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Perimenstrual Asthma in Aspirin-Exacerbated Respiratory Disease

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Abstract

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: Females age 18 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. 24% 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 NSAID-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.

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The Authors have no conflicts of interest to disclose.

Keywords

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 11–44% 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 and colleagues reported aspirin-sensitive asthma as the clinical characteristic most strongly associated with PMA in the Severe Asthma Research Program (SARP) cohort.⁴ To date, no study has evaluated the prevalence of PMA in a cohort of patients with aspirin-sensitive asthma.

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 which 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.

Materials and 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 (Figure E1). Subjects who reported the development of AERD after menopause were excluded from data analysis. Existing clinical data from the AERD registry was extracted and analyzed for survey respondents and non-respondents. Study data were collected and managed using REDCap electronic data capture tools hosted at Brigham and Women's Hospital.^{7, 8} Partners Human Research Committee approved the study (2013-P-001659), and all subjects provided written or online informed consent.

Definition of Perimenstrual Asthma:

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) N/A 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 demographical and clinical variables. Continuous variables were summarized by their mean and standard deviation and compared using two-sample t tests. Categorical variables were summarized by number and percentage and analyzed by chi-squared or Fisher’s 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, BMI, diagnosis of AERD prior to menarche, irregular menses, gastroesophageal reflux disease (GERD), hormone containing contraception (HCC) use and emergency department 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 (2018) Statistical Software: Release 17.

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 non-responders (Table E1). Survey responders were more likely to self-identify as white and reported more GERD, lower rates of hospitalization for asthma, fewer days on oral steroids per year and greater nasal steroid use than survey non-responders.

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 to non-PMA were younger at asthma diagnosis, first NSAID 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 prior to menses. Asthma and sinus symptom severity was more likely to change with HCC use and at menopause in females with PMA (Table 1). In addition, females with PMA were more likely to report worsening of sinus symptoms in the first and second trimester of their first pregnancy (Table E2).

Inflammatory Factors, Comorbidities and Asthma Severity

Females with and without PMA had similar IgE levels, peripheral eosinophil counts, and history of atopy, GERD, 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 (GINA) step scores as females without PMA; however, females with PMA visited the emergency department and were admitted to the hospital more than females without PMA (Table 2).

A multivariate logistic regression analysis was used to determine risk factors most strongly associated with PMA (Table 3). In the unadjusted model, younger age at first NSAID reaction, lack of HCC use, and more emergency department 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 (OR= 0.96, 95% CI: 0.92–0.99). In addition, asthmatics who had more ED visits per 10 years of asthma diagnosis had higher odds (OR = 1.12, 95% CI: 1.02–1.23) of reporting PMA.

Discussion:

During their childbearing years, 11–44% 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 and colleagues reported PMA in 11.3% of 480 actively menstruating asthmatics in Japan and found a significantly greater proportion of patients with AERD among the PMA group compared with non-PMA group.³ Rao and colleagues conducted a similar sized study using the SARP database and found AERD (reported as aspirin-sensitivity) to be the strongest distinguishing characteristic of PMA.⁴ Both studies were comprised of relatively few subjects with AERD, <10% and 12% respectively.

Our study is the first to assess for PMA in a well-characterized, large cohort comprised 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 and colleagues assessed PMA by questionnaire and reported PMA in 17% of the SARP database. While 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 to the non-PMA group (Table 1). In our adjusted model, earlier age of onset increased the odds of PMA (Table 3). There was no difference in the age of onset between survey responders and nonresponders limiting the possibility of response bias as the explanation for this finding (Table E1). Other studies reported females with PMA have earlier age of asthma onset than 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 females without PMA.^{4, 14} In SARP, females with PMA demonstrated an increase in healthcare

utilization even after controlling for asthma severity.⁴ Our study supports these findings and extends them to the AERD phenotype. While GINA step scores, FEV1% predicted, and use of oral steroids did not differ between PMA and non-PMA, females with PMA had increased hospitalizations and ED visits for asthma per 10 years of asthma diagnosis. In our adjusted model, emergency department visits for asthma increased the odds of PMA. These findings suggest women with concomitant AERD and PMA have increased healthcare 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. Studies of non-asthmatic females reported nasal reactivity increased with menstruation while 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 (PG)E₂ signaling and subsequent mast cell activation and cysteinyl leukotriene and PGD production.¹⁷ Given the association between PMA and perimenstrual worsening of sinus symptoms in females with AERD, it is possible these two 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 suggests that women with PMA report menopause alters the severity of asthma and sinus symptoms more frequently than 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. While studies reported 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 its lacks an objective evaluation of asthma and sinus symptoms throughout the menstrual cycle and is open to recall bias. Our questionnaire did not quantify frequency or severity of PMA symptoms. Future studies with objective parameters for diagnosis of PMA and with collection of PMA symptoms and severity over several cycles will aid in the further understanding PMA. As there are no established criteria for diagnosing PMA, a non-differential misclassification in the outcome may have nullified some of our results. Although survey participants were not specifically informed the goal of the survey was to collect information on PMA, we cannot exclude response bias impacts our results. The differences observed in prednisone use and hospitalization rates between the survey responders and non-responders (Table E1) suggests our responders either have less severe or better controlled asthma. Since PMA is consistently associated with greater asthma severity and healthcare 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 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 healthcare utilization. Female asthmatics reporting aspirin-intolerance should be counseled about asthma and sinus symptom worsening in relationship to menstruation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

