

REVIEW

Premenstrual Asthma and Symptoms Related to Premenstrual Syndrome

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Background. It is unclear whether premenstrual asthma is associated with premenstrual syndrome. The objective of this study is to compare premenstrual symptoms among asthmatic women according to whether they have premenstrual asthma or not. **Methods.** A questionnaire on respiratory symptoms during a single menstrual cycle was developed for asthmatics of fertile age, together with another on symptoms related to premenstrual syndrome. These included dysphoric-psychiatric symptoms (anxiety, depression, fatigue, irritability, and mood swings), edematous symptoms (abdominal and mammary tension, swelling, acne, and migraine), and other symptoms (leg pains, nausea, sweating, vomiting, and tiredness). Morning and evening peak flow scores were collected to evaluate lung function. Premenstrual asthma was determined to be a $\geq 20\%$ objective exacerbation in the premenstrual phase over the preovulatory phase in terms of both respiratory symptoms and/or peak flow. The intensity of the change in symptoms was evaluated according to the effect size. **Results.** The study examined 103 patients of fertile age, 46 of whom (44.7%) presented with premenstrual asthma. Practically all of the monitored symptoms increased in the premenstrual phase with respect to the preovulatory phase. This increase was greater in women with premenstrual asthma, especially for abdominal tension (effect size .88 against .33; $p = .009$) and mammary tension (.95 against .49; $p = .018$). **Conclusions.** A clear link was found between premenstrual asthma and the premenstrual exacerbation of dysphoric symptoms, and certain edematous symptoms such as abdominal and mammary tension as well as a swelling sensation.

Keywords: asthma; menstruation; premenstrual syndrome

INTRODUCTION

Premenstrual syndrome is defined as the cyclical recurrence of physical or psychological symptoms that appear after ovulation in the luteal phase of the cycle (1) and disappear a few days after the start of the next menstruation (2). More than 150 clinical manifestations have been attributed to the syndrome (3–5), mainly congestive edematous symptoms in terms of the physical point of view, and mood swings in the psychological.

The luteal phase displays an exacerbation of preexisting illnesses, such as bronchial asthma, acne, porphyria, epilepsy, migraine, Behçet syndrome, and myasthenia gravis (6). Premenstrual asthma (PMA), defined as an exacerbation of the respiratory symptoms and/or the peak flow scores, affects more than 30% of asthmatic women (7–9).

Studies have been performed on the relationship between asthmatic symptoms, premenstrual symptoms (physical and psychological) (10), and lung function. Agarwal et al. (8) reported that the exacerbation of asthma

during the perimenstrual phase is due to increased resistance in the airway, not just to a heightened perception of symptoms. In healthy nonasthmatic women, the variations in peak flow in relation to the menstrual cycle are minimal (11). Ensom et al. (10) found a significant correlation between respiratory and premenstrual symptoms during the menstrual cycle in the majority of women with PMA, and another important link, between peak flow scores and premenstrual symptoms, in 43% of these women. They analyzed all of the symptoms associated with premenstrual syndrome (physical and psychological), applying to them a single global score.

The aim of our study is to compare premenstrual symptoms (dysphoric-psychiatric, edematous, and others) among asthmatic women according to whether they have PMA or not.

METHODS AND MATERIALS

The general methodology and the partial results of this study that refer to the prevalence of premenstrual asthma based on the applied definition have been published previously (9). We concluded from the prior analysis of our data that clinical behavior was equivalent if we used one or two cycles, so it is probably sufficient to base the PMA

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definition on one cycle only. The methodology involves a daily record of respiratory symptoms and peak flow in asthmatic women of fertile age during the menstrual cycle taken at outpatient clinics at five hospitals in Andalusia, Spain. The exclusion criteria were pregnancy or lactation. After informed consent was given, data were collected on asthma severity, on whether the patient perceived an exacerbation in her asthma during the menstrual cycle, and if she was taking oral contraceptives. Women taking oral contraceptives were omitted from the analysis. Patients were asked to note respiratory symptoms (cough, dyspnoea, wheezing, and tightness across the chest) and morning and evening peak flow scores.

