
Clinical differences among women with and without self-reported perimenstrual asthma

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Background: Studies suggesting that 30% to 40% of asthmatic women report significant perimenstrual (late luteal phase) exacerbations of asthma are primarily retrospective, rely on subjective findings and do not demonstrate a consistent association between asthma and the menstrual cycle.

Objective: In this exploratory analysis, women with and without self-reported perimenstrual exacerbations of asthma (PMA) were examined prospectively to determine the association between asthma and the menstrual cycle and to characterize associated clinical factors.

Methods: Thirty-two adult asthmatic women with regular menstrual periods recorded daily asthma symptoms, medication use, and peak expiratory flow rate (PEFR) over six consecutive menstrual cycles, and underwent spirometry and methacholine bronchoprovocation during the luteal and follicular phases of 2 cycles.

Results: Nine of 32 subjects (28.2%) reported PMA. Daily means of rescue medication use and AM peak flow computed for each perimenstrual day demonstrated significant non-parallelism of group profiles; subjects with PMA had increasing inhaled short acting beta 2-agonist use and decreasing AM peak flow rates during the perimenstrual interval. Luteal-follicular phase differences in FEV₁ or methacholine bronchoprovocation between the groups were not detected. Subjects with PMA were older ($P = .007$), had longer duration of asthma ($P = .039$), and increased baseline asthma severity ($P = .076$) compared with subjects without PMA.

Conclusion: The findings of this study suggest that women with self-reported perimenstrual asthma demonstrate perimenstrual differences in rescue bronchodilator use and AM peak flow and appear to constitute a distinct subset of women with asthma who are older, have longer duration of asthma, and increased severity of asthma compared with women without self-reported perimenstrual asthma. These factors identify women who require close monitoring of their asthma during their menstrual cycles.

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INTRODUCTION

Asthma ranks among the most common chronic diseases in the United States, affecting 10 to 12 million individuals with trends toward increasing prevalence and severity.¹⁻⁵ While the precise reasons for this trend are un-

clear, the task of identifying high risk subgroups remains an important focus in the evolving understanding of asthma and the management of patients with the disease.

Sex differences may be an important determinant in the natural history of asthma.⁶⁻⁹ While the prevalence of asthma prior to the onset of puberty is greater in males, females appear to "catch up" after puberty suggesting a possible influence of the onset of menstruation.¹⁰ In general, the prognosis for asthma in women is worse than for men with increased asthma-associated hospitalization and morbidity after age

40 in women.¹¹ Women often experience changes in the character of asthma symptoms during early reproductive years, pregnancy, and menopause. A subset of asthmatic women experience significant exacerbations of their asthma at or near the time of menses.¹²⁻¹⁷ Skobeloff et al¹⁸ recently reported a 4-fold increase in asthma presentations to an emergency room during the perimenstrual interval, when serum estradiol levels decrease sharply after a prolonged peak. Finally, case reports of significant asthma morbidity and mortality in relation to the menstrual cycle provide additional evidence to suggest that asthma tends to be circamenstrual in some women.¹⁹⁻²²

Studies of the nature of perimenstrual asthma are generally inconclusive and suffer from retrospective study design, fail to demonstrate or examine objective changes in airway function, and inconsistently assess the association between asthma symptoms and the menstrual cycle.^{12,13,15-18,23,24} Several studies focus on the association between asthma symptoms or changes in airway reactivity during the menstrual cycle without regard to whether these women are symptomatic during the perimenstrual interval.^{23,24}

In the present study, a prospective, exploratory examination of women with and without self-reported perimenstrual exacerbations of their asthma was conducted in order to determine whether there was evidence of a true association between asthma and the menstrual cycle and to determine the factors that were associated with women who reported perimenstrual asthma. Improved characterization of these patients will lead to the increased recognition and development of spe-

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cific interventions for this high risk subgroup of asthmatic women.

METHODS

Design

Prospective, parallel-group, descriptive design.

