Respiratory Medicine (2012) 106, 1236–1243

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Clinical characteristics of women with menstrual-linked asthma

Jane Thornton [a], Jim Lewis [b], Constance M. Lebrun [c], Christopher J. Licskai [b,*]

[a] Fowler Kennedy Sport Medicine Clinic, University of Western Ontario, 1151 Richmond Street, London, Ontario N6A3K7, Canada
[b] St. Joseph's Health Care, University of Western Ontario, 268 Grosvenor Street, London, Ontario N6A 4V2, Canada
[c] Glen Sather Sports Medicine Clinic, University of Alberta, Edmonton, Alberta T6G 2H9, Canada

Received 18 February 2012; accepted 14 May 2012
Available online 14 June 2012

KEYWORDS
Allergy;
Asthma;
Human;
Menstrual cycle;
Respiratory

Summary
Background: Menstrual-linked asthma (MLA) is described in pre-menopausal women who experience a deterioration of asthma control peri-menstrually. The clinical characteristics of MLA remain incompletely defined. Our objective was to define the characteristics of MLA in a large female asthma cohort.
Methods: Cross-sectional population survey. A comprehensive health questionnaire that included questions about MLA was administered to 1260 consecutive female asthma patients aged 12–55 years. Univariate and multivariate analyses were completed.
Results: The survey response rate was 43% (540/1260). The prevalence of self-reported MLA was 11% (60/540). Univariate: women with MLA compared to women without MLA had more urgent/emergent asthma-related healthcare visits/year, 6.18 (SD = ±6.67) vs. 4.71 (SD = ±5.91) ($p = 0.033$), more emergency room visits, 1.50 (SD = ±3.57) vs. 0.88 (SD = ±2.27) ($p = 0.035$), higher asthma-related absenteeism, 33/60 (57%) vs. 170/471 (37%) ($p = 0.003$), and used almost twice the number of B_2-agonist rescue doses/day, 1.13 (SD = ±1.70) vs. 0.68 (SD = ±1.32) ($p = 0.015$). Multivariate: statistical significance was retained for absenteeism ($p = 0.016$) and B_2-agonist use ($p = 0.007$) but lost for urgent healthcare visits ($p = 0.150$) and emergency room visits ($p = 0.068$).
Conclusions: Self-reported MLA is common. Women with MLA in our population had a greater frequency of urgent healthcare visits, a higher rate of absenteeism, and used significantly

Abbreviation: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; LTRA, leukotriene receptor antagonist; LABA, long acting B_2-agonist; MLA, menstrual-linked asthma; PEF, peak-expiratory flow; SD, standard deviation.

* Corresponding author. Tel.: +1 519 646 6405; fax: +1 519 646 6064.
E-mail addresses: jane.s.thornton@gmail.com (J. Thornton), jflewis@uwo.ca (J. Lewis), connielebrun@med.ualberta.ca (C.M. Lebrun), clicskai@uwo.ca (C.J. Licskai).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2012.05.003

more B_2-agonist rescue than women without MLA. The association of increased health services use was not confirmed on multivariate analysis indicating that baseline characteristics associated with MLA in our population affected this outcome. MLA should be considered by healthcare providers when developing an asthma management plan.

Introduction

Menstrual-linked asthma (MLA) is a common clinical phenomenon described in pre-menopausal women who experience a deterioration of asthma control perimenstrually. MLA has published prevalence estimates ranging between 11% and 40%.[1–9] Identifying and characterizing the MLA asthma phenotype is a fundamental step toward understanding its pathobiology and toward facilitating the development of specific therapeutic strategies.

Physiologic changes occur during the menstrual cycle that are related to asthma pathophysiology. Fluctuations in the level of estrogen and progesterone are believed to affect airway inflammation, bronchial responsiveness, and expiratory airflow. Specifically, it has been identified that inflammatory modulators important in the pathophysiology of asthma including neutrophils, eosinophils, Th_2-cytokines, and leukotrienes, vary over the course of the menstrual cycle.[10–12] In addition, there is *in vitro* evidence of increased B_2-receptor responsiveness after exposure to progesterone, and clinical evidence of increased peak-expiratory flow (PEF) variability, bronchial responsiveness, symptoms, and B_2-agonist utilization in the late luteal and early follicular phase of the menstrual cycle, when progesterone levels are lowest.[3,4,7,12–16] Within this evolving knowledge base there is currently no unifying pathophysiologic model to explain the relationship between hormonal fluctuation, inflammatory mediators, and airway function in patients with MLA.

