

Near-fatal asthma related to menstruation

Eva Martínez-Moragón, MD, PhD,^a Vicente Plaza, MD, PhD,^b José Serrano, PhD,^b Cesar Picado, MD, MPH,^c Juan Bautista Galdiz, MD, PhD,^d Antolín López-Viña, MD, PhD,^e and Joaquín Sanchis, MD, MPH,^b on behalf of the Spanish High Risk Asthma Research Group* Valencia, Barcelona, Baracaldo, and Madrid, Spain

Background: Menstruation has been suggested as a possible trigger of near-fatal asthma (NFA), but the evidence supporting this association remains weak.

Objective: We sought to assess the role of menstruation as a contributing factor in the development of NFA episodes in women of reproductive age.

Methods: Forty-four female patients of reproductive age with near-fatal attacks were enrolled in a multicenter study. Data on patient and clinical characteristics were collected. We also performed spirometric and allergy studies when the patients were in stable condition.

Results: Significantly more NFA episodes were observed on the first day of menstruation (11 [25%] patients) than on the remaining days (33 [75%] patients, $P = .022$), and patients who presented for care on the first day of menstruation used more inhaled salbutamol as rescue medication (9 [9.5] vs 1.8 [3.7] $\mu\text{g/d}$ during the 7 days before the asthma exacerbation, $P = .003$).

Conclusion: Menstruation might act as a contributing factor in the development of NFA episodes in patients with unstable asthma. Specific recommendations should be included in educational programs, and the self-management plans of asthmatic women of reproductive age should include the systematic recording of their asthma symptoms and pulmonary function in the perimenstrual phase. (*J Allergy Clin Immunol* 2004;113:242-4.)

Key words: Asthma, near-fatal asthma, asthma exacerbation, menstruation, female sex

Menstruation has been implicated in worsening asthma in women of reproductive age since as early as 1938.¹

Abbreviation used

NFA: Near-fatal asthma

A more recent study has observed that asthma is more severe in women who report perimenstrual asthma than in women whose asthma does not worsen near menstruation.² The incidence of asthma exacerbation is high (4-fold) during the perimenstrual days,³ and menstruation has been suggested as a possible trigger in fatal or near-fatal asthma (NFA).⁴⁻⁶ The evidence supporting this association remains weak, however, because much of it is drawn from isolated clinical observations,⁴⁻⁶ and prospective studies analyzing the risk factors predisposing to NFA episodes in defined populations have sometimes failed to demonstrate a relationship.⁷ In a large group of patients with severe asthma exacerbations, Barr et al⁸ concluded that the severe attack could have been aggravated by menstruation in only 16 (1.7%) patients, but no information was provided with respect to the number of women of reproductive age included in the study. Because further prospective studies with large series of patients are needed to evaluate the hypothesized relationship between asthma exacerbation and menstruation, we aimed to assess its possible role as a contributing factor in the development of NFA episodes in women enrolled in the Spanish Multicenter Study of High Risk Asthma.

METHODS

Data were collected from April 1997 through March 1999 for the Spanish Multicenter Study of High Risk Asthma, the details of which have been published elsewhere.⁹ This cross-sectional, descriptive, hospital-based, multicenter study enrolled patients in participating Spanish hospitals who had a fatal attack or an NFA exacerbation. One hundred twenty-eight cases of NFA in women were identified for the purpose of the present study; data for 44 women of reproductive age (after menarche and before menopause) were included in the final analysis. None of them died as a consequence of the asthma crisis.

NFA was defined as a severe exacerbation with at least one of the following events: respiratory arrest, need for mechanical ventilation, PaCO_2 of greater than 50 mm Hg, and pH of less than 7.30. The variables analyzed were grouped under the following headings. The first was *demographic characteristics*. The second heading was *characteristics of chronic asthma during the previous 12 months*,

From ^aSección de Neumología, Hospital de Sagunto, Valencia; ^bthe Departament de Pneumologia, Hospital de la Santa Creu i Sant Pau, Barcelona; ^cServei de Pneumologia i Allèrgia Respiratòria, Hospital Clínic, Barcelona; ^dServicio de Neumología, Hospital de Cruces, Baracaldo; and ^eServicio de Neumología, Hospital Universitario Puerta de Hierro, Madrid.

*See the Appendix for the members of the Spanish High Risk Asthma Research Group.

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Reprint requests: Vicente Plaza, MD, PhD, Departament de Pneumologia, Hospital de la Santa Creu i Sant Pau, Sant Antoni M. Claret 167, 08025 Barcelona, Spain.