Sample

Non-smoking asthmatic women age 18 to 50 years with regular menstrual cycles between 26 to 35 days in duration during the 6 months prior to enrollment in this study and at least weekly asthma symptoms over the 4 weeks prior to enrollment that required inhaled bronchodilator use were recruited from the University subspecialty asthma/allergy clinic, and poster and newspaper advertising to participate in the study. Subjects were enrolled with a wide range of asthma severity best characterized from mild persistent to severe persistent disease.¹ Subjects with irregular menses, menopause, pregnancy, breastfeeding, chronic lung or heart disease, and those with regular use of non-steroidal anti-inflammatory drugs (NSAIDs) or hormonal contraceptive use were excluded during the screening period of the study. The subjects were not told that the study was specifically examining perimenstrual asthma worsening, but rather that a study was being conducted to determine the relationship of asthma to the menstrual cycle. All subjects granted informed consent and completed a baseline asthma questionnaire to assess demographics and clinical characteristics of their menstrual and asthma history including the presence or absence of specific triggers of their asthma, a physical examination and spirometry with and without bronchodilator. Subjects were categorized as reporting perimenstrual exacerbations of asthma (PMA) or reporting no perimenstrual exacerbations of asthma (NPMA). Subjects were identified by number and the investigators were blinded as to each subject's group. The study was approved by the Committee on Human Research of the University of California, San Francisco.

One hundred fifty subjects were screened to enroll 59 subjects who met the enrollment criteria. Twenty-nine subjects completed the study (defined as completing at least 6 cycles of diary data and at least one paired spirometry and/or bronchial provocation). Three additional subjects completed 6 diary cycles but did not complete spirometry or methacholine challenge (due to non-adherence to study protocol) and were included in the analysis of baseline clinical characteristics and diary recording. Thirty subjects dropped or failed to complete the protocol for the following reasons: inability to maintain contact with subjects despite repeated attempts by mail or telephone ($n = 8$), subjects having inadequate time to participate in the study ($n = 6$), personal reasons (not given) ($n = 3$), changed geographic location ($n = 1$), irregular menses ($n = 4$), primary doctor refused ($n = 1$), normal spirometry and bronchial provocation ($n = 2$), refused bronchial provocation ($n = 3$), or became pregnant ($n = 2$).

Measures

Symptom/Medication Diaries

Subjects were issued weekly diary cards to record daily symptoms of asthma (on a 10-point scale), nighttime asthma symptoms, emergency room (ER) or acute care visits for asthma, hospitalization, presence of respiratory infection, missed school or work due to asthma, medication use, menstrual calendar and twice daily peak expiratory flow measurement over 6 consecutive cycles. The diary used a 10-point numerical rating scale based on a visual analog scale that has been previously validated.^{25,26} Subjects were asked to record a daily symptom score for four symptoms of asthma: wheezing, cough, shortness of breath, and chest tightness. Subjects were instructed to record the best value of three peak flow measurements upon awakening and before retiring in the evening prior to medication use. An initial 2-month period was used to exclude non-compliant subjects and those with irregular menstrual cycles.

Non-compliant subjects were defined as subjects who completed less than 50% of the diary entries. Subjects with menstrual cycles less than 21 days or greater than 35 days in duration were excluded because of irregular cycles.

Assessment of Airway Function

Subjects were scheduled to perform spirometry and undergo methacholine bronchoprovocation at approximately seven days prior to and seven days after the anticipated onset of menses corresponding to the predicted peak and trough of serum progesterone levels. A subject was excluded from performing bronchoprovocation if she reported an upper respiratory infection in the previous 6 weeks, had $FEV_1 < 65\%$ on the day of testing, had used inhaled short acting β_2 agonists within the previous six hours, and had exposure to relevant allergen to which she was sensitive within the previous 24 hours. If she was unable to perform bronchoprovocation, spirometry was performed only and the subject was rescheduled for bronchoprovocation the following cycle. The study was designed to obtain two paired measurements in two cycles over a 6-month period.

