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Premenstrual Asthma: Prevalence, Cycle-to-Cycle Variability and Relationship to Oral Contraceptive Use and Menstrual Symptoms

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ORIGINAL ARTICLE

Premenstrual Asthma: Prevalence, Cycle-to-Cycle Variability and Relationship to Oral Contraceptive Use and Menstrual Symptoms

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The prevalence of asthma is higher in women than men of reproductive age and almost half of all hospitalisations for asthma in women occur during the perimenstrual phase of the cycle. The mechanisms of premenstrual asthma (PMA) are unknown and a definition of PMA has not been clearly presented in the literature. The objective of this study was to determine the prevalence of PMA using a variety of definitions, to investigate the cycle-to-cycle variation in PMA, the effects of oral contraceptive use and the relationship between PMA and premenstrual symptoms. Premenopausal women with asthma ($n = 28$) were prospectively followed for at least 12 weeks over 2–4 consecutive menstrual cycles. Asthma symptoms, β_2 -agonist and inhaled corticosteroid use and morning and evening peak expiratory flow were recorded daily. The following types of PMA definitions were investigated: self-reported PMA, increased symptoms, increased medication use, decreased peak flow or a combination of changes in symptoms, medication and peak flow. Changes of more than 20%, for at least 2 consecutive days of the luteal phase (last 14 days of the cycle prior to menstruation) compared to the early follicular phase average (first 7 days after menstruation) were considered PMA. Using a composite definition where subjects experienced increased symptoms and medication use with or without a change in peak flow, 16 subjects were classified as having PMA (57%), while 12 did not have PMA. Only 4 subjects (25%) had PMA in every cycle examined. Fifty-five percent of subjects who used oral contraceptives had PMA, while 59% of subjects who did not use oral contraceptives had PMA. Women who were defined PMA using the composite definition were more likely than those without PMA to experience a 20% decrease in peak flow during the luteal phase. There was no relationship between asthma symptoms and premenstrual symptoms on day 1 of the menstrual cycle in women with PMA. PMA resulting in increased symptoms and medication use occurred in 57% of subjects studied for 2–4 menstrual cycles. The use of oral contraceptives is not protective and further work is required to elucidate the mechanisms of PMA.

Keywords menstrual cycle, asthma, oral contraceptive, exacerbation, luteal, follicular

INTRODUCTION

Premenstrual exacerbations of asthma (PMA) have been described in the literature for many years, however, the prevalence and mechanisms of PMA are not well characterized. Understanding PMA may make a useful contribution to understanding gender differences in asthma and managing exacerbations in adult women.

There are gender differences in asthma prevalence in children and adults. In children prior to puberty, both asthma and hospitalization for asthma are more prevalent in boys than in girls. By age 25–34, this pattern is reversed, and current asthma and hospital admission for asthma are more prevalent in women than in men (1). One study found that almost half of all emergency department presentations for asthma in women occur perimenstrually (2), however, other studies have been conflicting, finding a similar rate of emergency visits for asthma in each phase of the menstrual cycle (3), or

an increase both preovulatory and perimenstrually (4). The hormonal mechanisms associated with these gender-specific relationships are not well understood.

Characterisation of PMA requires adequate recognition of the condition. At present this is limited because there is no consistent definition for premenstrual asthma (PMA) presented in the literature (Table 1). The majority of studies have grouped subjects based on subjective measures, most commonly self-reported PMA in answer to a question such as “Do you have premenstrual exacerbations of asthma?” or “Does your asthma ever seem worse before the menstrual period?” (5–13). Using a self-report definition, the prevalence of PMA varies from 11% to 40%. Three studies from the same research group have used symptom based definitions of PMA, finding a prevalence from 54% to 100% of subjects (14–16). Only two studies have used an objective measure of PMA, by examining decreased peak flow prior to menstruation (17, 18). Magadle *et al.* reported that 19.4% of subjects had a 20% decrease in peak flow prior to menstruation (18), while Nakasato *et al.* found that 11% of subjects had a 40% decrease in peak flow before or during menstruation (17).

Some of the major deficiencies of the existing studies of PMA in the literature are the lack of a consistent “baseline” period during the menstrual cycle to which the premenstrual changes are compared, and a lack of data on whether PMA consistently occurs from cycle-to-cycle. Only 4 studies have investigated objective changes in asthma associated with more than one menstrual cycle (14, 15, 17, 18);

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TABLE 1.—Definitions used in the literature to determine the prevalence of premenstrual asthma.

