

Original Article

Perimenstrual Asthma in Aspirin-Exacerbated Respiratory Disease

Ryan C. Eid, MD^{a,b}, Marina L. Palumbo, BA^c, and Katherine N. Cahill, MD^d *Boston, Mass; and Nashville, Tenn*

What is already known about this topic? Aspirin sensitivity is associated with perimenstrual asthma.

What does this article add to our knowledge? Twenty-four percent of females with aspirin-exacerbated respiratory disease report perimenstrual asthma, which is associated with younger age at aspirin-exacerbated respiratory disease onset, menstruation-related worsening of sinus symptoms, increased asthma-related health care utilization, and a change in respiratory symptom severity at menopause.

How does this study impact current management guidelines? Females with aspirin-exacerbated respiratory disease should be counseled about both upper and lower respiratory tract symptom deterioration with menstruation.

BACKGROUND: Aspirin-exacerbated respiratory disease (AERD) is a condition of the upper and lower respiratory tract characterized by reactions to nonsteroidal anti-inflammatory drugs. The Severe Asthma Research Program reported a strong association between perimenstrual asthma (PMA) and aspirin-sensitive asthma.

OBJECTIVE: To evaluate the prevalence and characteristics of PMA among a cohort of patients with AERD.

METHODS: Women 18 years and older enrolled in the Brigham and Women's AERD registry were surveyed about their reproductive, asthma, and sinus history. Subjects reporting the development of asthma before menopause were included. Continuous and categorical variables were compared between those reporting menstruation as a trigger for asthma symptoms and those who did not. Covariates expected *a priori* to have a positive effect on the odds of PMA were included in a multivariate logistic regression model to test associations between PMA and clinical factors.

RESULTS: Among females of childbearing potential, 369 of 695 responded to the survey and 322 met inclusion criteria. Twenty-

four percent of subjects ($n = 74$) reported PMA. Earlier age of AERD onset, concurrent worsening of sinus symptoms the week before or during menstruation, increased emergency department visits for asthma, and a change in the severity of respiratory symptoms at menopause were more common in PMA. Earlier age at first nonsteroidal anti-inflammatory drug-induced respiratory reaction and emergency department visits increased the odds of reporting PMA.

CONCLUSIONS: PMA and increased sinus symptoms with menstruation are common in females with AERD. Females with AERD should be counseled about upper and lower respiratory symptom deterioration with menstruation. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Perimenstrual asthma; Aspirin-exacerbated respiratory disease; Aspirin intolerance; Aspirin-sensitive asthma; Menopause; Pregnancy; Sinus

INTRODUCTION

A subset of females with asthma during their childbearing years describe worsening of asthma symptoms in relation to menstruation, an entity referred to as perimenstrual asthma (PMA) in the literature. Studies reporting on PMA are limited by the lack of a unifying definition, small sample sizes, and a deficient understanding of mechanism.¹ Between 11% and 44% of females with asthma during their childbearing years report perimenstrual worsening of asthma symptoms.^{2,3} Although PMA is poorly understood, it has been associated with severe and difficult-to-control asthma and increased asthma morbidity.⁴ Recently, PMA was found to be strongly associated with aspirin sensitivity, nasal polyposis, and chronic sinusitis.^{3,4} After adjusting for asthma severity, Rao et al⁴ reported aspirin-sensitive asthma as the clinical characteristic most strongly associated with PMA in the Severe Asthma Research Program (SARP).⁴ To date, no study has evaluated the prevalence of PMA in a cohort of patients with aspirin-sensitive asthma.

^aDepartment of Medicine, Beth Israel Deaconess Medical Center, Boston, Mass

^bHarvard Medical School, Boston, Mass

^cDepartment of Medicine, Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, Mass

^dDepartment of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University, Nashville, Tenn

This work was supported by the National Institutes of Health (grant nos. K23AI118804 and U19 AI095219), and by generous contributions from the Kaye and Vinik families.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication May 17, 2019; revised August 16, 2019; accepted for publication August 22, 2019.

Available online ■■

Corresponding author: Katherine N. Cahill, MD, Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University Medical Center, 2525 West End Ave, Ste 450, Nashville, TN 37203. E-mail: Katherine.cahill@vmc.org. 2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2019.08.054>

Abbreviations used

AERD- Aspirin-exacerbated respiratory disease
 BWH- Brigham and Women's Hospital
 ED- Emergency department
 HCC- Hormone-containing contraceptive
 PMA- Perimenstrual asthma
 SARP- Severe Asthma Research Program

Aspirin-sensitive asthma, better known as aspirin-exacerbated respiratory disease (AERD), is a condition of the upper and lower respiratory tract characterized by chronic rhinosinusitis with nasal polyps, asthma, tissue eosinophilia, and respiratory reactions to nonsteroidal anti-inflammatory drugs that inhibit cyclooxygenase-1. AERD develops at or after the onset of puberty and disproportionately impacts females.^{5,6} To evaluate the prevalence and characteristics of PMA in AERD, we performed the first investigation of PMA in a large cohort of females with AERD.