Methacholine challenges followed established procedures: dilutions of methacholine were prepared in doubling concentrations from 0.03 mg/mL to 8 mg/mL. The methacholine and control solutions were delivered from a hand-held nebulizer (DeVilbiss no. 646) connected to a dose-metering device driven by compressed air at 30 psi. The nebulizer was equipped with a critical orifice, 3 mm in diameter, at the inflow end to allow a maximal inspiratory flow of 0.5 L/sec. Inhalation triggered a solenoid valve in the dosimeter to open for approximately 0.5 seconds and deliver 10 μ L of methacholine from a 3-mL reservoir. Each subject took ten inhalations of aerosol breathing from functional residual capacity to total lung capacity. FEV_1 maneuvers were recorded one and three minutes after the subject inhaled PBS diluent and the best of these maneuvers was used as the baseline

FEV₁. A dose-response curve was constructed by administering serial doubling concentrations of methacholine at 5-minute intervals until the worst FEV₁ maneuver recorded at one or three minutes after methacholine was ≤20% of the baseline FEV₁. The PC20-methacholine was calculated by linear interpolation between the last two points on the dose-response curve.

Statistical Analyses

All analyses were implemented in SAS (SAS Institute Inc, Cary, NC). For group comparisons regarding baseline clinical characteristics, nonparametric median tests were used (unless otherwise specified) because of prevalent inequality of variance, skewness, and small sample sizes. To compare groups regarding baseline asthma severity, the nonparametric procedure of O'Brien for comparisons with multiple endpoints was employed.²⁷ Specifically, signs were changed on individual variables if necessary so that larger scores were "worse" on all variables. Ranks within the pooled groups were generated for each variable. For each subject, the ranks were summed over the variables, then the rank sums were compared between groups via t-test. Measurements for the luteal and follicular PC20-methacholine and FEV₁ (% predicted) were meaned over cycles and differences between the two phases were examined within each group and between groups. All PC20-methacholine values were transformed logarithmically before analysis to stabilize the variance.

To examine trends in symptom and peak flow variables in the perimenstrual period, a data reduction method was evolved. Cycles of length less than 21 days or over 35 days were excluded. The analysis of the perimenstrual interval began ten days prior to menstrual onset and extended to ten days after menstrual onset (days -10 to +10). For each of these days, a mean over the monthly perimenstrual periods was computed for each subject on each symptom variable. Subjects with less than four usable perimenstrual periods were excluded. For each

Table 1. Clinical Characteristics of Subjects

	NPMA* (n = 23)	PMA† (n = 9)	P
Age, yr	31.4 ± 7.1	40.2 ± 5.2	.007
Cycle length, days	28.2 ± 2.9	26.7 ± 3.0	.13
Hormonal contraceptive use	2/23 (8.7%)	1/9 (11.1%)	1.0
Age at menarche, yr	13.3 ± 1.8	12.6 ± 1.9	.46
Duration of menses, days	4.9 ± 1.2	4.9 ± 0.9	.36
Self-reported PMS, yes/no	17/23 (73.9%)	5/8 (62.5%)	.66
Self-reported depression, yes/no	8/23 (34.8%)	3/9 (33.3%)	1.0

* NPMA, no self-reported perimenstrual asthma.

† PMA, self-reported perimenstrual asthma.

‡ PMS, premenstrual syndrome.

Table 2. Asthma Severity

	NPMA* (n = 23)	PMA† (n = 9)	P
Years with asthma	15.6 ± 11.8	28.6 ± 15.9	.039
Number using daily bronchodilators	14/23 (60.9%)	8/9 (88.9%)	.21
Number using daily inhaled corticosteroids	14/23 (60.9%)	8/9 (88.9%)	.21
Number using regular oral corticosteroids	1/23 (4.3%)	3/9 (33.3%)	.06
Number of work days missed last year	2.4 ± 5.7	16.4 ± 39.0	.24
Number of ER/urgent care visits last year	1.4 ± 2.3	2.7 ± 4.8	.41
Number of hospitalizations last year	0.2 ± 0.5	0.6 ± 1.1	.53
Number of steroid bursts last year	1.1 ± 2.1	5.5 ± 10.3	.26
FEV ₁ at enrollment, % predicted	87.7 ± 23.5%	72.6 ± 17.9%	.34

* NPMA, no self-reported perimenstrual asthma.

† PMA, self-reported perimenstrual asthma.