Study Reference	Type of Definition	Definition	Method	Total Subjects (<i>n</i>)	Subject Characteristics	PMA <i>n</i> (%)
Hanley <i>et al.</i> , 1981 [5]	Self-report	Subjective perception of worsening symptoms at the time of menses	Questionnaire	102	Aged 16–55 years	36 (35%)
Gibbs <i>et al.</i> , 1984 [6]	Self-report	Answered “yes” to “Has your asthma ever varied with your monthly menstrual period?” or “Does your asthma ever seem worse before the menstrual period?”	Questionnaire	114	Aged 14–46 years, attending outpatient clinic for asthma	49 (43%) varied with period, 36 (40%) worse before period
Eliasson <i>et al.</i> , 1986 and 1987 [7, 8]	Self-report	Worsening asthma symptoms before or during the menstrual period	Questionnaire	57	Less than 50 years old, required medical treatment for asthma symptoms.	19 (33%)
Agarwal and Shah, 1997 [9]	Self-report	Perception of deterioration of asthma in relation to menstrual cycle (MLA) or subjective worsening of asthma in the premenstrual week (PMA)	Questionnaire	100	Asthma, 15–45 years, >15% reversibility in FEV ₁ or PEF, non-smokers, not on OCP or oral steroids	MLA: 23 (23%) PMA: 17 (17%)
Mirdal <i>et al.</i> , 1998 [10]	Self-report	Self-reported worsening of asthma around menstruation	Reported to psychologist or psychiatrist during therapeutic sessions	10	Moderate asthma, aged 20–45 years.	4 (40%)
Shames <i>et al.</i> , 1998 [11]	Self-report	Self-reported perimenstrual exacerbations of asthma	Asthma questionnaire	32	Non-smokers, aged 18–50 years, regular menstrual cycles, weekly asthma symptoms, no OCP use.	9 (28%)
Oguzulgen <i>et al.</i> , 2002 [12]	Self-report	Self-reported premenstrual worsening of asthma	Questioned about worsening asthma just before menstruation	40	Attending outpatient clinic	11 (28%)
Suzuki <i>et al.</i> , 2007 [13]	Self-report	Self-reported worsening of asthma related to menstruation	Questionnaire	480	Over 16 years, regularly attending hospital or clinic for asthma management in Japan	56 (11%)
Chandler <i>et al.</i> , 1997 [14] and Ensom <i>et al.</i> , 1999 [15]	Symptoms	Decrease in peak flow of $\geq 20\%$ and/or increase in asthma symptoms premenstrually	Symptoms and peak flow recorded daily for 9 weeks.	14	Aged 18–45 years, within 20% of ideal body weight, regular menstrual cycles, non-smoker, no OCP, not using oral steroids.	14 (100%), 5 (36%) by self-report alone
Ensom <i>et al.</i> , 2003 [16]	Symptoms	Decrease in peak flow of $\geq 20\%$ from maximum morning or evening peak flow and/or $\geq 20\%$ increase in asthma symptoms premenstrually	Symptoms and peak flow recorded daily during one complete menstrual cycle.	28	Within 30% of ideal body weight, no oral steroids, non-smokers, no OCP use, regular menstrual cycles.	15 (54%)
Nakasato <i>et al.</i> , 1999 [17]	Peak flow	>40% decrease in morning peak flow just before or during menstruation.	Daily peak flow measurements	45	Aged 16–43 years, attending outpatient clinic for asthma	5 (11%)
Magadle <i>et al.</i> , 2001 [18]	Peak flow	Decrease in peak flow of $\geq 20\%$ in the 10 days prior to menstruation.	Peak flow and β_2 -agonist use recorded for 3 menstrual cycles	67	Mild to severe asthma, using ICS	13 (19.4%)

OCP: oral contraceptive pill, ICS: inhaled corticosteroid, PEF: peak expiratory flow, FEV₁: Forced expiratory volume at 1 second.

however, the majority of these studies were testing effects of novel treatments (with estradiol (14, 15) or a leukotriene receptor antagonist (17)) during the second menstrual cycle, comparing to the first "control" cycle. Nakasato *et al.* studied 5 subjects with worsening asthma during every menstrual period (17). The PMA of these subjects was severe, with peak flow decreasing by more than 40% from baseline during the first menstrual cycle studied. It is unclear whether the majority of women with PMA have worsening asthma with every menstrual cycle.

The aims of our study were to examine the prevalence of PMA within one cohort of subjects using self-report, symptom, medication and peak flow based definitions of PMA. We also examined the cycle-to-cycle variability of PMA, the effect of oral contraceptive use on PMA and the relationship between PMA asthma symptoms and premenstrual symptoms.

MATERIALS AND METHODS

Ethics approval was provided by the University of Newcastle and Hunter Area Health Service Research Ethics Committees and all subjects gave written informed consent for participation. Premenopausal women with asthma ($n = 32$), aged 21–48 years with regular menstrual cycles entered the study and completed diary cards for at least 12 consecutive weeks. At the initial study visit, a brief menstrual history and history of asthma was obtained, including age of onset of menses, oral contraceptive (OCP) use, regularity of periods, length of menstrual cycle, average duration of period and presence of breakthrough bleeding. Patients were asked "Do you currently associate your period with any changes in your asthma symptoms?" and "Have you ever associated your period with any changes in your asthma symptoms?" and if yes was answered to either of these questions, subjects were considered to have self-reported PMA.

Spirometry was performed and patients were asked about asthma symptoms at night and when waking in the morning, activity limitation due to asthma and the use of reliever medication (rapid acting β_2 -agonist for symptom relief) and maintenance medication (inhaled corticosteroid, ICS). Subjects were provided with a peak expiratory flow meter (Mini Wright peak flow meter, Airmed, Essex, UK) and asked to record the best of three morning and evening peak expiratory flow values on a diary card.

The diary card also recorded details of ICS and β_2 -agonist medication use (puffs per day), and daily symptoms related to asthma, rhinoconjunctivitis and the menstrual cycle. Asthma related symptoms were cough, wheeze, eye irritation and nose irritation, rated as 0 (absent, none at all), 1 (mild discomfort), 2 (moderate discomfort) and 3 (severe discomfort). Menstrual symptoms were rated as 0 (absent), 1 (mild), 2 (moderate) or 3 (severe) and any treatment for these symptoms was recorded daily. A total of 17 symptoms were recorded and included mood symptoms (mood swings, depression/sadness, tension/irritability, anxiety/nervousness, anger/aggression/short tempered, crying spells) and physical symptoms (swelling of extremities, tenderness/fullness of breasts, abdominal bloating, lower abdominal cramping, generalised aches and pains, low backache, headaches, fatigue, increased or decreased appetite, cravings for sweets/salt, insomnia) (19).