We defined PMA from the semiobjective point of view based partly on the methodologies of Eliasson et al. (7) and Ensom et al. (10). The daily presence of the symptoms studied was catalogued from 0 to 3, 0 = absence of symptoms; 1 = mild symptoms (slight interference with normal activity); 2 = moderate symptoms (interference with normal activity without impeding work or school attendance); and 3 = severe symptoms (interference with normal activity leading to absence at work, school or cancellation of appointments). A daily score index was calculated, along with an average of score indices over two 6-day periods: from 5th to 10th days (the first day being the start of menstruation), which would correspond to the follicular or preovulatory phase; and the last 5 days of the cycle, including the first day of menstruation, corresponding to the premenstrual phase. The difference between these two values was considered significant if above 20%. PMA is also considered to be when premenstrual deterioration is higher than 20% of PF values.

In addition, a questionnaire validated by Mortola et al. (12) was completed for the same menstrual cycle that covered dysphoric-psychiatric symptoms (anxiety, depression, fatigue, irritability, and mood swings), edematous symptoms (abdominal and mammary tension, swelling, acne, and cephalalgia), and other symptoms (leg pains, nausea, sweating, vomiting, and tiredness). The interpretation of each group of symptoms was made in the same way as for the respiratory symptoms, on a scale of 0 to 3, with the mean calculated for each symptom in the preovulatory and premenstrual phases. To compare the changes in each symptom, the effect size was calculated as the quotient between the difference in the means of the two phases and the joint standard deviation (D/s) (13).

A database was designed from which, after the inclusion of data on symptoms and the peak flow scores on the days studied, it was determined whether the patient met the clinical (semi-objective) or functional criteria, or both, for PMA (an increase $\geq 20\%$ in symptoms or peak flow). In order to avoid the 0 denominator in the percentage computation, which would impair the calculation of variability, the constant 0.01 was added to the denominator in all cases.

The patients were distributed among the various groups according to the Global Initiative for Asthma (GINA)

2005 scale of severity. We also evaluated the patient's perception of exacerbation in her asthma based on a *Yes* answer to the question: "Does your asthma get worse before menstruation?" This question enabled us to classify the patients' asthma as worse/not worse from the subjective standpoint.

STATISTICAL ANALYSIS

The changes between the preovulatory and premenstrual phases were analyzed in all the asthmatic women using the paired Student *t* test. The increase in symptoms between both phases was compared for women with or without premenstrual asthma via the Student *t* test for independent samples in the case of similar variance, and with the Welch test for different variance. The relation between the premenstrual increase in symptoms and asthma severity was explored using the nonparametric Kruskal-Wallis test. A *p* value $< .05$ was considered significant. SPSS v.17 was used for all analysis.

RESULTS

There were originally 141 asthmatic patients of fertile age, 25 of whom did not register their symptoms and were excluded from the study. Of the 116 remaining patients who filled in the questionnaires on the complete menstrual cycle, 13 were omitted from the analysis as they were taking oral contraceptives. The baseline characteristics of the

TABLE 1.— Baseline patient characteristics.

	Global	Premenstrual asthma	No premenstrual asthma	<i>p</i>
Age: mean	28.6	26.9	28.78	.41
(typical deviation)	(8.8)	(6.5)	(9.93)	
Age range	14–47	16–37	14–47	
Weight: mean	63.23	63.65	62.97	.84
(typical deviation)	(12.3)	(14.15)	(11.23)	
FVC%: mean	93.69	91.25	95.22	.31
(typical deviation)	(13.66)	(12.49)	(14.31)	
FEV ₁ %: mean	90.61	88.2	92.11	.45
(typical deviation)	(18.1)	(15.9)	(19.4)	
FEV ₁ /FVC%: mean	79.98	80.2	79.8	.92
(typical deviation)	(1.6)	(11.5)	(11.9)	

TABLE 2.— Preovulatory and premenstrual peak flow values, according to premenstrual asthma.

Peak flow	<i>n</i>	Preovulatory Mean (L/min)	Premenstrual Mean (L/min)	<i>p</i>
Global PMA	103	362.87	357.19	.13
Yes	46	365.81	347.14	.000
No	57	360.5	365.3	.35

Note. PMA = premenstrual asthma.