Table 3. Perimenstrual Asthma Symptoms, Medication Use, and Peak Flow Rates

	NPMA* (n = 23)	PMA† (n = 9)	P
Wheeze	1.09	2.90	.008
Cough	1.03	2.10	.042
Breathlessness	1.09	2.52	.027
Chest tightness	1.34	2.15	.16
Total symptom score	4.55	9.66	.028
Nocturnal asthma	0.27	0.33	.08
Puffs of inhaled bronchodilator	3.66	7.32	.031
AM peak expiratory flow, L/min	395	340	.009
PM peak expiratory flow, L/min	412	368	.017

* NPMA, no self-reported perimenstrual asthma.

† PMA, self-reported perimenstrual asthma.

Means of subject means over at least 4 cycles for days -10 to +10 of a standardized menstrual calendar.

variable, means of subject means for each group (PMA and NPMA) were plotted versus perimenstrual day of cycle (-10 to +10). To test for group mean differences, subject means averaged over days were compared by standard analysis of variance, with and without age as a covariate, and age-adjusted group means were obtained (least squares means from procedure General Linear Model). Classical univariate repeated measures analyses on subject

means by perimenstrual day were used to test for nonparallelism of group profiles versus menstrual cycle day.

RESULTS

Clinical Characteristics of Subjects

Clinical Characteristics of the PMA (n = 9) and NPMA (n = 23) groups are compared in Table 1. The PMA group subjects were significantly older (40.2 ± 5.2 years versus 31.4 ± 7.1

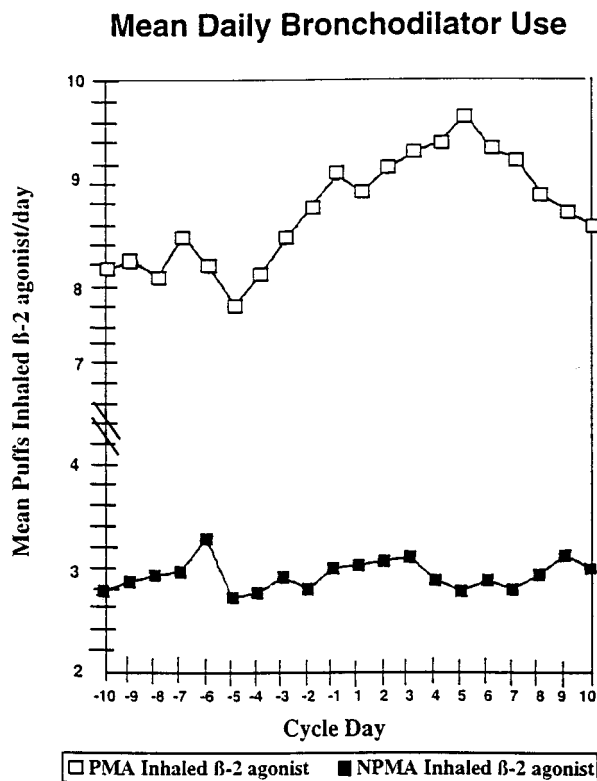


Figure 1. Mean daily use of short acting β_2 agonist for women with PMA and NPMA reported as total puffs per day is shown on a standardized menstrual calendar where day 1 is the onset of menses. Women with PMA demonstrated increasing bronchodilator use during the perimenstrual interval compared with NPMA. PMA = self-reported perimenstrual asthma and NPMA = no self-reported perimenstrual asthma.

years, $P = .007$) than NPMA group subjects. There were no significant differences between the groups in menstrual cycle length, age at menarche, duration of menses, self-reported premenstrual syndrome (scored yes/no), and self-reported psychologic depression (scored yes/no). Despite an attempt to exclude subjects on hormonal contraceptives, three of the subjects were on oral hormonal contraceptive medication at the time of enrollment. The inclusion of these subjects was unlikely to introduce significant bias since they were distributed approximately equally between the two groups: 2/23 in the NPMA group (8.7%) and 1/9 in the PMA group (11.1%) were using oral contraceptives ($P = 1.0$).