METHODS**Population and subject characterization**

The Brigham and Women's Hospital (BWH) AERD registry includes patients with a physician-confirmed diagnosis of AERD. All female subjects enrolled in the BWH AERD registry between September 2013 and September 2018 were invited to complete an electronic questionnaire about their menstrual history (see [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org). Subjects who reported the development of AERD after menopause were excluded from data analysis. Existing clinical data from the AERD registry were extracted and analyzed for survey respondents and nonrespondents. Study data were collected and managed using REDCap electronic data capture tools hosted at BWH.^{7,8} Partners Human Research Committee approved the study (2013-P-001659), and all subjects provided written or online informed consent.

Definition of PMA

PMA was assessed by questionnaire. Subjects were asked to report whether menstruation was a trigger for worsening asthma symptoms as (1) yes, (2) no, and (3) NA I do not have asthma. Subjects who answered "yes" were considered to have PMA, and those who answered "no" were considered non-PMA for the purposes of this study.

Statistical analysis

Subjects reporting PMA were compared with subjects without PMA across demographic and clinical variables. Continuous variables were summarized by their mean and SD and compared using 2-sample *t* tests. Categorical variables were summarized by number and percentage and analyzed by chi-square or Fisher exact analysis. Covariates expected a priori to have a positive effect on the odds of PMA were included in a multivariate logistic regression model. Covariates included age of first aspirin reaction, race, body mass index, diagnosis of AERD before menarche, irregular menses, gastroesophageal reflux disease, hormone-containing contraceptive (HCC) use, and emergency department (ED) visit frequency. Logistic regression assessed crude and adjusted associations between PMA and clinical demographical factors. The regression coefficients were reported as odds ratios. The Hosmer-Lemeshaw test was used to assess goodness of fit. Stability of our inferences was assessed in sensitivity analyses by categorizing the continuous variables and modeling different cutoffs. We used alpha of 0.05 for statistical

significance. All analyses were conducted using Stata/IC 15.1, StatCorp (2017) Statistical Software: Release 15 (StataCorp LLC, College Station, Texas).

RESULTS**Baseline characteristics**

Of the 695 females enrolled in the BWH AERD registry at the time of survey, 369 (53.1%) responded. Among the respondents, 30 developed AERD after menopause and were excluded from further analysis. Of the remaining 339 females, 322 reported having asthma, 10 reported not having asthma, and 7 failed to respond to this question. Ultimately, 322 females were included in this analysis ([Figure 1](#)). Age at development of the AERD clinical triad, atopy, maintenance asthma medications, and ED utilization did not differ between survey responders and nonresponders (see [Table E1](#) in this article's Online Repository at www.jaci-inpractice.org). Survey responders were more likely to self-identify as white and reported more gastroesophageal reflux disease, lower rates of hospitalization for asthma, fewer days on oral steroids per year, and greater nasal steroid use than survey nonresponders.

Twenty-four percent (*n* = 78) of females enrolled in the BWH AERD registry reported PMA, answering "yes" to menstruation as a trigger for asthma symptoms. Those with PMA compared without PMA were younger at asthma diagnosis, first nonsteroidal anti-inflammatory drug reaction, and diagnosis of nasal polyps. In addition, females with PMA were more likely to experience perimenstrual worsening of sinus symptoms, answering "yes" to menstruation as a trigger for sinus symptoms. Females with PMA and perimenstrual worsening of sinus symptoms tended to experience worsening of their symptoms concurrently the week before menses. Asthma and sinus symptom severity was more likely to change with HCC use and at menopause in females with PMA ([Table I](#)). In addition, females with PMA were more likely to report worsening of sinus symptoms in the first and second trimesters of their first pregnancy (see [Table E2](#) in this article's Online Repository at www.jaci-inpractice.org).

Inflammatory factors, comorbidities, and asthma severity

Females with and without PMA had similar IgE levels, peripheral eosinophil counts, and history of atopy, gastroesophageal reflux disease, and number of previous polypectomies. There was no difference in types of asthma medication used or baseline FEV₁% of predicted. In terms of asthma severity, females with PMA had similar Global Initiative for Asthma step scores as females without PMA; however, females with PMA visited the ED and were admitted to the hospital more than females without PMA ([Table II](#)).

A multivariate logistic regression analysis was used to determine risk factors most strongly associated with PMA ([Table III](#)). In the unadjusted model, younger age at first nonsteroidal anti-inflammatory drug reaction, lack of HCC use, and more ED visits were associated with PMA. In the final adjusted model, HCC use was no longer associated with PMA. Older age of first aspirin reaction was associated with significantly lower odds of reporting PMA (odds ratio, 0.96; 95% CI, 0.92-0.99). In addition, those with asthma who had more ED visits per 10 years of asthma diagnosis had higher odds (odds ratio, 1.12; 95% CI, 1.02-1.23) of reporting PMA.