A total "asthma symptom score" and "menstrual symptom score" was obtained for each day by summing the individual symptom scores. Diary cards were completed for at least 2 complete and consecutive menstrual cycles (starting on the first day of menstruation) by 28 women.

Following a review of the literature and a review of the data available in this study, five definitions of PMA were proposed, one of which was self-reported PMA (assigned by the subject prior to completing any diary cards, Definition 1). The remaining four definitions were assigned by the investigators after examining symptom, medication use and peak flow diaries over at least 2 consecutive menstrual cycles. These definitions were based on either changes in symptoms (Definition 2), changes in medication use (reliever or maintenance ICS, Definition 3), changes in peak flow ($>20\%$ decrease, Definition 4) or changes in a combination of these factors (increased symptoms and increased medication use with or without a change in peak flow, Definition 5).

The follicular phase was defined as the first 7 days after the completion of menstruation, while the luteal phase was defined as the final 14 days of the cycle prior to the onset of menstruation. Premenstrual changes in asthma were present if they occurred on at least 2 consecutive days of the luteal phase and were 20% greater (symptoms, medication use) or 20% lower (peak flow) compared to the follicular phase average. Patients were considered to have PMA if these changes occurred in any of the cycles (but not necessarily all cycles) examined.

Statistical analysis was conducted using GraphPad Instat version 3.05 (GraphPad Software, San Diego, CA) or Stata version 7 (Stata Corporation, College Station, TX). The two sample test of proportion was used to compare proportions. Group results are given as mean $\pm$ standard error of the mean or median (interquartile range) and compared using an unpaired *t*-test or Mann-Whitney test as appropriate. $p < 0.05$ was considered significant. Area under the curve (AUC) was calculated using GraphPad Prism version 4.02 (GraphPad Software, San Diego, CA). The AUC for each subject was calculated (the first PMA menstrual cycle for the PMA group, and the first menstrual cycle for the no PMA group) and the medians (interquartile range) of the group data were compared using a Mann-Whitney test.

RESULTS

Subject Characteristics

Twenty-eight women completed diary cards for at least two consecutive menstrual cycles and were included in the analyses. Subject characteristics are shown in Table 2.

TABLE 2.—Subject characteristics.

Age (years)	32.7 $\pm$ 1.6
Oral contraceptive use	39%
FEV ₁ % predicted	78.5 $\pm$ 4.8
FVC % predicted	89.7 $\pm$ 3.7
Maintenance ICS use	96.4%
Maintenance LABA use	53.6%

Values are mean $\pm$ standard error of mean, or % of subjects.

TABLE 3.—Prevalence of PMA using different definitions.

	Whole group (n = 28)	OCP sub-group (n = 11)	No OCP sub-group (n = 17)
Definition 1 (Self-report)	n = 13 46% (28%–65%)	n = 4 36% (8%–65%)	n = 9 53% (29%–77%)
Definition 2 (Symptoms)	n = 24 86% (73%–99%)	n = 9 82% (59%–105%)	n = 15 88% (73%–104%)
Definition 3 (Medication use)	n = 20 71% (55%–88%)	n = 7 64% (35%–92%)	n = 13 76% (56%–97%)
Definition 4 (Peak flow)	n = 4 14% (1%–27%)	n = 1 9% (0%–26%)	n = 3 18% (0%–36%)
Definition 5 (Composite)	n = 16 57% (39%–75%)	n = 6 55% (25%–84%)	n = 10 59% (35%–82%)

Values are proportions (95% confidence intervals).
OCP: Oral contraceptive pill.

Definitions of PMA

Table 3 shows the percentage of subjects with PMA based on the 5 proposed definitions, within the whole study group and with subjects grouped according to oral contraceptive use. The symptom based definition gave the highest prevalence of PMA within the study population (86%), followed by the medication use based definition (71%). The lowest prevalence was observed when defining PMA primarily on a decrease in peak flow (14%). Intermediate results were obtained with the self-report definition (46%) and the composite definition (57%). Two of the women who self-reported PMA (15%) reported ever having associated their period with changes in asthma, but did not report currently associating their period with changes in asthma. There were no significant differences in the prevalence of PMA between women who did or did not use oral contraceptives, regardless of the definition of PMA used. There were significantly more women who recorded an increase in symptoms in the luteal phase (definition 2), than who self-reported having PMA (definition 1, Fisher's exact test, $p = 0.0041$).

The agreement between definitions was assessed using the kappa statistic (20). There was good agreement between definition 5 and definition 3 (agreement = 85.7%, kappa = 0.696). Agreement between definition 5 and definition 1 was 67.9% (kappa 0.364), between definition 5 and definition 2 was 71.4% (kappa 0.364) and between definition 5 and definition 4 was 57.1% (kappa 0.222).

We chose to use definition 5 for the remaining analyses, since definition 1 (self-report) was potentially non-specific, while definition 4 (peak flow) was non-sensitive to clinically relevant events. However, definition 5 provided a clinically meaningful definition, since women reported increased symptoms which required them to increase their medication use.