It is postulated that physiologic factors related to the menstrual cycle contribute to increased asthma severity in women with MLA. Compared to women who do not report MLA, women with MLA have been shown to have a greater frequency of bronchodilator utilization, a lower forced expiratory volume in one second (FEV_1) or PEF, require a higher dose of inhaled corticosteroid to maintain asthma control; and they also have a higher frequency of emergency department visits, hospitalizations, and near-fatal asthma episodes.[2,3,7,8,12,16–19] However, there remain many conflicting observations in the published literature. While some investigators have reported that women with MLA have higher degrees of atopy,[20] are significantly older,[7] and have had asthma longer,[1,7] other studies report no differences in these factors among patients.[2,4,20]

Although there is currently very limited information on MLA specific therapeutic strategies, studies suggest that a more complete understanding of MLA pathophysiology may lead to specific targeted therapeutic interventions. For example, subjects reporting MLA with decreased PEF rates, and high levels of leukotriene C4 premenstrually, demonstrated improvements in PEF and symptom scores after treatment with leukotriene receptor antagonists.[12] In addition, subjects with MLA placed on oral contraceptive pills (which suppress the luteal phase of the menstrual cycle) demonstrated attenuation of cyclical changes in PEF and adenosine monophosphate bronchial responsiveness.[16] In another study, salmeterol was an effective method to reduce short-acting B_2-agonist utilization and to eliminate a premenstrual fall in PEF in women with MLA.[21]

In this study, we sought to identify and to define the clinical characteristics of the MLA phenotype in a large outpatient clinic population from primary and specialty care practices. Current descriptions of MLA are limited by observations derived predominantly from small studies, which are influenced by ascertainment bias. A more accurate definition of the MLA asthma phenotype will inform future investigation into pathophysiologic mechanisms and specific therapeutic strategies.

Methods

Study design

Within a cross-sectional design we administered a comprehensive health questionnaire to 1260 consecutive subjects attending two primary care community asthma projects and a specialty care asthma centre, between July 2004 and August 2008 in Ontario, Canada. The questionnaire was an integrated component of the patients' clinical evaluation and included demographic information, an asthma-specific history, medication use, symptom profile over the previous 4 weeks, healthcare utilization and absenteeism in the prior year, and co-morbid medical conditions. All regional asthma clinics utilizing this clinical questionnaire tool participated in the study.

Subjects aged 12–55 years self-identified *with* or *without* MLA by answering the question, "Does your asthma change during your menstruation?" If the response was affirmative, the subject was asked to qualify the change, as worse, better, or uncertain. Subjects answering that their asthma changed *and* that it worsened were designated as self-reported MLA.

Spirometric measurements were recorded for all subjects after the questionnaire was administered. Normal spirometry values are as described by Morris.[22] Symptom control benchmarks were recorded as defined by the Canadian Asthma Consensus Guidelines.[23–25] Urgent visits were defined as unscheduled healthcare encounters for asthma symptoms including: Family physician; walk-in clinic, or emergency department visits, and hospital admission. Absenteeism was defined as a day missed at school or work because of asthma.

Patient population

Women with a clinical diagnosis of asthma from primary and specialty care were included in the study. We excluded women aged <12 and >55 years of age.

Statistical analysis

Subjects with MLA were compared to those without MLA using chi-square tests for comparing proportions and unpaired *t*-tests for comparing continuous variables. The number of healthcare visits, number of medications, and doses of rescue medication were compared using a Wilcoxon two-sample test (non-parametric). To compare disease associations for conditions with a low frequency we used the Fisher's exact two-tailed test. Baseline characteristics found to be statistically significant at the 0.10 level were considered for covariate adjustment using logistic regression for proportions (i.e. symptom benchmarks), analysis of covariance for continuous variables (i.e. FEV_1), and negative binomial regression for count data (i.e. number of urgent healthcare visits).

Ethics

The study protocol was approved by the "Office of Research Ethics" at the University of Western Ontario (REB# 15913E). The data were collected prospectively using a questionnaire tool that was a component of the patients' clinical care, therefore a waiver of consent was granted for this analysis.