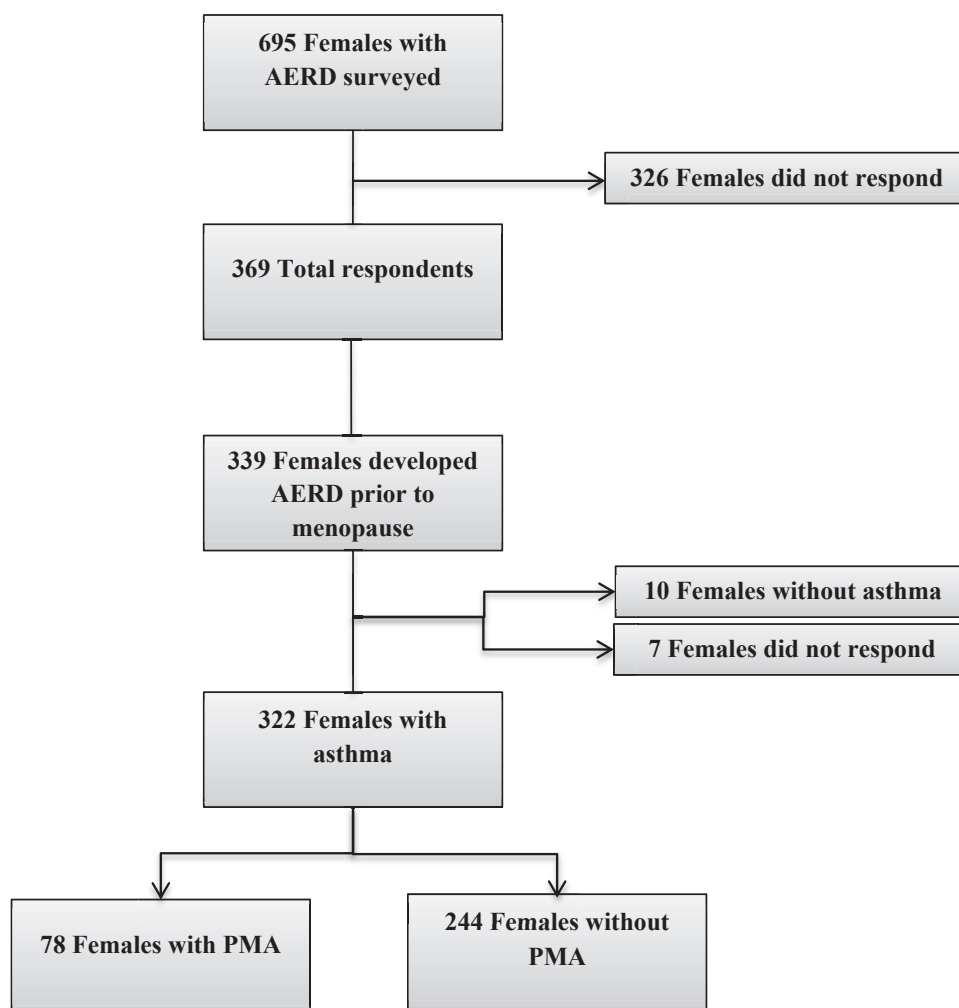


FIGURE 1. Flow diagram of study population. A total of 695 females in the BWH AERD registry were surveyed, with 369 females responding to the initial survey. Thirty females reported developing AERD after menopause and were excluded from the study. Of the remaining 339 females, 322 reported having asthma, 10 reported not having asthma, and 7 failed to respond to this question. Ultimately, 322 females with asthma were included in this analysis.

DISCUSSION

During their childbearing years, 11% to 44% of females with asthma report perimenstrual worsening of their asthma symptoms consistent with PMA.^{1,2,9-12} Two studies described an association between PMA and AERD.^{3,4} Suzuki et al³ reported PMA in 11.3% of 480 actively menstruating women with asthma in Japan and found a significantly greater proportion of patients with AERD among the PMA group than among the non-PMA group.³ Rao et al⁴ conducted a similar sized study using the SARP database and found AERD (reported as aspirin sensitivity) to be the strongest distinguishing characteristic of PMA. Both studies were composed of relatively few subjects with AERD, less than 10% and 12%, respectively.

Our study is the first to assess for PMA in a well-characterized, large cohort composed only of patients with AERD. Using the same self-reported criteria for PMA as previous studies, 24% of females with AERD report PMA.^{4,13,14} Like our study, Rao et al assessed PMA by questionnaire and reported PMA in 17% of the SARP database. Although our study supports a higher prevalence

of PMA in patients with AERD, an appropriate aspirin-tolerant cohort for direct comparison is required to confirm this observation.