Subject Demographics of the PMA and no PMA Groups

The baseline characteristics including age, height, weight, body mass index, lung function, asthma symptoms and activity limitation in the previous week, current ICS and reliever medication use, long acting β_2 -agonist use and age of onset of menses (Table 4) did not differ significantly between women who had PMA in at least one cycle, compared to those who did not have PMA during the study, using definition 5 (unpaired t -test or Mann Whitney test, $p > 0.05$). One subject in the PMA group did not use ICS at baseline. The median ICS dose

TABLE 4.—Baseline subject characteristics in women without PMA ($n = 12$) and women with PMA ($n = 16$) using definition 5.

	No PMA $n = 12$	PMA $n = 16$
Age (years)	33.3 $\pm$ 2.6	32.3 $\pm$ 2.1
Height (cm)	163.3 $\pm$ 1.5	166.0 $\pm$ 1.8
Weight (kg)	82.8 $\pm$ 8.9	79.8 $\pm$ 4.1
Body Mass Index	30.7 $\pm$ 2.9	29.0 $\pm$ 1.6
Oral contraceptive use (n, %)	5, 42%	6, 38%
Forced expiratory volume at 1 second, FEV ₁ (l)	2.38 $\pm$ 0.20	2.41 $\pm$ 0.19
% Predicted FEV ₁	79.5 $\pm$ 7.2	77.8 $\pm$ 6.8
Forced vital capacity, FVC (l)	3.17 $\pm$ 0.19	3.16 $\pm$ 0.19
% Predicted FVC	91.8 $\pm$ 6.0	88.1 $\pm$ 4.9
FEV ₁ :FVC ratio (%)	74.6 $\pm$ 4.0	74.9 $\pm$ 3.3
Nocturnal asthma symptoms (days/week)	0 (0–0.75)	1 (0–3)
Symptoms on waking (days/week)	1 (0.25–2.5)	0 (0–5.5)
Activity limitation (days/week)	0 (0–0)	0 (0–0.5)
Reliever medication use (days/week)	1 (0.25–5.5)	0 (0–0.5)
Reliever medication use (times/day)	1 (0.5–3)	3 (1.5–7)
Reliever medication use (times/week)	1 (0.25–10.75)	2 (1–3)
Inhaled corticosteroid (ICS) use (μ g/day)	1000 (800–2000)	2000 (1200–3500)
Age of onset of menses (years)	12.9 $\pm$ 0.5	12.7 $\pm$ 0.5
Length of menstrual cycle (days)	28 (28–30)	28 (26–28)
Use of long-acting beta agonists	50%	56%

Values given are mean $\pm$ standard error of mean or median (interquartile range).

was not significantly different between the PMA and no PMA groups (Mann-Whitney test, $p = 0.211$). Oral contraceptive (OCP) use was not significantly different between the groups (Fisher's exact test, $p = 1.000$).

Cycle-to-Cycle Variability of PMA

Of the 16 women with PMA (definition 5), overall, PMA was present in all menstrual cycles studied in 25% of women. Of the subjects with PMA, 2 menstrual cycles were examined in 5 women. Only one of these women had PMA in both cycles examined (20%). Three menstrual cycles were examined in 9 women. Four women had PMA in only one of the cycles examined, 3 women had PMA in 2 of the 3 cycles and 2 women had PMA in all 3 cycles (22%). Four menstrual cycles were examined in two subjects and one had PMA in all 4 cycles (50%) and one had PMA in 3 of the 4 cycles.

Changes in Morning Peak Flow During the Menstrual Cycle

Figure 1 shows the median change in morning peak flow across the menstrual cycle (compared to day 1) in subjects with PMA (Figure 1A) and subjects without PMA (Figure 1B). Area under the curve (AUC) was calculated for each individual and divided by total cycle length and the median (interquartile range) determined for each study group. The median of the individual AUCs for the PMA group was significantly higher than the no PMA group during the luteal phase (Table 5, $p = 0.026$). When adjusted for individual cycle length, the median of the AUCs for the PMA group during the entire menstrual cycle were not

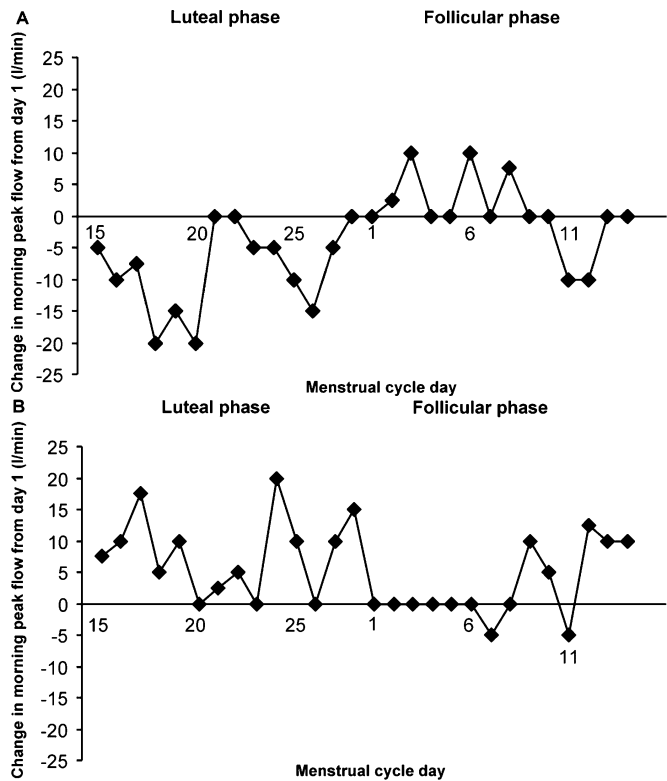


FIGURE 1.—Change in morning peak flow (l/min) across the menstrual cycle compared to the value at day 1 in the PMA group (Panel A) and no PMA group (Panel B). Values are medians.

significantly different from the no PMA group (Table 5, $p > 0.05$). Similarly there was no difference between groups in AUC for morning peak flow in either the full menstrual cycle or the luteal phase only (Figure 2, Table 5, $p > 0.05$).

