta Elena (Huelva) and involved in the critical review of the manuscript. José A Maldonado Pérez is the writer and involved in the analysis, interpretation of the data and is a researcher at Hospital Juan Ramón Jiménez (Huelva). Jose Manuel Bravo Nieto is involved in the analysis of data, critical review of the manuscript and is a researcher at Hospital Juan Ramón Jiménez (Huelva). Ignacio Vázquez Rico is involved in the analysis and interpretation of the laboratory data and also involved in the critical review of the manuscript. José M Ignacio García is a study coordinator at Hospital Comarcal de la Serranía de Ronda (Málaga) and involved in the Critical review of the manuscript. Pedro Romero Palacios is a study coordinator at Hospital de Baza (Granada) and involved in Critical review of the manuscript. Michael Alwakil Olbah involved in the analysis of data, critical review of the manuscript and is a researcher at Hospital Juan Ramón Jiménez (Huelva). Juan Francisco Medina Gallardo is a study coordinator at Hospital Virgen del Rocío (Sevilla) and is involved in critical review of the manuscript.

Acknowledgments

The authors acknowledge Evangelina Maldonado, Jose Antonio Bernal Rodríguez (Huelva), Maria José Chocrón Giráldez, Magdalena Pinto Tenorio (Ronda), Patricia Calvo Tudela (Baza) and Pablo Pérez Navarro (Sevilla) for fieldwork coordination.

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