Characteristics of Perimenstrual Asthma and Its Relation to Asthma Severity and Control

Data From the Severe Asthma Research Program

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Background: Although perimenstrual asthma (PMA) has been associated with severe and difficult-to-control asthma, it remains poorly characterized and understood. The objectives of this study were to identify clinical, demographic, and inflammatory factors associated with PMA and to assess the association of PMA with asthma severity and control.

Methods: Women with asthma recruited to the National Heart, Lung, and Blood Institute Severe Asthma Research Program who reported PMA symptoms on a screening questionnaire were analyzed in relation to basic demographics, clinical questionnaire data, immunoinflammatory markers, and physiologic parameters. Univariate comparisons between PMA and non-PMA groups were performed. A severity-adjusted model predicting PMA was created. Additional models addressed the role of PMA in asthma control.

Results: Self-identified PMA was reported in 17% of the subjects ($n = 92$) and associated with higher BMI, lower FVC % predicted, and higher gastroesophageal reflux disease rates. Fifty-two percent of the PMA group met criteria for severe asthma compared with 30% of the non-PMA group. In multivariable analyses controlling for severity, aspirin sensitivity and lower FVC % predicted were associated with the presence of PMA. Furthermore, after controlling for severity and confounders, PMA remained associated with more asthma symptoms and urgent health-care utilization.

Conclusions: PMA is common in women with severe asthma and associated with poorly controlled disease. Aspirin sensitivity and lower FVC % predicted are associated with PMA after adjusting for multiple factors, suggesting that alterations in prostaglandins may contribute to this phenotype.

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Abbreviations: FENO = fraction of exhaled nitric oxide; GERD = gastroesophageal reflux disease; HCU = health-care utilization; PG = prostaglandin; PMA = perimenstrual asthma; SARP = Severe Asthma Research Program

Asthma is a complex disease with recognized sex differences. Adult asthma affects more women than men, and women may be predisposed to greater severity.¹⁻⁴ Additionally, women report onset of asthma later in life, often associated with times of hormonal change.

In small studies, about 30% to 40% of women report worsening of asthma symptoms in relation to menstruation.⁵⁻⁸ The presence of perimenstrual asthma (PMA) has been related to increases in asthma-related ED visits, hospitalizations, ICU admissions,

intubations, and near-fatal and fatal events.⁵ Unfortunately, the small nature of previous studies limits the ability to characterize contributing factors or implications of PMA.

There is growing support for the concept that asthma consists of multiple phenotypes, which may be more easily recognized in severe asthma.^{9,10} Although the National Heart, Lung, and Blood Institute Severe Asthma Research Program (SARP), a large network to study severe asthma mechanisms, recently identified a female-predominant, late-onset phenotype,¹¹

no studies have focused on the relation of severe asthma to PMA. Therefore, data from SARP were used to identify and characterize patients with PMA to determine factors that might mechanistically contribute to this phenotype and to understand the relative contribution of PMA to asthma control. We hypothesized that PMA would be identified with specific clinical and immunologic characteristics and associated with greater asthma severity and poorer control.

MATERIALS AND METHODS

Population and Subject Characterization

Subjects were part of SARP, the details of which have been previously described.¹⁰ Severe asthma was defined by the 2000 American Thoracic Society workshop criteria, with a combination of one of two major and two of seven minor criteria.¹² All other subjects with asthma enrolled in SARP were termed “not severe” as detailed by Moore et al.¹⁰ All subjects completed questionnaires on a range of topics. Pulmonary function testing was performed according to American Thoracic Society guidelines as previously described.¹⁰ Blood was collected for total serum IgE level and CBC count and analyzed by each site’s clinical laboratory. Fraction of exhaled nitric oxide (FENO) was measured at 50 mL/s.¹³

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Atopy was addressed by skin prick testing to 12 common allergens as previously described.^{10,11} The individual institutional review boards approved all protocols, and subjects provided written informed consent. Refer to e-Appendix 1 for a detailed discussion of the methods.