AERD	Aspirin-exacerbated respiratory disease
PMA	Perimenstrual asthma
SARP	Severe asthma research program
PG	Prostaglandin
BWH	Brigham and Women's Hospital
HCC	Hormone containing contraceptives
GINA	Global initiative for asthma

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Highlights Box:**What is already known about this topic?**

- Aspirin sensitivity is associated with perimenstrual asthma (PMA).

What does this article add to our knowledge?

- 24% of females with AERD report PMA which is associated with younger age at AERD onset, menstruation-related worsening of sinus symptoms, increased asthma-related healthcare utilization, and a change in respiratory symptom severity at menopause.

How does this study impact current management guidelines?

- Females with AERD should be counseled about both upper and lower respiratory symptom deterioration with menstruation.

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.

Table 1 –

Univariate Analysis of Demographic and Clinical Characteristics in the PMA and Non-PMA Group

Characteristic	PMA (n=78)	Without PMA (n=244)	P-Value ^a
Age at survey, y	44.0 ± 10.5	46.5 ± 12.4	0.11
Race			
White	75 (96.2%)	227 (93.0%)	0.27
Other	3 (3.8%)	17 (7.0%)	
BMI (kg/m ²) ^b	26.8 ± 6.4	25.9 ± 5.2	0.28
Age at asthma diagnosis, y ^c	24.2 ± 11.4	27.7 ± 11.6	0.026
Age at first NSAID reaction, y ^d	26.8 ± 8.8	31.9 ± 10.8	<0.001
Age at first nasal polyp, y ^e	29.2 ± 9.0	31.9 ± 10.1	0.042
Age of menarche, mean, y ^f	12.9 ± 2.3	12.8 ± 2.3	0.89
Onset of AERD ^g			
Before menarche	6 (7.7%)	10 (4.1%)	0.23
After menarche	72 (92.3%)	234 (95.9%)	
Regular periods ^h	63 (82.9%)	193 (79.4%)	0.62
Time of asthma symptom worsening ⁱ			
Week before menses	48 (62%)	-	-
Week of menses	29 (38%)	-	-
Sinus symptom worsening with menses ^j	64 (83.1%)	21 (8.6%)	<0.001
Time of sinus symptom worsening			
Week before menses	41 (67%)	10 (53%)	0.28
Week of menses	20 (33%)	9 (47%)	
HCC use ^k	43 (55.1%)	164 (67.8%)	0.056
Changes to asthma/sinus symptoms with HCC			
Improvement	6 (15.4%)	4 (2.5%)	<0.001
Worsening	14 (35.9%)	6 (3.7%)	
No change	19 (48.7%)	151 (93.8%)	
Menopause ^l	20 (25.6%)	78 (32.1%)	0.32
Age at menopause, y	50.3 ± 5.6	50.6 ± 4.2	0.81
Asthma and menopause			
Improvement of asthma	6 (32%)	1 (1%)	<0.001
Worsening of asthma	7 (37%)	16 (21%)	
No change of asthma	6 (32%)	61 (78%)	
Sinus symptoms and menopause			
Improvement of sinus symptoms	6 (30%)	4 (5%)	<0.001
Worsening of sinus symptoms	7 (35%)	14 (18%)	
No change to sinus symptoms	7 (35%)	60 (77%)	

Data are presented as mean $\pm$ SD or No. (%). Y-year(s).

^a *P* values for comparison of means and percentages were calculated using Student's *t* test for continuous variables and χ^2 test for categorical variables.

^b BMI – body mass index; Available data in 65 subjects in PMA group and 226 subjects in non-PMA group.

^c Available data from 73 subjects in PMA group and 221 subjects in non-PMA group.

^d NSAID – non-steroidal anti-inflammatory drug; Available data from 70 subjects in PMA group and 222 subjects in non-PMA group.