Females with AERD and concomitant PMA reported earlier development of each clinical feature of AERD as compared with the non-PMA group (Table I). In our adjusted model, earlier age of onset increased the odds of PMA (Table III). There was no difference in the age of onset between survey responders and non-responders, limiting the possibility of response bias as the explanation for this finding (Table E1). Other studies reported that females with PMA have earlier age of asthma onset than do females without PMA.^{2,4,14} The relationship between earlier age of asthma/AERD onset and PMA is interesting and raises questions about a common pathobiological factor unique to early adulthood.

Females with PMA seek emergency care and are hospitalized more frequently than are females without PMA.^{4,14} In SARP, females with PMA demonstrated an increase in health care utilization even after controlling for asthma severity.⁴ Our study supports these findings and extends them to the AERD

TABLE I. Univariate analysis of demographic and clinical characteristics in the PMA and non-PMA groups

Characteristic	With PMA (n = 78)	Without PMA (n = 244)	P value*
Age at survey (y)	44.0 ± 10.5	46.5 ± 12.4	.11
Race			
White	75 (96.2)	227 (93.0)	.27
Other	3 (3.8)	17 (7.0)	
BMI (kg/m ²)†	26.8 ± 6.4	25.9 ± 5.2	.28
Age at asthma diagnosis (y)‡	24.2 ± 11.4	27.7 ± 11.6	.026
Age at first NSAID reaction (y)§	26.8 ± 8.8	31.9 ± 10.8	<.001
Age at first nasal polyp (y)	29.2 ± 9.0	31.9 ± 10.1	.042
Age of menarche (y),¶ mean	12.9 ± 2.3	12.8 ± 2.3	.89
Onset of AERD			
Before menarche	6 (7.7)	10 (4.1)	.23
After menarche	72 (92.3)	234 (95.9)	
Regular periods#	63 (82.9)	193 (79.4)	.62
Time of asthma symptom worsening**			
Week before menses	48 (62)	—	—
Week of menses	29 (38)	—	—
Sinus symptom worsening with menses††	64 (83.1)	21 (8.6)	<.001
Time of sinus symptom worsening			
Week before menses	41 (67)	10 (53)	.28
Week of menses	20 (33)	9 (47)	
HCC use‡‡	43 (55.1)	164 (67.8)	.056
Changes to asthma/sinus symptoms with HCC			
Improvement	6 (15.4)	4 (2.5)	<.001
Worsening	14 (35.9)	6 (3.7)	
No change	19 (48.7)	151 (93.8)	
Menopause§§	20 (25.6)	78 (32.1)	.32
Age at menopause (y)	50.3 ± 5.6	50.6 ± 4.2	.81
Asthma and menopause			
Improvement of asthma	6 (32)	1 (1)	<.001
Worsening of asthma	7 (37)	16 (21)	
No change in asthma	6 (32)	61 (78)	
Sinus symptoms and menopause			
Improvement of sinus symptoms	6 (30)	4 (5)	<.001
Worsening of sinus symptoms	7 (35)	14 (18)	
No change to sinus symptoms	7 (35)	60 (77)	

BMI, Body mass index; NSAID, nonsteroidal anti-inflammatory drug.

Data are presented as mean ± SD or n (%).

*P values for comparison of means and percentages were calculated using Student *t* test for continuous variables and χ^2 test for categorical variables. Bold indicates statistical significance (*P* < .05).

†Available data in 65 subjects in the PMA group and 226 subjects in the non-PMA group.

‡Available data from 73 subjects in the PMA group and 221 subjects in the non-PMA group.

§Available data from 70 subjects in the PMA group and 222 subjects in the non-PMA group.

||Available data from 73 subjects in the PMA group and 223 subjects in the non-PMA group.

¶Available data from 68 subjects in the PMA group and 219 subjects in the non-PMA group.

#Available data from 76 subjects in the PMA group and 243 subjects in the non-PMA group.

**Available data from 77 subjects in the PMA group.

††Available data from 77 subjects in the PMA group and 243 subjects in the non-PMA group.

‡‡Available data from 78 subjects in the PMA group and 243 in the non-PMA group.

§§Available data from 78 subjects in the PMA group and 243 in the non-PMA group.

phenotype. Although Global Initiative for Asthma step scores, FEV₁% predicted, and use of oral steroids did not differ between women with and without PMA, women with PMA had increased hospitalizations and ED visits for asthma per 10 years of asthma diagnosis. In our adjusted model, ED visits for asthma increased the odds of PMA. These findings suggest that women with concomitant AERD and PMA have increased health care utilization despite exhibiting similar markers of asthma severity.

Awareness of this high-risk phenotype by clinicians may lead to improved outcomes for these high-risk patients.

Our study is the first to describe perimenstrual worsening of sinus symptoms. Furthermore, it is the first study to describe a link between PMA and perimenstrual worsening of sinus symptoms. We are not aware of a study exploring menstruation-related sinus changes in females with asthma or PMA.