TABLE 5.—Comparison of area under the curve (AUC) calculations for the full menstrual cycle and luteal phase of the cycle for the PMA group and No PMA group.

	PMA Group	No PMA Group	<i>p</i> -value
A. Luteal phase [AUC]			
Change in morning peak flow from day 1	297.9 (188.1, 714.8)	144.2 (110.6, 248.8)	0.0259
Morning peak flow	4713 (4054, 5538)	4747 (4623, 5080)	0.7277
Reliever medication use	27 (12, 54)	5 (0, 62)	0.3529
Asthma symptoms	24.5 (18.5, 40.1)	12.5 (4, 17.25)	0.0107
Menstrual symptoms	38.5 (21.6, 86.0)	19.0 (9.0, 28.8)	0.0634
B. Full cycle [AUC/cycle length]			
Change in morning peak flow from day 1	20.3 (13.0, 39.3)	12.4 (10.3, 15.4)	0.074
Morning peak flow	356.9 (298.5, 414.8)	355.3 (341.0, 373.3)	1.0
Reliever medication use	1.63 (0.49, 3.39)	0.41 (0.03, 4.86)	0.546
Asthma symptoms	1.81 (1.38, 2.42)	1.04 (0.71, 1.45)	0.053
Menstrual symptoms	3.45 (1.85, 7.21)	2.33 (1.34, 3.8)	0.260

Results are median (interquartile range) for individual area under the curves (AUCs) during the luteal phase (A) or adjusted for total cycle length (B). p -values were determined using a Mann-Whitney test.

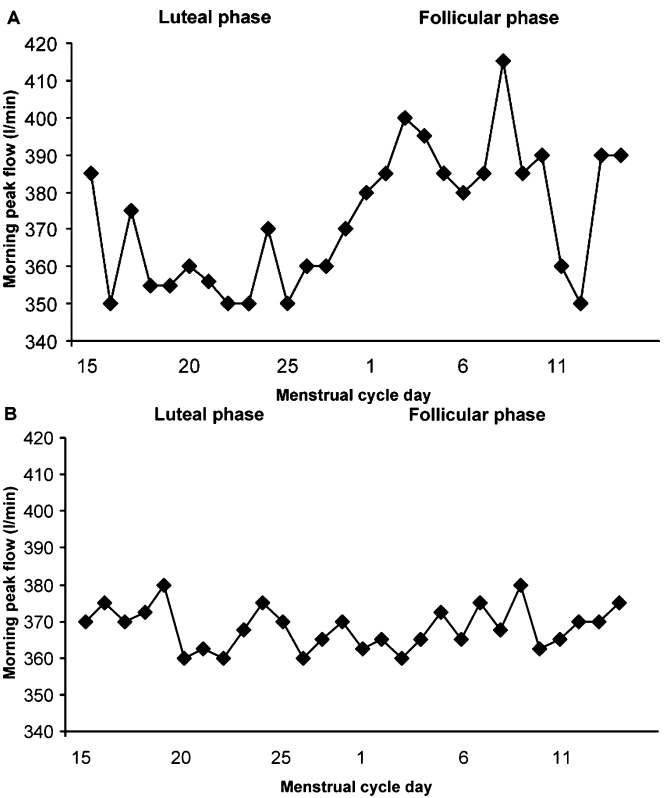


FIGURE 2.—Morning peak flow (l/min) across the menstrual cycle in the PMA group (Panel A) and no PMA group (Panel B). Values are medians.

Changes in Asthma Symptom Score During the Menstrual Cycle

Figure 3 shows the median change in asthma symptom score across the menstrual cycle in subjects with PMA (Figure 3A) and subjects without PMA (Figure 3B). The median of the individual AUCs in the PMA group was significantly higher than the no PMA group during the luteal phase (Table 5, $p = 0.011$).

Changes in Reliever Medication Use During the Menstrual Cycle

Figure 4 shows the median change in reliever medication use across the menstrual cycle in subjects with PMA and subjects without PMA. The median of the individual AUCs in the PMA group was not significantly different from the no PMA group (Table 5, $p > 0.05$).

Changes in Menstrual Symptom Score During the Menstrual Cycle

Figure 5 shows the median change in menstrual symptom score across the menstrual cycle in subjects with PMA and subjects without PMA. The median of the individual AUCs during the luteal phase was higher in the PMA group (38.5, interquartile range [21.6, 86.0]) compared to the no PMA group (19.0, [9.0, 28.8]), but this did not reach statistical significance (Table 5, $p = 0.063$).