^e Available data from 73 subjects in PMA group and 223 subjects in non-PMA group.

^f Available data from 68 subjects in PMA group and 219 subjects in non-PMA group.

^g AERD = aspirin exacerbated respiratory disease.

^h Available data from 76 subjects in PMA group and 243 subjects in non-PMA group.

ⁱ Available data from 77 subject in PMA group.

^j Available data from 77 subject in PMA group and 243 subjects in non-PMA group.

^k HCC = hormonal containing contraceptive; Available data from 78 subject in PMA group and 243 in non-PMA group.

^l Available data from 78 subject in PMA group and 243 in non-PMA group

Table 2—

Univariate Analysis of Clinical Factors Associated with AERD in PMA and Non-PMA groups

Characteristic	PMA (n=78)	Without PMA (n=244)	P-Value ^a
Number of polypectomies ^b	2.7 ± 4.2	2.6 ± 2.1	0.89
GERD ^c	38 (52.1%)	149 (62.3%)	0.13
Allergic sensitization ^d	14 (20.9%)	49 (21.8%)	1.00
Absolute eosinophils ^e	0.5 ± 0.4	0.5 ± 0.3	0.85
IgE level ^f	288.4 ± 412.0	113.7 ± 102.6	0.12
GINA asthma step score ^g			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%)	
FEV1 % of predicted ^h	89.6 ± 16.1	88.7 ± 15.7	0.86
ED frequency ⁱ	3.0 ± 6.3	1.2 ± 2.4	<0.001
Hospitalization frequency ^j	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 ^k	32.2 ± 48.1	35.4 ± 68.6	0.75

Data are presented as mean ± SD or No. (%).

^aP-values for comparison of means and percentages were calculated using Student's t test for continuous variables and χ^2 test for categorical variables.^bAvailable data in 69 subjects in PMA group and 221 subjects in non-PMA group^cGERD = gastroesophageal reflux disease; Available data in 73 subjects in PMA group and 239 subjects in non-PMA group^dAvailable data in 67 subjects in PMA group and 225 subjects in non-PMA group^eAvailable data in 9 subjects in PMA group and 20 subjects in non-PMA group^fAvailable data in 9 subjects in PMA group and 16 subjects in non-PMA group^gGINA asthma step score = global initiative asthma step score; Available data in 22 subjects in PMA group and 50 in non-PMA group^hFEV = forced expiratory volume; Available data in 13 subjects in PMA group and 35 subjects in non-PMA groupⁱED frequency= number of visits to the ED for asthma for every 10 years the patient has had asthma; Available data in 66 subjects in PMA group and 219 subjects in non-PMA group^jHospitalization frequency= number of admissions to the hospital for asthma for every 10 years patient has had asthma; Available data in 67 subjects in PMA group and 207 subjects in non-PMA group^kAvailable data in 52 subjects in PMA group and 185 subjects in non-PMA group

Table—3

Modeling PMA as a Function of Demographic and Clinical Measures (N=239)

Variable	Odds Ratio	P-value ^a	Adjusted Odds Ratio	P-value ^b
Age of first aspirin reaction (years)	0.95 (0.92 – 0.98)	0.001	0.96 (0.92 – 0.99)	0.02
Race				
White	1.0 (reference)			
Other	0.53 (0.15 – 1.87)	0.33	1.11 (0.27 – 4.60)	0.88
BMI (kg/m ²) ^c	0.97 (0.93 – 1.02)	0.28	0.97 (0.91 – 1.03)	0.30
Age of developing AERD ^d				
After menstruation	1.0 (reference)			
Before menstruation	1.95 (0.69–5.55)	0.211	0.81 (0.18–3.62)	0.78
Periods				
Irregular	1.0 (reference)			
Regular	1.26 (0.64–2.46)	0.50	1.37 (0.55–3.42)	0.50
GERD ^e	0.66 (0.37–1.11)	0.12	0.64 (0.33–1.23)	0.18
HCC Use ^f	0.58 (0.35–0.98)	0.04	0.80 (0.41–1.58)	0.52
ED visit frequency ^g	1.12 (1.04–1.23)	0.005	1.12 (1.02–1.23)	0.017

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

^aHosmer and Lemeshaw goodness-of-fit test $p = 0.50$ ^bFully adjusted model for all other variables^cBMI = body mass index^dAERD= aspirin exacerbated respiratory disease^eGERD = gastroesophageal reflux disease^fHCC =hormonal containing contraceptive^gED frequency= number of visits to the ED for asthma for every 10 years the patient has had asthma