TABLE II. Univariate analysis of clinical factors associated with AERD in PMA and non-PMA groups

Characteristic	With PMA (n = 78)	Without PMA (n = 244)	P value*
No. of polypectomies†	2.7 ± 4.2	2.6 ± 2.1	0.89
GERD‡	38 (52.1)	149 (62.3)	0.13
Allergic sensitization§	14 (20.9)	49 (21.8)	1.00
Absolute eosinophils	0.5 ± 0.4	0.5 ± 0.3	0.85
IgE level¶	288.4 ± 412.0	113.7 ± 102.6	0.12
GINA asthma step score#			0.91
1	1 (5)	4 (8)	
2	4 (18)	9 (18)	
3	4 (18)	13 (26)	
4	8 (36)	16 (32)	
5	5 (23)	18 (16)	
FEV ₁ % of predicted**	89.6 ± 16.1	88.7 ± 15.7	0.86
ED frequency††	3.0 ± 6.3	1.2 ± 2.4	<0.001
Hospitalization frequency‡‡	0.5 ± 1.0	0.3 ± 0.8	0.045
Montelukast use	40 (51.3)	128 (52.5)	0.90
Inhaled corticosteroid use	23 (29.5)	93 (38.1)	0.18
Systemic corticosteroid use	14 (17.9)	34 (13.9)	0.37
Days of oral steroid use in past year§§	32.2 ± 48.1	35.4 ± 68.6	0.75

GERD, Gastroesophageal reflux disease; GINA, Global Initiative for Asthma.

Data are presented as mean ± SD or n (%).

*P values for comparison of means and percentages were calculated using Student *t* test for continuous variables and χ^2 test for categorical variables. Bold indicates statistical significance ($P < .05$).

†Available data in 69 subjects in the PMA group and 221 subjects in the non-PMA group.

‡Available data in 73 subjects in the PMA group and 239 subjects in the non-PMA group.

§Available data in 67 subjects in the PMA group and 225 subjects in the non-PMA group.

||Available data in 9 subjects in the PMA group and 20 subjects in the non-PMA group.

¶Available data in 9 subjects in the PMA group and 16 subjects in the non-PMA group.

#Available data in 22 subjects in the PMA group and 50 subjects in the non-PMA group.

**Available data in 13 subjects in the PMA group and 35 subjects in the non-PMA group.

††ED frequency = number of visits to the ED for asthma for every 10 y the patient has had asthma; Available data in 66 subjects in the PMA group and 219 subjects in the non-PMA group.

‡‡Hospitalization frequency = number of admissions to the hospital for asthma for every 10 y patient has had asthma; Available data in 67 subjects in the PMA group and 207 subjects in the non-PMA group.

§§Available data in 52 subjects in the PMA group and 185 subjects in the non-PMA group.

TABLE III. Modeling PMA as a function of demographic and clinical measures (N = 239)

Variable	OR	P value*	Adjusted OR	P value†
Age of first aspirin reaction (y)	0.95 (0.92-0.98)	.001	0.96 (0.92-0.99)	.02
Race				
White	1.0 (reference)			.88
Other	0.53 (0.15-1.87)	.33	1.11 (0.27-4.60)	
BMI (kg/m ²)	0.97 (0.93-1.02)	.28	0.97 (0.91-1.03)	.30
Age of developing AERD				
After menstruation	1.0 (reference)			
Before menstruation	1.95 (0.69-5.55)	.211	0.81 (0.18-3.62)	.78
Periods				
Irregular	1.0 (reference)			
Regular	1.26 (0.64-2.46)	.50	1.37 (0.55-3.42)	.50
GERD	0.66 (0.37-1.11)	.12	0.64 (0.33-1.23)	.18
HCC Use	0.58 (0.35-0.98)	.04	0.80 (0.41-1.58)	.52
ED visit frequency‡	1.12 (1.04-1.23)	.005	1.12 (1.02-1.23)	.017

BMI, Body mass index; GERD, gastroesophageal reflux disease; OR, odds ratio.

Data are presented as OR (95% CI). Bold indicates statistical significance ($P < .05$).*Hosmer and Lemeshaw goodness-of-fit test $P = .50$.

†Fully adjusted model for all other variables.

‡ED frequency = number of visits to the ED for asthma for every 10 y the patient has had asthma.

Studies of females without asthma reported that nasal reactivity increased with menstruation whereas nasal patency and nasal peak flow did not change.^{15,16} In AERD, asthma symptoms coexist with chronic sinusitis and nasal polyposis partially due to dysregulation of prostaglandin E₂ signaling and subsequent mast cell activation and cysteinyl leukotriene and prostaglandin D₂ production.¹⁷ Given the association between PMA and perimenstrual worsening of sinus symptoms in females with AERD, it is possible these 2 phenomena are linked by a common mechanistic pathway. We postulate that PMA and perimenstrual worsening of sinus symptoms may be mediated by lipid mediators and/or mast cell activation.