Individual curves depicting asthma symptoms, reliever use and menstrual symptoms were further analysed for the overall peak score (representing the severity of symptoms), the

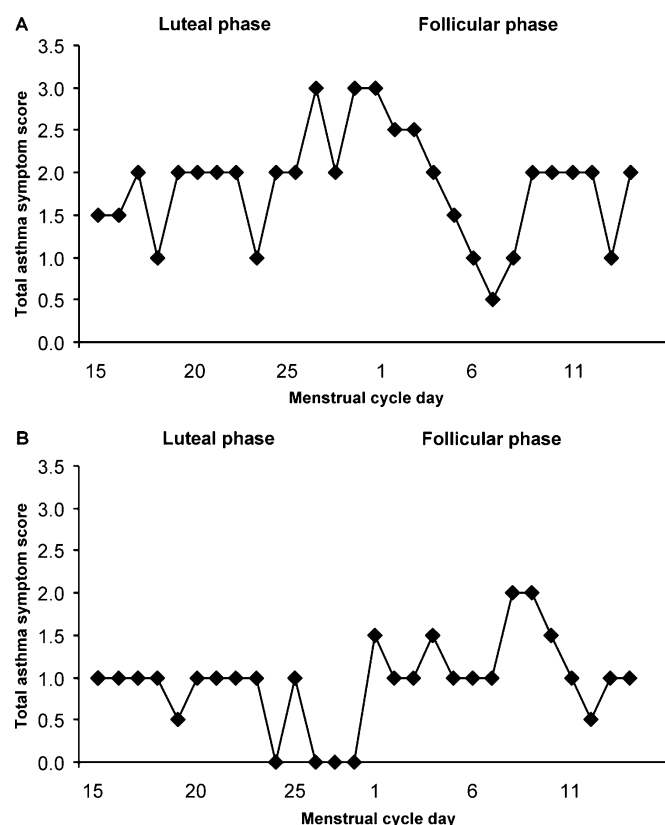


FIGURE 3.—Total asthma symptom score across the menstrual cycle in the PMA group (Panel A) and no PMA group (Panel B). Values are medians.

percentage of days above or below a certain threshold value (representing the symptom burden) and the slope of the curve between the last day of the menstrual cycle and the first (representing the premenstrual change in symptoms). For the morning peak flow curves, the number of subjects with a 20% fall from best was determined, along with the slope of the curve between the last day of the menstrual cycle and the first day. The only significant differences between the PMA and no PMA groups were observed in the morning peak flow. The change in peak flow between the last and first day of the menstrual cycle was significantly greater in the PMA group (Table 6, $p = 0.0484$), while there were more subjects who experienced greater than 20% falls in peak flow in the PMA group compared to the no PMA group (Table 6, $p = 0.0235$).

Relationship Between Asthma Symptoms and Menstrual Symptoms in the PMA Group

There was no significant correlation between the asthma symptom score and the menstrual symptom score on day 1 (when scores tended to peak) in the PMA group (Figure 6, Spearman rank correlation, $r = 0.15$, $p = 0.541$).

DISCUSSION

The results of this study indicate that premenstrual asthma resulting in increased symptoms and medication use is a clinically relevant problem, experienced in at least one menstrual cycle by approximately 57% of subjects studied prospectively over 12 weeks. The definition of PMA used re-

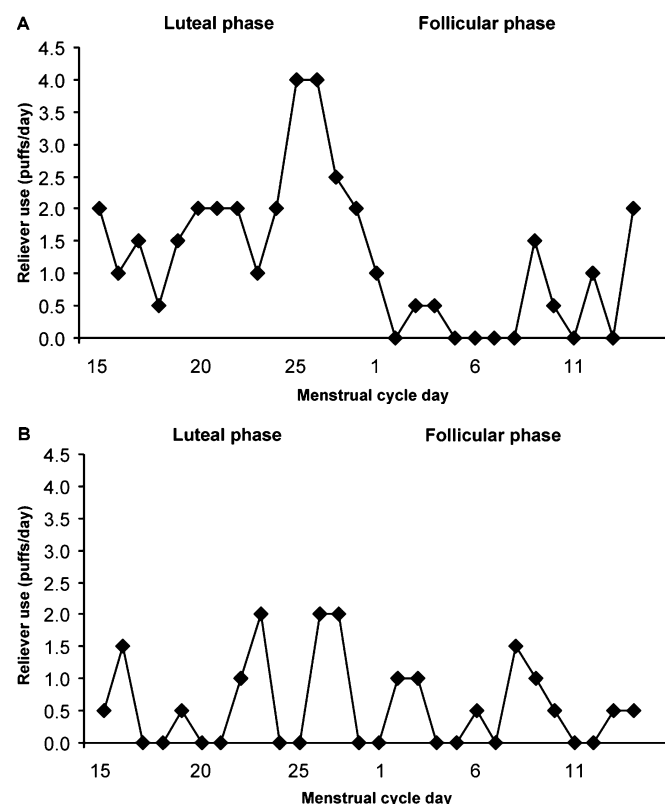


FIGURE 4.—Reliever medication use (puffs/day) across the menstrual cycle in the PMA group (Panel A) and no PMA group (Panel B). Values are medians.

sults in different percentages of women who are affected. Using a definition based primarily on symptoms or medication use gives the greatest proportion of women with PMA (86% or 71% respectively), while using a definition based solely on

TABLE 6.—Curve characteristics in the PMA and no PMA groups.