Subjects with PMA were noted to have had longer duration of asthma

compared with NPMA subjects (28.6 ± 15.9 years versus 15.6 ± 11.8 years, $P = .039$). Baseline asthma severity based on daily bronchodilator use, inhaled steroid use, emergency asthma visits in the previous year, asthma hospitalizations in the previous year, prior intubation, and enrollment FEV₁ (% predicted) was also found to be greater in the PMA group subjects ($P = .076$, see statistical analysis). Table 2 compares the baseline asthma severity between the two groups.

Subject means of daily symptom variables summed over at least four cycles demonstrated significantly increased asthma symptoms, increased rescue bronchodilator use and decreased AM and PM peak expiratory flow rates overall in the PMA subjects compared to the NPMA subjects (all $P < .05$, Table 3) supporting the dif-

ferences in baseline severity. When adjusted for differences in subject age, PMA subjects had significantly increased wheeze score ($P = .042$) and a tendency toward increased cough, chest tightness, breathlessness, medication use, peak flow rates and total symptom score (all $P > .05$) than NPMA subjects.

Perimenstrual Differences

Mean daily symptom scores, rescue inhaled bronchodilator use and peak expiratory flow rates were compared on a standardized menstrual calendar from the interval beginning ten days before the onset of menses to ten days after the onset of menses. Plots of mean daily use of short acting inhaled β_2 agonist for subjects demonstrated nonparallelism of group profiles (see statistical analyses), indicating that the perimenstrual use of rescue medication was different between the two groups (Fig 1). A test for nonparallelism of the plots was highly significant ($P < .001$). PMA group subjects demonstrated increasing use of bronchodilator during the perimenstrual interval from approximately day -5 to day +5.

Mean daily morning peak flow also demonstrated differences between the two groups (Fig 2). Analysis for nonparallelism of the plots was highly significant ($P < .005$). Subjects with PMA demonstrated decreasing morning peak flow during the perimenstrual interval compared with NPMA group subjects.

Plots of mean daily symptom scores for wheezing, cough, chest tightness, breathlessness, nocturnal asthma, evening peak expiratory flow rates, and total asthma symptoms examined over the interval beginning ten days before the onset of menses to ten days after the onset of menses were not statistically different for the two groups (not shown).

Comparisons between the groups for differences in luteal-follicular FEV₁ (% predicted) in all subjects showed a mean difference that was not statistically significant. PC20-methacholine in the four subjects in the PMA group who completed the test were not sta-

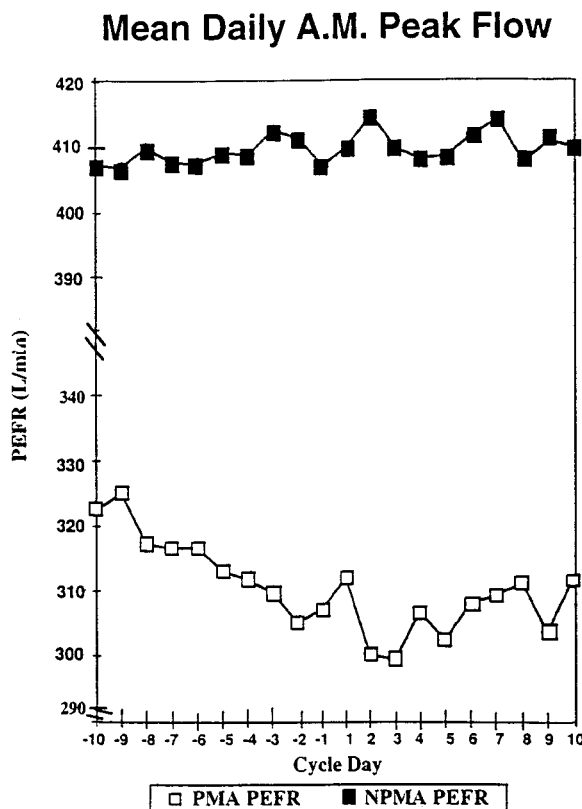


Figure 2. Mean daily morning peak flow for women with PMA and NPMA is shown on a standardized menstrual calendar where day 1 is the onset of menses. Women with PMA demonstrated worsening AM peak flow during the perimenstrual interval compared with women with NPMA. PMA = self-reported perimenstrual asthma and NPMA = no self-reported perimenstrual asthma.

tistically different from the 15 subjects in the NPMA group who completed the challenge (Table 4).