Definition of PMA

PMA was assessed by questionnaire. Subjects were asked to rate menses as a trigger for asthma symptom onset or worsening as (1) yes, (2) never, and (3) I don’t know. Subjects who answered yes were considered to have PMA for the purpose of this study.

Statistical Analysis

Subjects reporting PMA were compared with those reporting no PMA across demographic, clinical, hormonal, and inflammatory variables. Continuous variables were compared using two-sample *t* tests and categorical variables by χ^2 or Fisher exact analyses. We used multiple logistic regressions to assess the set of factors most highly associated with PMA. Any variable significant at the .15 level was considered for inclusion in a multivariable model using a hierarchical approach (demographic and clinical, hormonal, and inflammatory). Variables were dropped if $P > .10$, with the exception of severity class, which was always included in the model. ORs and 95% CIs are reported. In sensitivity analyses, we used multiple imputation to run final multiple logistic models to account for the 122 subjects missing IgE data.

Simple logistic regression and multivariable logistic regression assessed crude and adjusted associations between PMA and symptoms experienced at least once daily (cough, sputum, chest tightness, wheezing, shortness of breath, and nighttime symptoms) with Bonferroni correction of $P = .008$ and health-care utilization (HCU) (ED visits, hospitalizations, ICU admission, intubation, three or more oral corticosteroid bursts for asthma) with Bonferroni correction of $P = .01$ and PMA. Multivariable models were adjusted for severity and variables found to be highly associated with PMA. Multiple imputation was used in addition to assessing the impact of missing IgE data on the ORs and 95% CIs.

RESULTS

Baseline Characteristics

Of the 756 female subjects enrolled into SARP, those aged < 12 years ($n = 47$) and > 50 years ($n = 146$) were excluded from analysis. In the remaining 563, 14% ($n = 80$) did not know whether menses exacerbated their asthma and were eliminated from further analysis, suggesting that most subjects could answer the question. Ultimately, 483 subjects were included in this analysis. Women unable to answer the PMA question (e-Tables 1, 2) generally had a more severe condition but did not differ in other phenotypic characteristics. Seventeen percent ($n = 92$) of subjects enrolled in SARP self-reported PMA, answering yes to menses as a trigger for asthma symptoms. Those with PMA compared with those without were older, had a higher BMI, and were more likely to be classified as severe. Fifty-two percent of subjects in the PMA group were classified as severe, whereas 30% in the non-PMA group were so classified. The

FEV₁ % predicted and FVC % predicted were lower in the PMA group (Table 1).

PMA in the Severe Asthma Subset: Given the high percentage of women with PMA and severe asthma, analysis based on severity classification was performed to determine whether increased reporting was related to more symptomatic, severe disease in general. Twenty-four percent of subjects with severe asthma reported PMA. These women were older at enrollment but did not differ in BMI, age of onset, race, or FEV₁ % predicted compared with those in the non-PMA group. However, subjects with severe asthma and PMA were more likely to use systemic corticosteroids and had a lower FVC % predicted (Table 1).

Hormonal, Immunoinflammatory Factors, and Comorbidities

Aspirin sensitivity and gastroesophageal reflux disease (GERD) were more likely in the PMA group than in the non-PMA group (Table 2). Overall, both groups were similar in use of oral contraceptives, historical pneumonia rates, and FENO. IgE levels tended to be lower in the PMA group, and atopy was less common. Subjects with PMA were more likely to have nasal polyps, sinusitis, and aspirin sensitivity.

PMA in the Severe Asthma Subset: Aspirin sensitivity, lower total IgE level, and less atopy were more

often present in subjects with severe asthma and PMA. There were no differences in rates of GERD, pneumonia, and FENO, but differences in nasal polyps remained (Table 2).