Results

Data from all individual questionnaires were reviewed for completeness and 548 complete records were identified on our primary review — 224 from primary care asthma clinics and 324 from a specialty care asthma centre. Upon secondary review, a further 8 records were excluded because of incomplete data, leaving 540 records for a response rate of 43% (540/1260). Subjects completing the questionnaire compared to non-participants were younger with a mean age of 34.1 (SD = ±12.2) vs. 38.4 (SD = ±12.2) ($p < 0.001$) and more likely to be non-smokers with a non-smoking prevalence of 67.8% vs. 61.2% ($p = 0.022$).

Sixty-nine (69) subjects reported that their asthma changed during the menstrual cycle; 2/69 (3%) reported that their asthma improved and 7/69 (10%) were uncertain about how their asthma changed. These 9 subjects could not be classified as MLA or non-MLA and were excluded. Sixty (60) subjects reported that their asthma changed and that it became 'worse', meeting our defined criteria for self-reported MLA. The prevalence of MLA in our population was therefore 60/540 (11%).

Subject data were stratified by the source as primary or specialty care. As the comparative results did not differ, the combined results are presented.

General characteristics

Women who reported MLA were similar to women without MLA when comparing multiple general characteristics including age, age at diagnosis, duration of asthma, and smoking status (Table 1). In contrast, women with MLA were significantly more likely to report a family history of hayfever, 32/60 (71%) vs. 211/471 (51%), ($p = 0.010$) or a family history of allergies or eczema, 47/60 (94%) vs. 304/471 (70%) ($p < 0.001$) and 23/60 (51%) vs. 149/471 (35%), respectively, and were more likely to report asthma worsening during pregnancy, 13/24 (54%) vs. 39/129 (30%) ($p = 0.023$) than women without MLA (Table 1).

Asthma medication

Prescribed asthma control medications were similar in both groups (Table 1). We did not identify that subjects with MLA were prescribed more asthma control medications. Of note, the majority of subjects in both groups were on anti-inflammatory therapy and almost half were on inhaled corticosteroid (ICS)/long-acting B_2-agonist (LABA) combination therapy. Subjects with MLA used asthma rescue medications more frequently and had a higher total reported dose of B_2-agonist than non-MLA subjects. Specifically, a higher proportion of MLA subjects used rescue medication doses ≥4 times/week, 29/60 (55%) vs. 159/471 (37%) ($p = 0.010$), and more doses per day, 1.13 (SD = ±1.70) vs. 0.68 (SD = ±1.32) ($p = 0.015$) (Table 2). Statistical significance was maintained in a multivariate model (Table 2: adjusted *p*-values).

Asthma symptoms

These data are presented as individual symptoms and as a composite of ≥2 symptoms outside of the Canadian Asthma Consensus Guidelines benchmark criteria for acceptable control.[23–25] The symptom profile describes symptoms during the 4 weeks prior to the subject's initial clinical visit. Composite and individual symptom measures were similar between the two groups (Table 2).

Absenteeism

Women with MLA were much more likely to miss school or work because of asthma than women without MLA, 33/60 (57%) vs. 170/471 (37%) ($p = 0.003$) (Table 2). Subjects in the MLA group had an almost 3-fold higher mean number of days absent vs. the non-MLA group, 13.6 vs. 4.2 days ($p = 0.043$). Statistical significance was maintained in a multivariate model (Table 2: adjusted *p*-values).

Lung function

The FEV_1, forced vital capacity (FVC), and FEV_1/FVC ratio were not different in the MLA and non-MLA groups (Table 2).

Healthcare utilization

Women with MLA had more urgent/emergent asthma-related healthcare visits in the past 12 months, 6.18 (SD = ±6.67) vs. 4.71(SD = ±5.91) ($p = 0.033$), including more emergency room visits, 1.50 (SD = ±3.57) vs. 0.88 (SD = ±2.27) ($p = 0.035$), than women without MLA. Although women with MLA were more likely to have ever been admitted to the intensive care unit for asthma, 5/60 (10%) vs. 18/471 (4%), this difference is not significant ($p = 0.163$). The statistical significance identified in the

Table 1 Patient characteristics.