Comparisons between subjects who completed the study and those who failed to complete the study revealed no differences in the distribution of PMA and NPMA subjects, age of subjects, and asthma severity (data not shown).

DISCUSSION

Perimenstrual exacerbations of asthma have long been reported to be a common finding in women with asthma. Previous studies, however, have failed to examine this phenomenon in women who specifically report these symptoms, but rather, have examined the relationship of asthma to the menstrual cycle in asthmatic women in general. These studies have largely been retro-

spective, short term, have failed to demonstrate objective changes in airway function during the perimenstrual period, and have not convincingly demonstrated a consistent association between asthma symptoms and the menstrual cycle. The current study is the longest prospective evaluation to date of the association between asthma symptoms, peak expiratory flow rates, and objective measures of asthma severity in women with and without self-reported perimenstrual asthma.

The findings suggest that women with PMA demonstrate changes in asthma severity during the perimenstrual interval compared with women with NPMA. Women with PMA appear to constitute a distinct subset of women with asthma who are older, report longer duration of asthma, and

increased severity of asthma compared with women with NPMA.

Perimenstrual asthma is difficult to characterize because it is based largely on patient self-report, case reports and population studies that support an association between asthma morbidity and the menstrual cycle. Corresponding objective changes in airway function are not readily demonstrated, and the pathophysiology underlying the symptom exacerbation is unknown. This study suggests that women with PMA experience increased severity of asthma during the perimenstrual interval marked by increasing rescue medication use and decreasing peak flow rates, although perimenstrual changes in spirometry or airway responsiveness were not demonstrated between the groups. The plots of medication use and peak expiratory flow rates on a standardized cycle calendar suggest that the largest increases in medication use and decreases in peak flow rates occur immediately after the onset of menses (approximately days +1 to +4). Most studies have reported PMA symptoms to occur mainly prior to the onset of menses, although some subjects in these studies have reported symptoms to occur during the menses or during both the premenstrual and menstrual intervals.^{12,13,16,17}

The inability to demonstrate changes in spirometry or airway responsiveness may be due to the small sample size, the insensitivity of trying to detect airflow obstruction with a single measure of FEV₁ or PC20-methacholine, or the timing of the measurements. Further, ten subjects (five of nine eligible subjects with PMA and five of 20 eligible subjects with NPMA) were excluded from the methacholine challenge because their asthma episodes were too severe on the day of the testing (FEV₁ <65% predicted). Their data, therefore, were not included in the analysis of PC20-methacholine. In this study, spirometry and methacholine responsiveness were measured at two points in the cycle estimated to correspond to the peak (day -7) and trough (day +7) levels of progesterone. Serial measurements

Table 4. Spirometry and Methacholine Responsiveness

Subject No.	FEV ₁ (% pred)		PD ₂₀ Methacholine	
	Luteal	Follicular	Luteal	Follicular
NPMA*				
1	67.0	69.5	0.263	2.27
3	71.5	57.5	ND	ND
4	98.0	93.5	0.307	0.545
5	32.0	38.0	ND	ND
6	107.0	106.3	1.569	1.531
7	86.8	84.3	0.160	0.100
8	84.3	77.7	ND	ND
17	68.0	64.0	ND	ND
19	92.5	85.0	0.095	0.080
21	103.0	107.5	0.240	0.315
22	93.5	87.0	0.230	0.170
33	85.5	83.0	0.355	0.260
38	106.0	103.0	0.460	0.386
40	64.0	49.0	ND	ND
44	64.0	93.5	0.270	1.385
46	81.0	77.0	1.750	1.075
49	112.5	114.0	0.210	0.230
50	66.5	71.0	0.200	0.450
52	87.5	94.0	0.120	0.120
56	90.0	92.0	0.133	0.082
Mean	83.03	82.34	0.424	0.600
PMA†				
11	56.0	61.0	ND	ND
16	76.5	69.0	0.060	0.140
20	50.5	60.0	ND	ND
35	56.0	97.0	ND	ND
41	45.0	44.0	ND	ND
45	117.5	115.0	2.145	1.550
47	64.0	65.5	ND	ND
48	78.5	74.0	0.250	0.365
55	92.5	93.5	0.365	0.545
Mean	70.72	75.44	0.705	0.650
	<i>P</i> = .29		<i>P</i> = .33	

* NPMA, no self-reported perimenstrual asthma.