Prediction of PMA

A multivariable logistic regression analysis determined risk factors most strongly associated with PMA (Table 3). In the final nonimputed model controlling for severity, lower FVC % predicted, lower IgE level, and aspirin sensitivity were associated with PMA. For every 10% increase in FVC % predicted, the odds of PMA decreased 21%. For each 10-fold increase in IgE level, there was a 15% decrease in the odds of PMA. Severity was consistently associated with PMA. GERD was associated with PMA but was strongest in the imputed model. These results remained after multiple imputations were performed to allow subjects missing IgE (n = 122) and FVC % predicted (n = 3) data to be included.

PMA in Relation to Symptom Severity: Univariate analysis supported an association of PMA with greater symptoms (Table 4). After adjusting for severity, all differences remained except chest tightness (Fig 1). When aspirin sensitivity, GERD, IgE level, and FVC % predicted were included in the model, the relationships to symptoms weakened but remained directionally similar for all symptoms. Following imputation of IgE level, a third model continued to

Table 1—Univariate Analysis of Baseline Demographic Characteristics, Spirometry, and Hormonal Influences in the PMA vs Non-PMA Group and Specifically in Severe Asthma

Characteristic	All Women			Women With Severe Asthma		
	With PMA (n = 92)	Without PMA (n = 391)	P Value ^a	With PMA (n = 48)	Without PMA (n = 116)	P Value ^a
Age at enrollment, y	35.2 ± 9.3	32.2 ± 9.9	.007	38.1 ± 9.0	34.4 ± 10.6	.05
Race			.22			.56
White	51 (55)	242 (62)		31 (65)	63 (54)	
Black	31 (34)	114 (29)		12 (25)	42 (36)	
Other	10 (11)	35 (9)		5 (10)	11 (10)	
Age of onset, y	12.9 ± 11.1	13.1 ± 11.4	.73	13.0 ± 11.3	13.4 ± 12.5	.99
BMI, kg/m ²	32.5 ± 11.1	29.8 ± 8.6	.03	32.5 ± 12.4	32.2 ± 9.7	.68
Severity class			.0003	...	...	...
Mild	31 (34)	195 (50)		...	...	
Moderate	14 (14)	80 (20)		...	...	
Severe	48 (52)	116 (30)		...	...	
Inhaled corticosteroid use	76 (83)	268 (69)	.005	46 (96)	115 (99)	.18
Systemic corticosteroid use	34 (37)	56 (14)	<.0001	31 (66)	50 (43)	.008
FEV ₁ , % predicted	74.7 ± 21.7	81.6 ± 20.2	.007	65.1 ± 21.7	67.7 ± 21.9	.56
FVC, % predicted	84.2 ± 18.8	92.1 ± 17.5	.0007	76.5 ± 19.4	83.4 ± 19.7	.05
OCP use	21 (23)	115 (29)	.28	12 (25)	25 (21.5)	.63
Hormone therapy use	7 (0.08)	11 (3)	.11	6 (13)	8 (7)	.38
History of oophorectomy ^b	8 (0.09)	26 (7)	.53	6 (13)	11 (10)	.43
History of hysterectomy ^b	5 (0.05)	32 (8)	.52	4 (8)	13 (11)	.60

Data are presented as mean ± SD or No. (%). OCP = oral contraceptive; PMA = perimenstrual asthma.

^aP values for comparison of means and percentages were calculated using Wilcoxon rank sum test for continuous variables and χ^2 test for categorical variables.

^bHistorical PMA reported in subject's status after hysterectomy and oophorectomy.