Characteristic	Women without MLA ($n = 471$)	Women with MLA ($n = 60$)	p Value
Age			
Mean age (SD)	33.8 (12.4)	36.6 (10.3)	0.097
Mean age at diagnosis	18.8 (13.0)	19.0 (10.3)	0.934
Age at diagnosis categories			0.318
Age ≤12	109 (36.5%)	9 (25.0%)	
Age ≥13 to ≤19	59 (19.7%)	10 (27.8%)	
Age >19	131 (43.8%)	17 (47.2%)	
Duration of asthma (SD)	14.7 (10.6)	15.7 (10.3)	0.594
General characteristics			
BMI	28.3 (7.6)	29.6 (9.0)	0.210
Caucasian	420 (96.1%)	52 (98.1%)	0.464
Smoking status			0.401
Former	74 (15.9%)	13 (22.0%)	
Current	75 (16.1%)	7 (11.9%)	
Family history of asthma	248 (57.8%)	33 (63.5%)	0.435
Asthma worsening during pregnancy	39/129 (30.2%)	13/24 (54.2%)	0.023
Allergy			
Personal history of allergy	320 (69.4%)	44 (78.6%)	0.156
Family history			
Hayfever	211 (51.0%)	32 (71.1%)	0.010
Eczema	149 (35.4%)	23 (51.1%)	0.038
Allergies	304 (70.4%)	47 (94.0%)	<0.001
Asthma control medication			
Any controller	368 (78.1%)	46 (76.7%)	0.797
ICS only	129 (27.4%)	20 (33.3%)	0.334
ICS + LABA	235 (49.9%)	28 (46.7%)	0.638
LTRA only	83 (17.6%)	15 (25.0%)	0.165
Total number	1.00 (0.70)	1.17 (0.87)	0.170

Data presented as mean (SD) and as frequency (%) as appropriate. SD = standard deviation; ICS = inhaled corticosteroid; LTRA = leukotriene receptor antagonist; LABA = long acting B_2-agonist; BMI = body mass index; and MLA = menstrual-linked asthma.

univariate model is lost in a multivariate model (Table 2: adjusted p-values).

Disease associations

Women with MLA were almost twice as likely to report having eczema, 21/60 (36%) vs. 87/471 (19%) ($p = 0.002$), three times as likely to report heart disease, 6/60 (10%) vs. 15/471 (3%) ($p = 0.021$), and more than twice as likely to report rheumatoid arthritis, 7/60 (12%) vs. 22/471 (5%) ($p = 0.033$) (Table 3).

Discussion

In a large cohort of pre-menopausal asthmatic women who received care in primary and specialty care asthma clinics, we identified that 11% have self-reported menstrual-linked asthma. MLA in our population was characterized by a significantly greater frequency of urgent healthcare visits, a higher rate of absenteeism, and a more than 2-fold increase in the frequency of near-fatal asthma episodes; although the latter comparison did not reach statistical significance. We also found that women with MLA have significantly higher B_2-agonist utilization and we identified an association with other inflammatory conditions including heart disease, rheumatoid arthritis, and eczema (Table 3). To our knowledge, our study is the largest to date to examine the clinical characteristics of women with menstrual-linked asthma, the only study to explore disease associations, and only the second study to use multivariate analysis to adjust for potentially confounding patient characteristics.[2]

While it is clinically concerning to identify a statistically significant increase in total urgent/emergent visits, an increase in emergency room visits, and a near statistically significant increase in hospitalizations and near-fatal asthma episodes on univariate analysis; in a multivariate model these increases lose statistical significance. This suggests that this difference is not related to the MLA phenotype, or that other factors account for a portion of the identified difference, or that the association is real but our data lacks the precision required to reach a statistically significant conclusion. Although consistent with the reported literature the univariate associations identified in our study must be interpreted cautiously.[1,2,8,17] Eliasson and colleagues published the only study to date that reports increased hospitalization based on a multivariate analysis.[2]

Table 2 Symptoms, spirometry, absenteeism, and health services utilization.