	PMA Group	No PMA Group	p-Value
Morning Peak Flow			
Number of subjects with any 20% falls in peak flow from best	10/16 (63%)	2/12 (17%)	0.0235*
Slope of curve (day -1 to 1)	25 [-3.75, 42.5]	-10 [-20, 2.5]	0.0484*
Asthma Symptoms			
Peak Score	5 [4, 6.25]	3 [2.75, 5.25]	0.094
% of days above threshold score of 2	31.8 [22.5, 56.5]	13.8 [2.5, 42.8]	0.0818
Slope of curve (day -1 to 1)	0 [-0.25, 1]	0 [-1.25, 1]	0.7264
Reliever Use			
Peak Score	5.5 [2, 8]	2 [0, 7.25]	0.2265
% of days above threshold score of 2	29 [0, 62.5]	0 [0, 94.6]	0.7437
Slope of curve (day -1 to 1)	0 [-2, 0]	0 [-0.25, 0]	0.3008
Menstrual Symptoms			
Peak Score	13 [8.75, 20.5]	10.5 [8, 22]	0.8164
% of days above threshold score of 4	34.5 [10.5, 71.0]	10.2 [7.3, 32.4]	0.1198
Slope of curve (day -1 to 1)	6 [1, 8]	8 [1.75, 11.75]	0.4163

Values are median [interquartile range]. Medians were compared using the Mann-Whitney test.

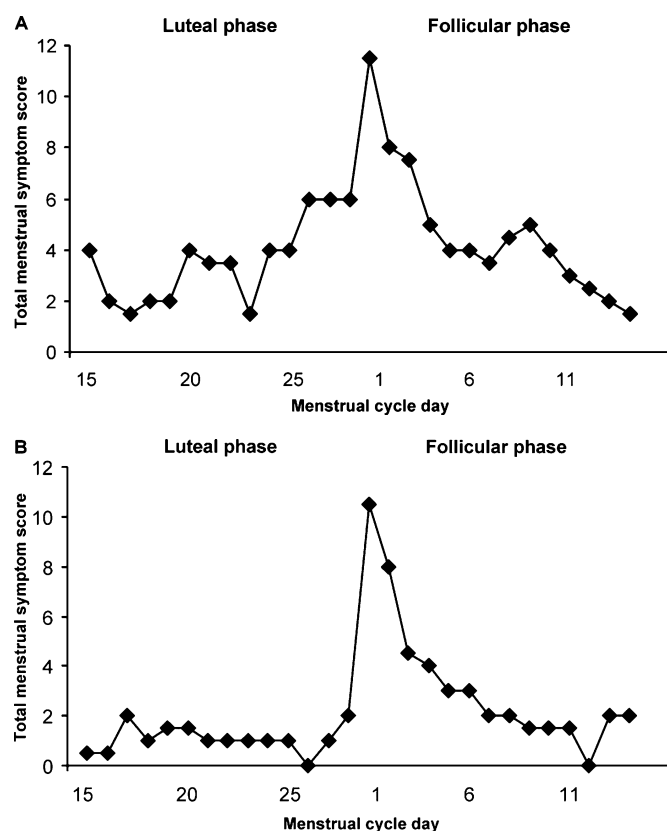


FIGURE 5.—Total menstrual symptom score across the menstrual cycle in the PMA group (Panel A) and no PMA group (Panel B). Values are medians.

a reduction in peak flow gives the lowest proportion of women with PMA (14%). These data suggest that altered symptom perceptions may contribute to PMA, since almost all women in our study reported increased asthma symptoms around the time of menstruation, along with other menstrual cycle related symptoms. Only 46% of women self-reported PMA prior to the commencement of the study, a figure similar to that reported in most previous studies based on questionnaire (5–7, 10).

We believe that the best definition to use is one based on a combination of clinical features (such as increased symptoms

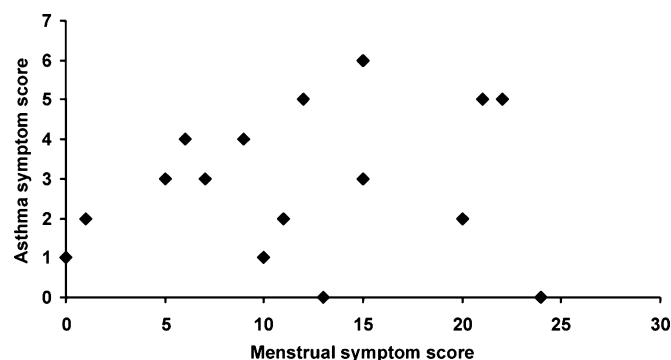


FIGURE 6.—Relationship between asthma symptom score and menstrual symptom score on day 1 of the menstrual cycle in the PMA group ($n = 16$).

and increased medication use), with a clearly defined baseline (follicular phase) and premenstrual phase (luteal phase). A limitation of our study was the inclusion of eye and nose irritation in the overall symptoms of asthma, which may have led to some misclassification of asthma symptoms. However, the specificity of definition 5 for detecting PMA comes from the requirement for both symptoms and asthma medication use to be increased. In addition, there was a strong relationship between PMA using definition 5 and changes in peak flow results around menstruation, which would be specific for asthma, indicating that the effect of any misclassification was minimal.