Table 2—Univariate Analysis of Baseline Immune and Inflammatory Markers and Comorbid Conditions in the PMA vs Non-PMA Group and Specifically in Severe Asthma

Marker or Condition	All Women			Women With Severe Asthma		
	With PMA (n = 92)	Without PMA (n = 391)	P Value ^a	With PMA (n = 48)	Without PMA (n = 116)	P Value ^a
% peripheral eosinophils	3.4 ± 2.9	3.4 ± 2.6	.85	3.2 ± 2.8	3.1 ± 2.6	.85
Mean IgE level ^b	208.4 ± 325.7	292.2 ± 540.9	.06	161.3 ± 272.1	367.4 ± 523.9	.006
Log FENO ^c	1.4 ± 0.4	1.4 ± 0.4	.84	1.5 ± 0.4	1.4 ± 0.4	.66
Atopy	60 (76)	297 (88)	.01	27 (71)	80 (88)	.03
Number of positive SPTs ^d			.08			.21
0	19 (24)	41 (12)		11 (29)	11 (12)	
1-3	25 (32)	126 (37)		14 (37)	30 (33)	
4-6	18 (23)	99 (29)		7 (18)	29 (32)	
7-9	15 (19)	55 (17)		4 (11)	16 (18)	
10-12	2 (2)	17 (5)		2 (5)	5 (5)	
GERD	37 (41)	87 (23)	.0008	21 (45)	47 (41)	.66
Pneumonia history	45 (53)	163 (43)	.09	23 (55)	77 (68)	.14
History of recurrent sinusitis	52 (57)	161 (42)	.009	28 (58)	50 (44)	.09
Aspirin sensitivity	23 (30)	36 (10)	< .0001	12 (31)	15 (15)	.04
Nasal polyps present	15 (16)	20 (5)	.0007	12 (25)	13 (11)	.03

Data are presented as mean ± SD or No. (%). FENO = fraction of expired nitric oxide; GERD = gastroesophageal reflux disease; SPT = skin prick test. See Table 1 legend for expansion of other abbreviation.

^aP values for comparison of means and percentages were calculated using Wilcoxon rank sum test for continuous variables and χ^2 test for categorical variables.

^bMissing data in 20 subjects in PMA group and 102 subjects in non-PMA group.

^cMissing data in 18 subjects in PMA group and 94 subjects in non-PMA group.

^dMissing data in 13 subjects in PMA group and 53 subjects in non-PMA group.

show that shortness of breath was more likely in subjects with PMA.

HCU and PMA: HCU measures were higher in subjects with PMA in univariate analysis (Fig 2). Controlling for severity, adjusting for confounders, and imputing missing IgE and FVC % predicted data were performed (Table 5). Even after controlling for these factors, HCU remained higher in subjects with PMA.

DISCUSSION

It is increasingly clear that hormonal influences affect asthma phenotypes and severity. Although asthma is more common in boys, at the time of puberty

and beyond, it becomes more common in girls and women.¹⁴ The subset of women with PMA remains poorly characterized. Definitions have differed across studies, and no large-scale analyses have been performed.^{15,16} To this end, > 500 women with a range of asthma severity recruited for SARP were analyzed for PMA. The data from this largest study to date that we know of strongly suggest that PMA represents a unique, highly symptomatic, and exacerbation-prone asthma phenotype associated with aspirin sensitivity, less atopy, and lower lung capacity.

PMA was defined in this analysis as present in premenopausal women with asthma answering yes to a question endorsing menses as a trigger for onset or worsening of symptoms. Although some small studies have defined PMA with objective criteria, including

Table 3—Modeling PMA as a Function of Severity, Clinical, and Inflammatory Measures (N = 483)

Variable	Crude	P Value	Adjusted ^a	P Value	Adjusted (Multiple Imputation) ^b	P Value
GERD	2.35 (1.45-3.80)	.0005	1.39 (0.74-2.60)	.31	1.73 (1.03-2.91)	.04
ASA	3.29 (1.83-5.89)	< .0001	4.96 (2.37-10.40)	< .0001	3.42 (1.83-6.37)	.0001
Severity		.0003		.03		.07
Moderate	1.02 (0.51-2.05)		0.59 (0.24-1.43)		0.64 (0.29-1.42)	
Severe	2.60 (1.57-4.32)		1.75 (0.84-3.63)		1.45 (0.76-2.73)	
FVC % (10% increment) ^c	0.79 (0.69-0.89)	.0002	0.79 (0.65-0.95)	.01	0.82 (0.70-0.96)	.02
IgE level (log10) ^c	0.85 (0.72-1.00)	.05	0.85 (0.71-1.02)	.08	0.85 (0.71-1.00)	.06

Data are presented as OR (95% CI). See Table 1 and 2 legends for expansion of abbreviations.