Premenstrual increase in symptoms Effect size: D/s

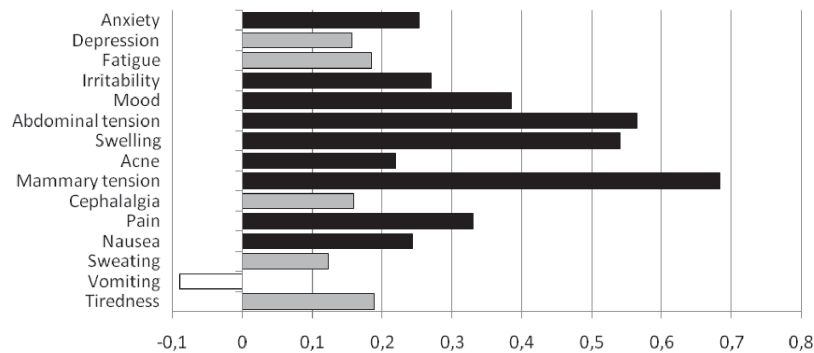


FIGURE 1.—Effect size: change in the average of each symptom between the preovulatory and premenstrual phases in relation to the standard deviation of variance. ■ : statistically significant increases. PMA = premenstrual asthma.

definitive 103 patients (age, weight, and spirometer rates) are shown in Table 1.

Those presenting with PMA criteria were 44.7% (46/103; 95% confidence interval [CI]: 35.3%–54.3%). Changes in the peak flow scores between the preovulatory and premenstrual phases are shown in Table 2. Although women with PMA exhibited worse peak flow scores in the premenstrual phase (347.14 L/min) than in the preovulatory phase (365.3 L/min; $p < .001$), only three patients deteriorated by more than 20% in the premenstrual phase, and they all fulfilled the PMA criteria for clinical exacerbation of their respiratory symptoms, so the peak flow analysis, at least on this criterion, did not provide evidence for new PMA cases.

One aim of our study was to examine the evolution of symptoms related to premenstrual syndrome, comparing the intensity of change between the preovulatory and premenstrual phases. Overall, asthmatic women experience a premenstrual increase in almost all of the analyzed symptoms related to premenstrual syndrome (Figure 1), in particular edematous symptoms such as mammary and abdominal tension as well as a sensation of swelling.

We also aimed to check whether this increase occurred in a different way in asthmatic women who had PMA and in those who did not. For those women with premenstrual asthma, there was clearly a greater increase in dysphoric symptoms (Figure 2), edematous symptoms (Figure 3),

Dysphoric symptoms Effect size: D/s

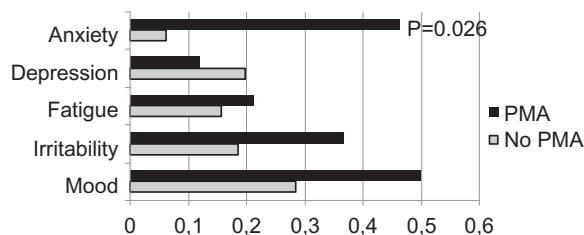


FIGURE 2.—Effect size and the dysphoric symptoms. PMA = premenstrual asthma.

Edematous symptoms Effect size: D/s

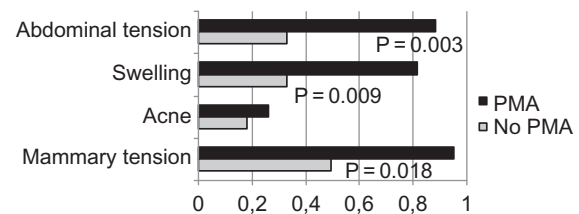


FIGURE 3.—Effect size and the edematous symptoms. PMA = premenstrual asthma.

Other symptoms Effect size: D/s

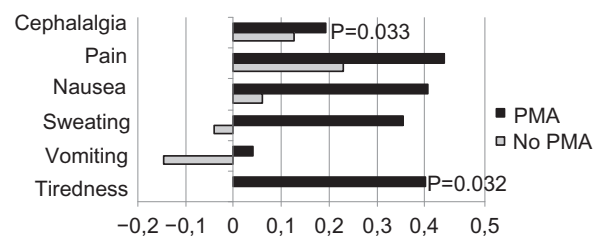


FIGURE 4.—Effect size and other symptoms. PMA = premenstrual asthma.

and other symptoms (Figure 4). The exacerbation of the majority of symptoms, especially those in the edematous group, was significantly greater in the PMA group, particularly abdominal tension (effect size D/s: .88 against .33; $p = .003$), sensation of swelling (D/s: .82 versus .33; $p = .009$), and mammary tension (D/s: .95 against .49; $p = .018$).

The subjective appreciation of the worsening of asthma, presented by 45 of the 103 women (47.3%), as indicated by an affirmative response to the question “Does your asthma get worse before menstruation?”, is closely associated with the exacerbation of specific premenstrual symptoms, particularly dysphoric-psychiatric symptoms such as anxiety and depression, abdominal tension, and

TABLE 3.— Effect size (D/s) according to the subjective recognition of premenstrual exacerbation of asthma.