Finally, our data suggest that women with PMA report that menopause alters the severity of asthma and sinus symptoms more frequently than do women without PMA. This finding is important given the limited data on the impact of menopause on disease severity or symptoms in undifferentiated asthma and the AERD phenotype. Although studies reported that asthma onset is higher, lung function decline greater, and exacerbations increased after menopause, those generalizations may not hold true for the PMA and AERD phenotypes.¹⁸⁻²⁰ Future studies are needed to explore the effect of menopause, as well as hormone replacement therapy, on asthma and sinus symptoms in the setting of AERD and PMA.

The primary limitation of this study is that it lacks an objective evaluation of asthma and sinus symptoms throughout the menstrual cycle and is open to recall bias. Our questionnaire did not quantify the frequency or severity of PMA symptoms. Future studies with objective parameters for a diagnosis of PMA and with collection of PMA symptoms and severity over several menstrual cycles will aid in further understanding of PMA. Because there are no established criteria for diagnosing PMA, a nondifferential misclassification in the outcome may have nullified some of our results. Although survey participants were not specifically informed that the goal of the survey was to collect information on PMA, we cannot exclude that response bias impacts our results. The differences observed in prednisone use and hospitalization rates between the survey responders and nonresponders (Table E1) suggest that our responders either have less severe or better-controlled asthma. Because PMA is consistently associated with greater asthma severity and health care utilization, the observed differences between responders and nonresponders may underestimate the true incidence of PMA in AERD. Despite these limitations, the large sample size and well-characterized population with AERD strengthen our findings.

This work confirms that females with AERD frequently report PMA and identifies a novel association between menstruation and increased sinus symptoms. It strengthens the argument for a common etiology linking the AERD and PMA subphenotypes of asthma. Future studies should explore the pathophysiology of

PMA and AERD. Clinicians need to be aware that the overlap of PMA and AERD represents a population at risk for health care utilization. Females with asthma reporting aspirin intolerance should be counseled about asthma and sinus symptom worsening in relationship to menstruation.

REFERENCES

1. Vrieze A, Postma DS, Kerstjens HA. Perimenstrual asthma: a syndrome without known cause or cure. *J Allergy Clin Immunol* 2003;112:271-82.
2. Sanchez-Ramos JL, Pereira-Vega AR, Alvarado-Gomez F, Maldonado-Perez JA, Svanes C, Gomez-Real F. Risk factors for premenstrual asthma: a systematic review and meta-analysis. *Expert Rev Respir Med* 2017;11:57-72.
3. Suzuki K, Hasegawa T, Sakagami T, Koya T, Toyabe S, Akazawa K, et al. Analysis of perimenstrual asthma based on questionnaire surveys in Japan. *Allergol Int* 2007;56:249-55.
4. Rao CK, Moore CG, Bleecker E, Busse WW, Calhoun W, Castro M, et al. Characteristics of perimenstrual asthma and its relation to asthma severity and control: data from the Severe Asthma Research Program. *Chest* 2013;143:984-92.
5. Berges-Gimeno MP, Simon RA, Stevenson DD. The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2002;89:474-8.
6. Szczeklik A, Nizankowska E, Duplaga M. Natural history of aspirin-induced asthma. AIANE Investigators. European Network on Aspirin-Induced Asthma. *Eur Respir J* 2000;16:432-6.
7. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
8. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377-81.
9. Beynon HL, Garbett ND, Barnes PJ. Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone. *Lancet* 1988;2:370-2.
10. Chhabra SK. Premenstrual asthma. *Indian J Chest Dis Allied Sci* 2005;47:109-16.
11. Enright T, Lim DT, Devnani R, Mariano R. Cyclical exacerbation of bronchial asthma. *Ann Allergy* 1987;58:405-6, 52-53.
12. Nakasato H, Ohnishi T, Sekizawa K, Matsui T, Yamaya M, Tamura G, et al. Prevention of severe premenstrual asthma attacks by leukotriene receptor antagonist. *J Allergy Clin Immunol* 1999;104:585-8.
13. Farha S, Asosingh K, Laskowski D, Hammel J, Dweik RA, Wiedemann HP, et al. Effects of the menstrual cycle on lung function variables in women with asthma. *Am J Respir Crit Care Med* 2009;180:304-10.
14. Agarwal AK, Shah A. Menstrual-linked asthma. *J Asthma* 1997;34:539-45.
15. Paulsson B, Gredmark T, Burian P, Bende M. Nasal mucosal congestion during the menstrual cycle. *J Laryngol Otol* 1997;111:337-9.
16. Haeggstrom A, Ostberg B, Stjerna P, Graf P, Hallen H. Nasal mucosal swelling and reactivity during a menstrual cycle. *ORL J Otorhinolaryngol Relat Spec* 2000;62:39-42.
17. Cahill KN, Boyce JA. Aspirin-exacerbated respiratory disease: mediators and mechanisms of a clinical disease. *J Allergy Clin Immunol* 2017;139:764-6.
18. Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA* 1992;268:3437-40.
19. Triebner K, Johannessen A, Puggini L, Benediktsdottir B, Bertelsen RJ, Bifulco E, et al. Menopause as a predictor of new-onset asthma: a longitudinal Northern European population study. *J Allergy Clin Immunol* 2016;137:50-57.e6.
20. Triebner K, Matulunga B, Johannessen A, Suske S, Benediktsdottir B, Demoly P, et al. Menopause is associated with accelerated lung function decline. *Am J Respir Crit Care Med* 2017;195:1058-65.