^aSeverity included in the crude model.

^bHistory of GERD, aspirin sensitivity, FVC % predicted, and IgE level included using multiple imputed data (IgE level and FVC % predicted) to include 125 subjects previously excluded due to missing data.

^cThree subjects were missing FVC % predicted and 122 were missing IgE data.

Table 4—Modeling Symptom Frequency as a Function of PMA

Outcome: $\geq$ Daily Symptoms	Crude ^a PMA	Severity Adjusted ^b PMA	Severity + Confounders Adjusted ^c PMA	Severity + Confounders Adjusted PMA (Multiple Imputation) ^d
Cough	1.62 (0.99-2.63)	1.33 (0.80-2.20)	1.11 (0.60-2.08)	1.15 (0.67-1.96)
Sputum	1.84 (1.11-3.07)	1.62 (0.96-2.73)	1.19 (0.62-2.28)	1.29 (0.74-2.24)
Chest tightness	2.07 ^e (1.27-3.38)	1.73 (1.04-2.88)	1.40 (0.75-2.61)	1.50 (0.88-2.57)
Wheeze	2.54 ^e (1.56-4.13)	2.02 ^e (1.20-3.39)	1.16 (0.60-2.24)	1.64 (0.95-2.84)
Shortness of breath	2.87 ^e (1.81-4.57)	2.44 ^e (1.49-3.98)	1.91 (1.05-3.47)	2.14 ^e (1.28-3.58)
Nighttime symptoms	2.71 ^e (1.66-4.42)	2.26 ^e (1.36-3.77)	1.67 (0.88-3.17)	1.85 (1.08-3.19)

Data are presented as OR (95% CI). See Table 1 and 2 legends for expansion of abbreviations.

^aPMA is the only independent variable in the model for symptom outcome.

^bSeverity included in crude model.

^cHistory of GERD, aspirin sensitivity, FVC % predicted, and IgE level included in model (125 subjects were excluded because of missing data).

^dHistory of GERD, aspirin sensitivity, FVC % predicted, and IgE level included using multiple imputed data (IgE level and FVC % predicted) to include the 125 subjects previously excluded because of missing data.

^e $P < .05$.

lung function or FENO, population-based studies have defined PMA using subjective criteria similar to the present study.¹⁷⁻²¹ Despite the simplicity of this definition, only 14% of women were unable to answer the question on PMA. Only a minority (17%) of women reported PMA, suggesting that this question is one that the majority of women with asthma are able to recognize. Of note, this prevalence is still higher than the 8.5% reporting PMA in a recent UK report.²² The reasons for the higher prevalence of reported PMA in the present study are not clear but may be attributable to substantial population differences.

Other small retrospective studies suggested that PMA identifies a group of high-risk women with asthma with similar prevalence.^{15,23-25} In a study of 57 women, 33% reported worsening asthma symptoms perimenstrually,¹⁵ and a retrospective study of 44 near-fatal asthma events in women with asthma reported that 25% occurred perimenstrually.²⁴ Similarly, 46% of 182 women visiting the ED for asthma exacerbations presented during their perimenstrual phase (day 26 to day 4 of a 28-day cycle).²⁵

Previous data associate PMA with exacerbation-prone asthma. The current study expands on this by associating PMA with strictly defined severe asthma

FIGURE 1. Comparison of common asthma symptom frequency between subjects with PMA and subjects without PMA, adjusted for severity. Symptom scores are based on a six-point scale ranging from never to more than once daily. * $P < .05$. PMA = perimenstrual asthma.