	Symptoms	Worse	Not worse	p
Dysphoric	Anxiety	.44	.05	.02
	Depression	.39	−.04	.03
	Fatigue	.30	.08	.21
	Irritability	.42	.13	.07
	Mood swings	.50	.28	.16
Edematous	Abdominal tension	.77	.40	.02
	Swelling	.59	.50	.21
	Acne	.40	.05	.04
	Mammary tension	.72	.69	.12
Other	Cephalalgia	.30	.00	.08
	Leg pains	.58	.11	.01
	Nausea	.45	.02	.01
	Sweating	.19	.06	.40
	Vomiting*	−.13	−.04	.41
	Tiredness	.26	.12	.34

*A negative value means the symptom in the premenstrual phase was less intense; a positive number means the opposite.

others (Table 3). The increases in premenstrual symptoms were similar for all levels of asthma severity (Table 4). Although the premenstrual increase in abdominal tension was different at the various levels of asthma severity, there was no linear relation to asthma severity.

DISCUSSION

During the premenstrual phase, the majority of women of fertile age experience physical and/or psychological symptoms related to premenstrual syndrome. Likewise, some women with bronchial asthma suffer an exacerbation of their asthmatic symptoms and/or lung function in the luteal phase of the menstrual cycle, especially in the days leading up to menstruation and/or the days

immediately after it starts, constituting what is known as PMA. However, PMA is not considered to be indicative of premenstrual syndrome (1).

The definition of PMA varies according to studies. Whereas some authors require only a *Yes* answer to the question “Does your asthma get worse after menstruation?” (subjective criteria) (8, 14–16), others insist on a methodology for interpreting the data on symptoms reported by patients (semiobjective criteria) (7, 10), and still others demand premenstrual exacerbation be demonstrated via objective criteria, such as peak flow or nitric oxide (NO) (17, 18) (objective criteria). In addition, fulfillment of criteria can be required for one (8, 10, 19, 20) or several cycles (4). Our study defines PMA by the fulfillment of semiobjective criteria in a single menstrual cycle (9).

Few studies have investigated the relationship between bronchial asthma and premenstrual syndrome. Skrzypulec et al. (21) determined the incidence of premenstrual syndrome in girls aged from 12 to 19, with or without bronchial asthma, finding values of 20% and 46.67%, respectively, data that suggest that bronchial asthma is associated with a diminution of the prevalence of premenstrual syndrome in girls. Their study found no link between the severity of symptoms, bronchial asthma duration, treatment with glucocorticoids, and the diagnosis and intensity of premenstrual syndrome. The authors stated that their results could not be compared to either those of Ensom et al. (10), who found a high frequency of premenstrual syndrome in women with PMA, or Dorhofer and Sigmon (22), who reported greater anxiety and psychological distress in asthmatic women, as these two studies analyzed different age groups, all of which suggest that more studies are needed to clarify these results.

Our study has examined asthmatic women of fertile age whose mean age was 28.24 years. Like Ensom and Dohofer, we found an increase in practically all of the

TABLE 4.— Premenstrual increase in symptoms according to asthma severity (GINA 2005).

	Total	Intermittent	Light persistent	Moderate persistent	Severe persistent	p
No. of patients	103	39	19	16	29	
Anxiety	0.18	0.04	0.19	0.23	0.29	.66
Depression	0.08	0.06	0.09	0.06	0.06	.77
Fatigue*	0.11	0.07	0.23	−0.03	0.07	.61
Irritability	0.19	0.18	0.18	0.11	0.13	.98
Mood	0.24	0.17	0.37	0.21	0.19	.42
Abdominal tension	0.37	0.23	0.61	0.2	0.41	.035
Swelling	0.35	0.24	0.7	0.28	0.29	.08
Acne	0.12	0.06	0.08	0.32	0.19	.27
Mammary tension	0.43	0.37	0.51	0.29	0.51	.58
Cephalalgia	0.13	0.11	0.05	0.09	0.08	.96
Leg pain	0.19	0.06	0.35	0.27	0.14	.41
Nausea	0.09	0.05	0.19	0.06	0.04	.33
Sweating*	0.05	−0.02	0.13	−0.05	0.14	.24
Vomiting*	−0.01	−0.004	−0.009	0	−0.05	.72
Tiredness*	0.15	0.12	0.31	0.03	−0.006	.2

*A negative value means the symptom in the premenstrual phase was less intense; a positive number means the opposite.

symptoms related to premenstrual syndrome (Figure 1). However, we have not studied nonasthmatic women, and here we differ from the Skrzypulec study (21).