Asthma in women may be related to an imbalance of sex hormones. A significant proportion of women experience worsening asthma during pregnancy (21, 22) and following puberty, girls are more likely than boys to have asthma and to be hospitalised for asthma (1). During menopause, some studies have found an increased risk of asthma in women using hormone replacement therapy (23, 24). An epidemiological study found an association between asthma and self-reported irregular menstruation among women aged 26 to 42 years, which was unrelated to asthma medication use (25) and recently, similar results were reported from the European Community Respiratory Health Survey, with oligomenorrhea associated with more asthma symptoms and lower FVC (26). A disadvantage of our study was that sex hormone concentrations were not measured. It will be important to establish whether women with PMA have abnormal levels of estrogens or progesterone. One study found that among 30 women with asthma, 80% had at least one hormone (either progesterone, estradiol or cortisol) in the abnormal range, with the most common abnormality being reduced progesterone on day 21 of the menstrual cycle (27).

A recent study of 7 women with exercise-induced bronchoconstriction and normal menstrual cycles, who were not using oral contraceptives found that in the mid-luteal phase (day 21), there was a significantly larger fall in lung function in response to exercise compared to the mid-follicular phase (day 5) (28). This was accompanied by significantly higher asthma symptom scores and bronchodilator use in the mid-luteal phase. In addition, the exercise-induced fall in lung function was related to changes in salivary progesterone, but not estradiol, between days 5 and 21 (28). Few studies have investigated alterations in sex hormone concentrations in women with confirmed PMA and therefore a role for abnormal hormonal status in PMA has not been clearly established.

There have been conflicting reports regarding the effects of oral contraceptive use on asthma. While some authors have suggested oral contraceptives as a treatment for PMA (29), there have been case reports of asthma exacerbations with the commencement of OCP use (30). There are few prospective cohort studies that have adequately investigated this issue. The results of our work indicate that even women using the oral contraceptive pill can have premenstrual asthma and that the proportion of women who use the contraceptive pill is not different between the PMA and no PMA groups. This result is similar to that reported by Gibbs *et al.*, who found a similar rate of PMA among women who did or did not use oral contraceptives (6). This suggests that ovulation is not a necessary requirement for PMA, and supports hormonal withdrawal as a possible mechanism leading to PMA.

Approximately 25% of women experienced PMA in every menstrual cycle examined in this study. This cycle-to-cycle variability of PMA indicates that host asthma factors are also important in the pathogenesis of PMA. These could be exposure to asthma triggers, variable compliance with asthma maintenance therapy, and variable airway responsiveness to the effects of hormonal changes during the menstrual cycle. While there seems to be a necessary hormonal event, this is not sufficient on its own to cause PMA. There are no other studies which have prospectively examined PMA in consecutive menstrual cycles without treatment changes, to examine cycle-to-cycle variability of this condition.

We examined the relationship between asthma symptoms and menstrual symptoms in the PMA group and found no correlation between these measures on day 1 of the menstrual cycle. This data suggests that PMA is not simply a manifestation of the premenstrual syndrome, but rather that increased symptom perception may be an important variable, resulting in the need for more medication use at the end of the menstrual cycle. We also observed that reporting of increased symptoms in the luteal phase on the diary card was significantly more common than reporting previous or current PMA at the start of the study.

Many more women were defined as having PMA when using the symptom or medication based definitions (57% using the composite definition 5), when compared to the peak flow based definition (14%). However, the women with PMA defined by symptoms and medication use were also more likely to have a 20% fall in peak flow in the luteal phase, compared to women who did not have PMA by this definition. The supports the use of the composite definition as one that is clinically relevant.

PMA is experienced by a significant number of women and may lead to an increased requirement for treatment (9) or utilisation of health services on a regular basis. Several studies have found that PMA may contribute to an increased rate of hospitalisations (2, 7) and that women with PMA have more severe asthma than women without PMA. Eliasson *et al.* found that among women with self-reported PMA, 68% had been previously hospitalised for asthma, while among women without PMA, only 26% had been previously hospitalised for asthma (7). In addition, women with PMA had used a significantly greater number of medications and reported more severe symptoms than those without PMA (7). It has also been suggested that the menstrual cycle may play a role in near fatal asthma attacks, with one study finding that more near fatal asthma occurred on the first day of menstruation than on other days of the menstrual cycle (31). The women with PMA who participated in our study did not appear to have more severe asthma than those without PMA, as indicated by similar lung function and medication requirements at baseline.

There is a lack of controlled studies investigating the treatment of PMA. While some small case series (<6 patients) have described the beneficial effects of treatments such as intramuscular progesterone (32), estradiol (33), leukotriene receptor antagonists (17) and gonadotropin-releasing hormone analogs (34), no larger studies have confirmed these findings. One small trial of estradiol administration in 12 women with PMA found no beneficial effect (16). However,

there were promising findings reported by Magadle *et al.* regarding the use of long acting β_2 -agonists for PMA (18). Thirteen women who had premenstrual exacerbations of asthma were given 50 μ g salmeterol or placebo (randomised cross-over design) in the 10 days prior to menstruation. Seven patients had no PMA following salmeterol treatment, while another 2 had a partial reduction in PMA symptoms with salmeterol treatment (18). In our study, a similar proportion of women in the PMA and no PMA groups used long acting β_2 -agonists, however, the subjects were not instructed to increase LABA and the dose and use of these medications was not recorded.

In conclusion, PMA which results in both increased asthma symptoms and increased medication use affects 57% of women with asthma, while 14% of women have a significant decrease in peak flow in the late luteal phase of the menstrual cycle. Most women with PMA do not experience it in every menstrual cycle, and oral contraceptive use does not appear to be protective. In addition, asthma symptoms associated with PMA are not correlated with premenstrual symptoms. Further investigation into the mechanisms and suitable treatments for PMA is required.

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