ONLINE REPOSITORY

TABLE E1. Univariate analysis of demographic and clinical factors associated with asthma and AERD among survey responders and survey nonresponders

Characteristic	Responder (n = 369)	Nonresponder (n = 326)	P value*
Age at survey (y)	47.5 ± 12.7	45.7 ± 12.5	.061
Race†			
White	347 (94.0)	287 (88.3)	.003
Other	22 (6.0)	38 (11.7)	
BMI (kg/m ²)‡	26.8 ± 6.1	27.4 ± 7.0	.23
Age at asthma diagnosis (y)§	28.1 ± 12.8	28.2 ± 13.1	.96
Age at first NSAID reaction (y)	33.0 ± 12.5	32.2 ± 11.7	.46
Age at first nasal polyp (y)¶	33.0 ± 11.5	32.8 ± 11.4	.77
GERD#	216 (60.5)	158 (50.5)	.010
FEV ₁ % of predicted**	88.0 ± 16.6	83.6 ± 17.2	.11
No. of polypectomies††	2.5 ± 2.7	2.4 ± 2.3	.69
Allergic sensitization‡‡	257 (77.6)	234 (80.7)	.37
Absolute eosinophils§§	0.5 ± 0.3	0.5 ± 0.4	.78
IgE level	231.6 ± 467.9	207.1 ± 301.1	.78
ICS inhaler	129 (35.0)	103 (31.6)	.38
Nasal corticosteroid	274 (74.3)	198 (60.7)	<.001
Combination ICS/LABA inhaler	173 (46.9)	161 (49.4)	.54
Montelukast/zafirlukast	193 (52.3)	166 (50.9)	.76
Zileuton	26 (7.0)	17 (5.2)	.35
Omalizumab	11 (3.0)	13 (4.0)	.54
Oral steroids	50 (13.6)	46 (14.1)	.91
Aspirin	82 (22.2)	55 (16.9)	.086
Asthma step¶¶			.96
1	6 (7.1)	9 (8.5)	
2	14 (16.5)	21 (19.8)	
3	19 (22.4)	23 (21.7)	
4	30 (35.3)	33 (31.1)	
5	16 (18.8)	20 (18.9)	
ED frequency##	1.8 ± 4.0	2.3 ± 4.9	.22
Hospitalization frequency***	0.4 ± 1.2	1.3 ± 6.4	.017
Days of oral steroid use in past year†††	33.1 ± 60.8	46.9 ± 82.8	.030

BMI, Body mass index; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; NSAID, nonsteroidal anti-inflammatory drug. Data are presented as mean $\pm$ SD or n (%). Bold indicates statistical significance ($P < .05$).

*P values for comparison of means and percentages were calculated using Student *t* test for continuous variables and χ^2 test for categorical variables.

†Available data from 369 responders and 325 nonresponders.

‡Available data from 335 responders and 286 nonresponders.

§Available data from 327 responders and 295 nonresponders.

||Available data from 332 responders and 263 nonresponders.

¶Available data from 339 responders and 303 nonresponders.

#Missing data from 12 responders and 13 nonresponders.

**Available data from 309 responders and 93 nonresponders.

††Available data from 300 responders and 301 nonresponders.

‡‡Available data from 331 responders and 300 nonresponders.

§§Available data from 39 responders and 54 nonresponders.

|||Available data from 31 responders and 49 nonresponders.

¶¶Available data from 85 responders and 106 nonresponders.

##ED frequency = number of visits to the ED for asthma for every 10 y the patient has had asthma; Available data from 306 responders and 262 nonresponders.

***Hospitalization frequency = number of admissions to the hospital for asthma for every 10 y patient has had asthma; Available data from 305 responders and 267 nonresponders.

†††Available data from 93 responders and 86 nonresponders.