FIGURE 2. Frequency of health-care utilization unadjusted for severity between PMA and non-PMA groups. OR and 95% CI values are adjusted for severity. *Events reported in the 12 months prior to administration of questionnaire. #Events reported as lifetime history. OCS = oral corticosteroid. See Figure 1 legend for expansion of other abbreviation.

criteria, lower lung function, and more symptoms and HCU compared with no PMA. Twenty-four percent of subjects with severe asthma reported PMA, whereas 11% of subjects without severe asthma reported PMA. Controlling for severity had little impact on differences in asthma symptoms and exacerbations between those with and without PMA, suggesting that PMA is not merely explained by generally more severe asthma. Distinguishing characteristics of PMA identified through the comprehensive modeling made possible by the rich SARP database included lower FVC % predicted; GERD; and, most strongly, aspirin sensitivity. Of note, lower IgE levels were seen in subjects with severe asthma and PMA. In contrast, factors

such as age, BMI, and FEV₁ % predicted were not associated when controlling for severity. Thus, PMA identifies a phenotype of asthma in women predisposed to poorly controlled severe asthma, with novel contributing factors (aspirin sensitivity and lower IgE level) that distinguish it from traditional allergic asthma.

The association of PMA with aspirin sensitivity is especially novel and intriguing.²⁶ The additional association of PMA with chronic sinusitis and nasal polypsis (Table 2), long associated with aspirin sensitivity, supports this relationship.^{27,28} Aspirin and nonsteroidal antiinflammatory drugs inhibit cyclooxygenase, decreasing the generation of prostaglandins (PGs),

Table 5—Modeling Outcomes as a Function of PMA, Severity of Asthma, and Potential Confounders

Outcome	Crude ^a		Severity Adjusted ^b		Severity + Confounders Adjusted ^c		Severity + Confounders Adjusted (Multiple Imputation) ^d	
	P Value	P Value	P Value	P Value	P Value	P Value	P Value	P Value
ED visits	4.35 (2.18-8.64)	<.0001	3.57 (1.75-7.31)	.005	2.91 (1.27-6.66)	.01	3.16 (1.51-6.60)	.002
Hospitalization	2.47 (1.54-3.95)	.0002	1.85 (1.09-3.14)	.02	1.40 (0.75-2.61)	.29	1.63 (0.94-2.83)	.08
ICU admission	3.01 (1.78-5.08)	<.0001	2.23 (1.26-3.93)	.006	1.48 (0.72-3.06)	.29	2.05 (1.13-3.71)	.02
Intubation history	3.15 (1.71-5.82)	.0002	2.40 (1.27-4.56)	.007	1.86 (0.80-4.32)	.15	2.29 (1.17-4.51)	.02
≥ 3 OCS bursts	4.55 (2.81-7.36)	<.0001	3.96 (2.22-7.08)	<.0001	4.32 (2.10-8.87)	<.0001	3.14 (1.70-5.81)	.0003

Data are presented as OR (95% CI). OCS = oral corticosteroid. See Table 1 and 2 legends for expansion of other abbreviations.

^aPMA is the only independent variable in the model for symptom outcome.

^bSeverity included in crude model.

^cHistory of GERD, aspirin sensitivity, FVC % predicted, and IgE level included in model (125 subjects were excluded because of missing data).

^dHistory of GERD, aspirin sensitivity, FVC % predicted, and IgE level included using multiple imputed data (IgE level and FVC % predicted) to include the 125 subjects previously excluded because of missing data.

which are strongly linked with menstruation. Stimulated by progesterone withdrawal, PGE2 increases prior to and during the onset of menstruation, causing vasodilation and contributing to endometrial edema.²⁹ PGF2 α , a potent vasoconstrictor, increases in the premenstrual endometrium at onset of menses.²⁵ Whether and how systemic levels of these eicosanoids affect the lung in asthma and link to their inhibition by cyclooxygenase inhibitors are unclear. However, reductions in perimenstrual-associated increases of PGE2 could adversely affect asthma through loss of protective levels of PGE2.³⁰⁻³² Thus, it is reasonable that abnormalities in PGs tie these two conditions together. Alternatively, increased recognition of aspirin sensitivity in women with PMA (who use nonsteroidal antiinflammatory drugs to treat perimenstrual symptoms) is possible, although a small study found that unlikely.²⁶