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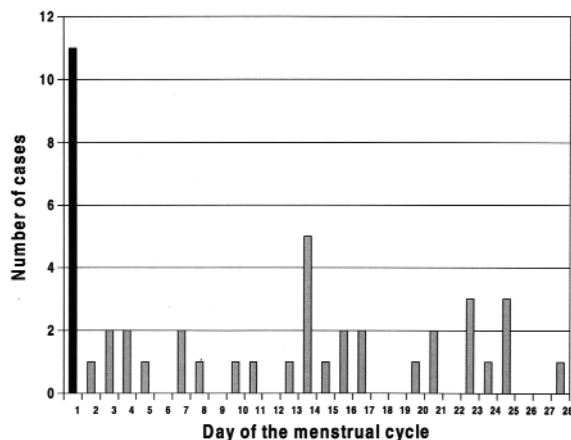


FIG 1. Women experiencing an NFA episode on the first or other days in the menstrual cycle. A significant cluster of NFA episodes occurred on the first day of menstruation (11 patients, 25%; $P = .022$).

including morbidity variables, asthma severity (according to the Global Initiative for Asthma¹⁰) before the NFA, and antiasthmatic drugs used (regular use of inhaled corticosteroids was assumed when patients had been using them daily during the previous 12 months), with such information coming from previous hospital records or, if records were unavailable, from the patient or a relative. The dose of salbutamol inhaled in the 7 days before the NFA episode was obtained by asking the patients how many puffs of salbutamol they had inhaled per day during the 7 days before hospital admission and then converting the mean of the number of puffs into micrograms per day. The third heading was *characteristics of the NFA crisis*, including probable trigger (acute bronchial infection was defined as a patient temperature of $>37^{\circ}\text{C}$ and the presence of cough, purulent sputum, or both), clinical data, arterial blood gases, and day of the menstrual cycle when the NFA brought the patient to the emergency department. The fourth heading was *course of the NFA*, including days or hours of hospitalization and whether mechanical ventilation was needed. The fifth and final heading was *studies performed in stable condition*, including tests after discharge and while a patient was receiving between 5 and 15 mg daily of oral prednisone, such as spirometry before and after salbutamol inhalation, skin prick tests (for *Dermatophagoides pteronyssinus*, grass and tree pollens, *Parietaria judaica*, cat and dog dander, soybean dust, and *Alternaria* species), and ELISAs (UNICAP; Pharmacia, Uppsala, Sweden) to determine total IgE levels.

The sample was distributed into 2 groups according to the menstrual cycle day (either the first day or any other day) on which the NFA episode occurred. The results from the 2 groups were compared with the χ^2 or Fisher exact tests for qualitative variables and either a t test or a Mann-Whitney U test for quantitative variables, depending on their distribution. A P value of less than .05 was considered significant. The analyses were carried out by using the Statistical Package for Social Science software (SASS Inc, Chicago, Ill).

RESULTS

Significantly more NFA episodes were observed on the first day of menstruation (11 [25%] patients) than on the remaining days (33 [75%] patients, $P = .022$, Fig 1). A nonsignificant ($P = .391$) peak of 5 cases was also observed on day 14, coinciding with ovulation.

Table I shows the clinical asthma characteristics, NFA course, and follow-up studies performed in the 11 women with a mean age of 29 (SD, 11) years who experi-

TABLE I. Clinical asthma characteristics, course, and follow-up studies performed on women distributed into 2 groups according to the menstrual cycle day (first vs any remaining day) on which the NFA crisis developed

	First day (n = 11)	Remaining days (n = 33)	P value
Asthma characteristics			
Moderate-to-severe asthma, %	81	69	NS
No. of hospitalizations for asthma in the past year per patient	0.41 (0.9)	0.22 (0.6)	.062
Regular use of inhaled corticosteroids, %	73	34	.056
Salbutamol inhaled in the previous 7 days, $\mu\text{g/d}$	9 (9.5)	1.8 (3.7)	.003
Clinical characteristics and course of the NFA crisis			
Trigger suspected of the NFA, %			
Unknown	7 (64)	16 (49)	NS
Respiratory infection	3 (27)	10 (30)	NS
NSAID intake	1 (9)	0	NS
Other	0	7 (21)	NS
Tracheal intubation required, %	82	48	.085
pH	7.08 (0.12)	7.17 (0.12)	.061
PaCO_2 , mm Hg	76 (16)	66 (22)	NS
Days in hospital, median	8.6 (3)	13.4 (14)	NS
Hours of mechanical ventilation, median	26 (29)	56 (164)	NS
Studies performed after the NFA episode			
Total IgE, IU/mL	1.071 (1.571)	538 (739)	NS
Positive skin prick test response,* %	91	78	NS
FEV_1 , % of reference value	78 (16)	84 (21)	NS
ΔFEV_1 postBD, %	5.1 (6)	7.4 (6)	NS

Values are means unless indicated as percentages, with SDs between brackets. NS, Not significant; NSAID, nonsteroidal anti-inflammatory drug; ΔFEV_1 postBD, percentage FEV_1 increase after inhaling salbutamol.