† PMA, self-reported perimenstrual asthma.

Comparisons are made for differences between L and F means between groups PMA and NPMA.

of airway function may be necessary to determine the precise time at which airway changes occur.

Statistically significant differences in patterns of perimenstrual bronchodilator use and peak flow changes were observed between the two groups. Differences in baseline asthma severity between the two groups were unlikely to influence these different patterns of

medication use and AM peak flow rates observed during the perimenstrual interval. Although overall differences in symptoms, medication use, and peak flow rates can be attributed to differences in baseline severity, the women with PMA demonstrated a clear pattern of increasing medication use and decreasing peak flow rates during the perimenstrual interval compared with

women with NPMA who exhibited little variation in these variables during the perimenstrual interval. The increased asthma severity found in the patients with PMA in this study has been noted previously by Eliasson et al¹⁷ who reported in a retrospective survey of 95 asthmatic women, that PMA subjects appeared to have more severe asthma, 68% requiring hospital-

ization compared with 26% of controls. By NIH criteria, the subjects with PMA in the current study would be categorized with moderate persistent asthma compared with subjects with NPMA who had mild persistent asthma.¹ Perimenstrual asthma may be a function of severe or long-standing disease or increased age. A larger study that controls for differences in baseline asthma severity will be necessary to determine whether increased asthma severity characterizes women with perimenstrual asthma.

Although there remain no well-defined criteria for establishing a diagnosis of perimenstrual asthma, the profile of increased age, longer duration of asthma, and more severe asthma in women who self-report perimenstrual exacerbations may identify a group of patients who need to be followed closely through their menstrual cycles. Serial peak flow monitoring may assist in corroborating the diagnosis.

While treatment issues were not examined in this study, the pattern of increasing bronchodilator use and decreasing peak flows during the perimenstrual interval suggest the need for more aggressive asthma therapy during this time. A number of unproven treatment methods for PMA have been previously advanced including diuretics,²⁸ nonsteroidal anti-inflammatory medications (NSAIDs),²⁹ oophorectomy,³⁰ ovarian irradiation,³¹ and exogenous progesterone or estrogen.^{22,32,33} Only the NSAID meclofenamate has been studied in a controlled clinical trial and was found to be ineffective.²⁹ Investigators have reported a benefit of high dose intramuscular progesterone in three patients with PMA.²² Exogenous estradiol was associated with improvements in asthma symptoms and dyspnea index scores in an open label study of 14 subjects with premenstrual asthma.³³ Further examination of potential therapies awaits a greater understanding of the underlying pathophysiology of this disorder, such as changes in hormonal levels inducing airway symptoms, changes in airway reactivity and underlying inflammation, or in-

creased airway hydration leading to mucosal edema and airway narrowing.

There was a nearly 50% attrition of enrolled subjects from the study primarily due to the rigors of participating in the lengthy protocol. Such large loss of subjects may indicate the difficulty in performing long-term epidemiologic studies that do not provide any perceived direct benefit to the enrollees. Providing suitable reimbursement to subjects and employing electronic data collection instruments may improve compliance and participation in future similar studies.

In conclusion, this study suggests that women who report perimenstrual asthma demonstrate increasing perimenstrual medication use, decreased perimenstrual peak flow rates, increased age, increased severity, and longer duration of asthma who require close monitoring during the perimenstrual interval. A large scale prospective study is required to define changes in airway function, underlying mechanisms, and specific interventions. Identification of these patients will lead to the increased recognition and development of specific interventions for a high risk subgroup of asthmatic women.

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