Women with severe asthma and PMA, even after adjusting for confounders, had significantly lower IgE levels. This trend was also present in all subjects with PMA, but it did not reach statistical significance, implying that women with severe asthma and PMA are less likely to have traditional allergic asthma. Supporting this further, both atopy and number of positive skin prick tests were lower in subjects with PMA. Future studies are needed to confirm this observation.

The final factor associated with PMA in the multivariable analysis was lower FVC % predicted. Lung volumes are needed to confirm whether this is due to air trapping, obesity-related effects, or a true restrictive process. Air trapping and obesity have both been associated with severe, exacerbation-prone asthma.³³⁻³⁵ Lower FVC % predicted could also contribute to greater symptom frequency, specifically shortness of breath, a symptom long associated with air trapping (and obesity).³³ Of note, the modeling results suggest that low FVC % predicted was more significantly associated with PMA than was obesity.

It is noteworthy that Farha et al¹⁸ reported cyclic changes in FEV₁, FVC, and gas transfer during the menstrual cycle in women with asthma that were not enhanced for patients with PMA. These differences in pulmonary function have been linked to angiogenic processes or remodeling over the menstrual cycle and were suggested to worsen airflow obstruction.¹⁸ Whether these fluctuations are more pronounced in women with PMA and contribute to the lower FVC remains to be determined.

The clinical importance of these findings relates to the strong relationships between PMA and frequent HCU and severe symptoms. Realizing that women with more severe asthma, aspirin-sensitive asthma, and air trapping could also manifest poor levels of asthma control, the relation of PMA to exacerbations and symptoms was controlled for multiple factors. In

all cases, a positive association of symptom frequency and exacerbations with PMA remained.

A major limitation of this study is its cross-sectional design, which did not include evaluation throughout the menstrual cycle. In contrast, the novelty lies in its large-scale design and its structured, systematic approach in identifying factors associated with PMA and assessment of the association of PMA with asthma control. We performed extensive analyses that allowed us to control for multiple factors, including severity and factors that predicted PMA. Because of the high prevalence of severe asthma among subjects with PMA, we conducted additional analyses only among those with severe asthma to attempt to reduce the amount of confounding by disease severity.

Other limitations include the questionnaire-based definition of PMA and associated recall bias for PMA. The definition used here is typical of large-scale epidemiologic studies and, in fact, the SARP database allowed us to study > 500 women, 90% of whom definitively answered yes or no to the PMA question. Women aged > 50 years were excluded to minimize recall bias in postmenopausal women. Finally, IgE levels were not collected in every subject. The inclusion of imputed levels did not change the analysis substantially, supporting the overall validity. The questionnaire in this study did not quantify frequency of PMA symptoms or provide more-specific details, making it difficult to interpret frequency or severity of PMA and to allow for comparison among all women reporting PMA. Menstrual diaries kept over several cycles detailing symptoms timing and frequency would better establish a PMA relationship and comparison among subjects.

In conclusion, the findings support PMA as a distinct phenotype of asthma that is associated with more severe, poorly controlled disease; aspirin sensitivity; and lower FVC % predicted. Further studies should improve our understanding of the features unique to PMA, focusing on the roles of PGs, sex hormones, and immune and physiologic processes. Finally, awareness of this high-risk phenotype by clinicians treating women with difficult-to-control and severe asthma may eventually improve outcomes in these high-risk patients.

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Dr Rao: contributed to the data analysis and preparation and critical review of the manuscript.

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Additional information: The e-Appendix and e-Tables can be found in the "Supplemental Materials" area of the online article.

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