TABLE E2. Asthma and sinus symptoms with pregnancy

Characteristic	With PMA (n = 78)	Without PMA (n = 244)	P value*
Have you been pregnant since your diagnosis of AERD?			
Yes	38 (48.7)	93 (38.1)	0.11
No	40 (51.3)	151 (61.9)	
First-trimester first-pregnancy asthma symptoms			
Improved	8 (26)	13 (19)	0.072
Same	11 (35)	41 (59)	
Worsened	12 (39)	15 (22)	
Second-trimester first-pregnancy asthma symptoms			
Improved	10 (32)	18 (26)	0.59
Same	11 (35)	34 (49)	
Worsened	6 (19)	9 (13)	
NA	4 (13)	8 (12)	
Third-trimester first-pregnancy asthma symptoms			
Improved	7 (23)	20 (29)	0.25
Same	10 (32)	30 (44)	
Worsened	9 (29)	9 (13)	
NA	5 (16)	9 (13)	
First-trimester first-pregnancy sinus symptoms			
Improved	4 (11)	8 (9)	0.012
Same	15 (41)	62 (67)	
Worsened	18 (49)	22 (24)	
Second-trimester first-pregnancy sinus symptoms			
Improved	5 (14)	13 (14)	0.015
Same	8 (22)	45 (49)	
Worsened	16 (43)	19 (21)	
NA	8 (22)	15 (16)	
Third-trimester first-pregnancy sinus symptoms			
Improved	5 (14)	16 (18)	0.19
Same	11 (30)	42 (46)	
Worsened	12 (32)	17 (19)	
NA	9 (24)	16 (18)	
Considering all your symptoms, pregnancy:			
Improved symptoms	8 (22)	24 (27)	0.014
Had no effect	7 (19)	38 (43)	
Worsened symptoms	14 (38)	19 (21)	
Improved some symptoms	8 (22)	8 (9)	
Have you had any additional pregnancies?			
Yes	24 (63)	64 (70)	0.54
No	14 (37)	28 (30)	
First-trimester second-pregnancy asthma symptoms			
Improved	1 (5)	5 (10)	1.00
Same	14 (70)	34 (67)	
Worsened	5 (25)	12 (24)	
Second-trimester second-pregnancy asthma symptoms			
Improved	1 (5)	6 (12)	0.95
Same	12 (60)	27 (52)	
Worsened	5 (25)	14 (27)	
NA	2 (10)	5 (10)	
Third-trimester second-pregnancy asthma symptoms			
Improved	1 (5)	7 (14)	0.87
Same	11 (55)	25 (49)	
Worsened	6 (30)	14 (27)	
NA	2 (10)	5 (10)	

(continued)

TABLE E2. (Continued)

Characteristic	With PMA (n = 78)	Without PMA (n = 244)	P value*
First-trimester second-pregnancy sinus symptoms			
Improved	2 (9)	2 (3)	0.37
Same	12 (52)	40 (63)	
Worsened	9 (39)	21 (33)	
Second-trimester second-pregnancy sinus symptoms			
Improved	2 (9)	4 (6)	0.27
Same	7 (30)	33 (53)	
Worsened	11 (48)	19 (31)	
NA	3 (13)	6 (10)	
Third-trimester second-pregnancy sinus symptoms			
Improved	2 (9)	5 (8)	0.67
Same	9 (39)	32 (51)	
Worsened	8 (35)	19 (30)	
NA	4 (17)	7 (11)	
Considering all your symptoms, pregnancy:			
Improved symptoms	2 (9)	6 (10)	0.13
Had no effect	7 (30)	28 (46)	
Worsened symptoms	9 (39)	24 (39)	
Improved some symptoms	5 (22)	3 (5)	
Have you had any additional pregnancies?			
Yes	11 (46)	28 (41)	0.81
No	13 (54)	37 (59)	
First-trimester third-pregnancy asthma symptoms			
Improved	2 (25)	0 (0)	0.12
Same	4 (50)	16 (70)	
Worsened	2 (25)	7 (30)	
Second-trimester third-pregnancy asthma symptoms			
Improved	1 (12)	0 (0)	0.23
Same	3 (38)	12 (55)	
Worsened	4 (50)	7 (32)	
NA	0 (0)	3 (14)	
Third-trimester third-pregnancy asthma symptoms			
Improved	1 (12)	1 (5)	0.77
Same	5 (62)	12 (55)	
Worsened	2 (25)	6 (27)	
NA	0 (0)	3 (14)	
First-trimester third-pregnancy sinus symptoms			
Improved	1 (10)	1 (4)	0.85
Same	6 (60)	14 (56)	
Worsened	3 (30)	10 (40)	
Second-trimester third-pregnancy sinus symptoms			
Improved	1 (10)	1 (4)	0.46
Same	7 (70)	12 (50)	
Worsened	2 (20)	7 (29)	
NA	0 (0)	4 (17)	
Third-trimester third-pregnancy sinus symptoms			
Improved	1 (10)	2 (8)	0.52
Same	7 (70)	11 (46)	
Worsened	2 (20)	7 (29)	
NA	0 (0)	4 (17)	

(continued)

TABLE E2. (Continued)

Characteristic	With PMA (n = 78)	Without PMA (n = 244)	<i>P</i> value*
Considering all your symptoms, pregnancy:			
Improved symptoms	1 (10)	2 (8)	0.25
Had no effect	1 (10)	11 (44)	
Worsened symptoms	6 (60)	8 (32)	
Improved some symptoms	2 (20)	4 (16)	

NA, Not applicable/available.

Data are presented as mean $\pm$ SD or n (%).

**P* values for comparison of means and percentages were calculated using Student *t* test for continuous variables and χ^2 test for categorical variables. Bold indicates statistical significance (*P* < .05).