Characteristic	Women without MLA ($n = 471$)	Women with MLA ($n = 60$)	p Value	Adjusted p value
Symptoms				
2 Parameters > benchmark	107 (23.1%)	12 (20.7%)	0.679	0.429
Cough ≥4× weekly	235 (51.8%)	24 (43.6%)	0.255	0.229
Wheeze ≥4× weekly	127 (28.4%)	16 (29.6%)	0.852	0.815
Dyspnea ≥4× weekly	154 (33.9%)	17 (29.8%)	0.537	0.389
Chest tightness ≥4× weekly	126 (28.2%)	21 (38.9%)	0.103	0.340
Nocturnal symptoms ≥1× weekly	116 (26.3%)	18 (33.3%)	0.273	0.481
Rescue/relief medication				
Doses ≥4× weekly	159 (36.5%)	29 (54.7%)	0.010	0.007
Average use (doses/day)	0.68 (1.32)	1.13 (1.70)	0.015	0.012
Asthma-related absenteeism				
Absent from school or work past year	170 (36.9%)	33 (56.9%)	0.003	0.016
Mean days absent	4.2 (12.6)	13.6 (52.9)	0.043	0.010
Spirometry				
FEV_1 (Litres)	2.82 (0.67)	2.69 (0.70)	0.189	0.457
FEV_1 % predicted	94.3 (24.8)	93.5 (20.8)	0.590	0.971
FVC (Litres)	3.56 (0.66)	3.46 (0.69)	0.378	0.680
FEV_1/FVC % ratio	78.7 (11.4)	77.2 (10.6)	0.182	0.373
Asthma-related health service use — visits in the prior year				
Total # of urgent/emergent care visits	4.71 (5.91)	6.18 (6.67)	0.033	0.150
Hospital admissions	0.09 (0.50)	0.23 (0.87)	0.065	0.083
Unscheduled family MD visits	2.63 (3.64)	3.02 (3.22)	0.181	0.442
Walk-in clinic visits	1.12 (2.22)	1.43 (2.51)	0.601	0.653
Emergency room visits	0.88 (2.27)	1.50 (3.57)	0.035	0.068

Data presented as mean (SD) and as frequency (%). SD = standard deviation; FEV_1 = forced expiratory volume in 1 s; and FVC = forced vital capacity. Calculation of mean days absent includes those with no absences; MLA = menstrual-linked asthma. Adjusted p value derived from the multivariate analysis.

Table 3 Disease associations.

Medical condition	Women without MLA ($n = 471$)	Women with MLA ($n = 60$)	p Value
Anaphylaxis	44 (9.5%)	6 (10.3%)	0.846
ASA reactions	11 (2.4%)	1 (1.7%)	>0.999[a]
Cancer	7 (1.5%)	1 (1.7%)	>0.999[a]
Diabetes	23 (5.0%)	7 (12.1%)	0.065[a]
Eczema	87 (18.9%)	21 (36.2%)	0.002
Gastrointestinal bleeding	9 (2.0%)	2 (3.5%)	0.353[a]
Heartburn (GERD)	133 (28.9%)	23 (39.7%)	0.091
Heart disease	15 (3.3%)	6 (10.3%)	0.021[a]
High blood pressure	51 (11.1%)	5 (8.6%)	0.572
Hives	152 (33.0%)	15 (25.9%)	0.275
Inflammatory bowel disease	24 (5.2%)	6 (10.3%)	0.130[a]
Kidney disease	8 (1.7%)	1 (1.7%)	>0.999[a]
Liver disease	6 (1.3%)	2 (3.5%)	0.222[a]
Nasal polyps	21 (4.6%)	2 (3.5%)	>0.999[a]
Other lung disease	25 (5.4%)	4 (6.9%)	0.552[a]
Peptic ulcer disease	11 (2.4%)	3 (5.2%)	0.198[a]
Rheumatoid arthritis	22 (4.8%)	7 (12.1%)	0.033[a]
Rhinosinusitis	163 (35.4%)	19 (32.8%)	0.696
None apply	101 (21.9%)	8 (13.8%)	0.153

[a] Statistical comparisons made using Fisher's exact two-tailed test. All other comparisons made using chi-square tests for comparing proportions.