*Response to at least one of the common allergens tested.

enced NFA on the first day of menstruation and in the remaining 33 women aged 31 (SD, 9) years who experienced attacks on any other day in their cycle. Patients whose attacks were on the first day had used more rescue medication (inhaled salbutamol; $P = .003$) on the 7 days before the asthma exacerbation than had the other women. Women whose attack occurred on the first day also tended to have a history of more severe asthma ($P < .10$ for prior hospitalizations and regular inhaled steroid use) and more severe NFA episodes ($P < .10$ for intubations and acidosis). Similarly, although the mean IgE level for the group experiencing NFA on the first day of the cycle was 2-fold higher than the mean of the other group, the great dispersion of results for those patients meant that the difference was not statistically significant.

DISCUSSION

To our knowledge, this is the first study associating menstruation and NFA conducted in a large group of patients. Menstruation was not the isolated trigger of the cases of NFA studied, but it appears to be a contributing factor in patients whose asthma was unstable, as suggested by their increased use of rescue medication in the days preceding the NFA. Tendencies were observed in some

clinical variables in women with first-day menstrual NFA, suggesting that these patients had more severe asthma before the NFA (number of patients taking regular inhaled corticosteroid therapy and hospitalizations for asthma in the previous year) and during the NFA itself (pH level and frequency of tracheal intubation) than were women with cases of NFA starting on other days. Our findings are consistent with those of Shames et al,² who observed greater asthma severity, increased use of rescue medication, and decreased morning peak flow rates in patients with self-reported perimenstrual exacerbations of asthma in comparison with patients without self-reported perimenstrual asthma. Such observations, like ours, appear to distinguish a patient group with a tendency toward more severe asthma before a case of NFA and more severe NFA, even though our findings contrast with those of a population-based study by Mitchell et al¹⁷ in which menstruation was not identified as a precipitating factor of severe asthma attack. Differences between the disease severity in our patients with NFA and those in the broader population of asthmatic patients studied by Mitchell et al, as well as differences in how data on menstruation were collected, might account for the discrepancy.

The mechanisms of the worsening of asthma symptoms in relation to menstruation remain unexplained. Psychologic features, the intake of nonsteroidal anti-inflammatory drugs, and changes in estradiol levels, progesterone levels, or both have been suggested. Sex hormone swing and worsening asthma can be due to increases or decreases in these hormone levels. However, there is a time lag between the decrease in hormonal levels and worsening asthma. Even though female sex hormones have effects on several cells, cytokines, and leukotrienes involved in asthma inflammation,¹¹ their relationship is uncertain. Another hypothesis can be made on the basis of our observation of increased use of salbutamol in the days before the NFA episode in the women we studied. Short-acting β -adrenergic agonists reduce the numbers of β -receptors available on many cells, including circulating leukocytes.¹² This long-lasting effect leaves these cells without the homeostatic control of circulating epinephrine, could reduce the responsiveness to exogenous β -adrenergic medications, and could promote inflammation because increased cyclic AMP dampens processes involved in airway inflammation in several relevant cells, such as lymphocytes and eosinophils.^{13,14} Likewise, some studies observed a loss of the cyclic variation of β -receptor function during the luteal phase¹⁵ and a down-regulation of the lymphocyte β -receptor density and cyclic AMP response when exposed to progesterone in female patients with asthma.¹⁶ As described above, this downregulation of β -receptors could lead asthmatic women to have severe asthma exacerbations.

A possible limitation of the study is the lack of information regarding menstrual history or oral contraceptive use, but the present study is part of a larger description of clinical characteristics of fatal asthma and NFA,⁹ and we did not collect specific gynecologic data. A prospective study, including these variables, should be designed.

In conclusion, in the present study 25% of reproduc-

tive-aged women experiencing NFA had their exacerbation on the first day of menstruation. Women with asthma that worsens during menstruation should be on the alert to prevent NFA episodes. Specific recommendations should be included in educational programs, and these women's self-management plans should probably include the systematic recording of their asthma symptoms and pulmonary function in the perimenstrual phase.

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APPENDIX

Spanish High Risk Asthma Research Group: J. Abal, J. Ancochea, J. Armengol, S. Bardagí, J. Barrio, J. M. Benítez, J. Botey, E. Chacón, N. Cobos, F. J. Cosano, A. de Diego, A. Escribano, J. B. Gáldiz, G. García-Hernández, I. González-M, E. G. Pérez-Yarza, J. L. Heredia, J. Izquierdo, J. Korta, A. López-Viña, P. Martín Escribano, J. J. Martín-Villasclaras, E. Martínez-Moragón, R. Melchor, J. M. Merino, J. de Pablo, M. Perpiñá, C. Pellicer, C. Planell, J. Ramos, R. Sánchez-Gil, J. Serra, and B. Sureda.

Scientific Committee: S. Bardagí, A. de Diego, E. González-PY, A. López-Viña, J. de Pablo, C. Picado, V. Plaza, J. Sanchis, and J. Serrano.