Regarding the link between PMA and symptoms of premenstrual syndrome, Ensom et al. (10) analyzed the connection between the latter, respiratory function, and asthmatic symptoms in 14 women of fertile age who were diagnosed with light chronic bronchial asthma and presented with moderate PMA criteria. Premenstrual syndrome was detected in 50% of the women with PMA. The authors show a significant link between symptoms for asthma and premenstrual syndrome in 10 of the women, and an important connection between peak flow and symptoms of premenstrual syndrome in six of them. Our study divides the symptoms related to premenstrual syndrome into three groups (2, 5): dysphoric-psychiatric, edematous, and others of different origin. PMA was related to these symptoms in all three groups. The connection to dysphoric-psychiatric symptoms can be explained by the known relationship between asthma and psychosomatic factors, with PMA considered both from the semiobjective (Figures 2–4) and subjective perspectives (Table 3).

On the other hand, we believe that the link found between PMA and the edematous group of symptoms may originate in the generalized edema seen in the luteal phase of the menstrual cycle. In the case of PMA, an edema of the bronchial mucus may occur, which would imply an exacerbation of the asthma in the premenstrual phase.

Dorhofer and Sigmon (22) have analyzed the link between asthma severity and the symptoms related to premenstrual syndrome. The authors demonstrated a greater incidence of anxiety and psychological changes in women whose asthma symptoms and/or peak flow deteriorate in the premenstrual phase. Our study, however, found no relation between asthma severity and the symptoms of premenstrual syndrome (Table 4).

The limits of our research are typical of transverse studies, as it analyses relationships but cannot differentiate between cause and effect. Although we have not included tobacco consumption, its effects on the symptoms would occur throughout the entire menstrual cycle and not just in the premenstrual phase. Neither have we included the use of aspirin and nonsteroidal anti-inflammatory medication. The use of these as treatment for premenstrual symptoms could exacerbate respiratory symptoms. However, Eliasson et al. (23) show that this theoretical effect would occur in the preovulatory phase but not in the premenstrual phase. Nor have we defined premenstrual syndrome; instead, during the course of the cycle we closely examined the evolution of some of the symptoms that form part of it. This methodology does not allow us to compare our study to others published previously, and there is no common definition of premenstrual syndrome in studies on the links to asthma. The method used to record the symptoms related to premenstrual syndrome is validated, and is reliable as an instrument applicable to clinical and some

research settings (12). The influence of potential allergens as triggers to justify the symptoms is not fully known. However, the study was conducted over an extended period of time, and not at a specific time, so that the influence of a particular allergen should not be decisive.

The treatment of asthma could be a confounding factor that impedes clarification in the study of the relation between PMA and premenstrual symptoms. A confounding factor must meet three criteria: (a) the treatment is a factor associated to PMA; (b) the treatment is a risk factor in premenstrual symptoms; and (c) the treatment is not a link in the “causal” chain between PMA and premenstrual symptoms. With regard to the first point, the treatment would be the same *a priori* for women with or without PMA, except in the use of stronger rescue medication during the premenstrual phase. The level of asthma severity (GINA), which *would* condition the base treatment, not associated to PMA (9) or premenstrual symptoms. The second point is more controversial. The possible effect of treatment as a factor that increases premenstrual symptoms would be limited to the possible increase in irritability linked to a greater use of β_2 -agonists. This symptom is not significantly associated to PMA. In terms of anxiety, there are doubts about whether this is caused by the medication or precisely because of the increase in the respiratory symptomatology. The use of β_2 -agonists would not justify the other associations detected: abdominal tension, sweating, mammary tension, cephalalgia, or tiredness. Therefore, we believe that the treatment of asthma is not a confounding factor in this context.

Our conclusion is that there exists a relation between PMA and symptoms associated with premenstrual syndrome. We have found a clear link between PMA and the psychopathological sphere, as shown by symptoms such as depression and anxiety, and certain edematous symptoms, such as abdominal tension, mammary tension, and the sensation of swelling. Our data suggest a common ethiopathogeny for both sets of clinical symptoms; in this case, a future line of investigation could be the study of this mechanism regarding a common treatment for the two sets of symptoms.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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