There are surprisingly few contemporary studies that have evaluated MLA in a clinical setting.[1–4,7,8,12,18,21] (Table 4). Until this study, the largest evaluation was published by Suzuki and colleagues, who used univariate analysis to examine 480 women in Japan. They identified a prevalence of 11% in their population.[8] Also similar to our study, Suzuki determined that women with MLA had more severe asthma, a higher frequency of exacerbation, and increased health services use compared to women without MLA. Distinct from our study their MLA cohort had more smokers and had a higher utilization of asthma control medications.[8]

Our finding that women with MLA used B_2-agonists more frequently, and at higher doses, contrasts sharply with our finding that other measures of current asthma control were not different. Despite the similarity of baseline symptoms and FEV_1, a higher proportion of women with MLA used more than three B_2-agonist doses per week; and this cohort used almost twice the mean daily dose of B_2-agonist compared to women without MLA. This observation aligns with the hypothesis that a hormonally mediated reduction in B_2-receptor responsiveness is important in the pathophysiology of MLA[13] and may contribute to our understanding of disease severity in MLA. In MLA it has been demonstrated that the bronchoconstrictor effects of ozone are greater during the early follicular phase of menstruation, when progesterone levels are lowest.[14] Furthermore, regular B_2-agonist utilization has been independently associated with a loss of bronchoprotection and with an increased risk of fatal and near-fatal asthma exacerbations.[26–28] Although speculative, it is interesting to consider that physiologic changes during the menstrual cycle could contribute directly to disease severity: via

Table 4 Research in context — identification and evaluation of women with MLA in clinical practice.

Study	Total subjects	Subjects with MLA	Prevalence (%)	Self-report[a]	Self-report related to physiology	Comparative findings MLA vs. non-MLA
Agarwal (1997)[1]	100	23	23	Y	Y	MLA had longer duration of asthma, were more symptomatic, increased frequency of emergency visits and hospitalizations. Peak flow values fell peri-menstrually in MLA but not in non-MLA ($n = 10$).
Eliasson (1986)[2]	57	19	33	Y	N	Pulmonary symptom scores worsened peri-menstrually in MLA vs. non-MLA. Higher frequency of hospitalization in MLA.
Nakasato (1999)[12]	45	5	11	Y[b]	Y	Leukotrienes were increased in MLA and MLA was attenuated by a leukotriene receptor antagonist.
Gibbs (1984)[3]	91	36	40	Y	Y	21/36 women with MLA compared to 12 controls. A peri-menstrual fall in peak flow was identified in MLA but not in controls.
Hanley (1981)[4]	102	36	36	Y	Y	Peak flow rate was reduced peri-menstrually in subjects who reported MLA and not in subjects without MLA.
Shames (1988)[7]	32	9	28	Y	Y	Subjects with MLA were older with a longer duration of asthma, and had peri-menstrual differences in B_2-agonist use and peak flow.
Magadle (2001)[21]	67	13	19	N	N	MLA defined by peak flow and B_2-agonist use. Salmeterol prevented MLA related changes in 54% of subjects.
Suzuki (2007)[8]	480	56	11	Y	N	MLA cohort had more severe disease, increased medication use including more oral corticosteroid, and had more 'asthma attacks'.
Current study 2012	540	60	11	Y	N	MLA cohort characterized by a higher frequency of urgent health services utilization, absenteeism, higher frequency and dose of B_2-agonist, and a higher prevalence of heart disease, rheumatoid arthritis, and eczema.

[a] MLA defined by self-report means questionnaire and/or patient symptom dairy.
[b] MLA diagnosis required peak flow changes in addition to self-report. Inclusion criteria: clinical studies identified by electronic search strategies published after 1970, that identify and characterize MLA, and >10 subjects with known asthma. Y = yes and N = no.

hormonally mediated changes in B_2-receptor responsiveness, or symptom perception, or via changes in bronchoprotection; and indirectly because of the increase in B_2-agonist utilization that these physiologic changes lead to.

Despite its strengths, this study has some limitations. A lower than expected response rate to our comprehensive questionnaire may have been secondary to subject fatigue as the questionnaire was lengthy. Given our response rate we cannot exclude that selection bias influenced our results. We compared the characteristics of participants to non-participants and found that participants were younger and were more likely to be non-smokers than non-participants. Additionally, it is possible that subjects with more severe menses-related symptoms responded disproportionately and are over-represented in our cohort increasing the reported prevalence. We noted, however, that our reported prevalence is consistent with that of Suzuki and colleagues.[8] In our analysis of disease associations we did not adjust for multiple comparisons, therefore the described associations must be considered exploratory.

Despite its reported prevalence and decades after the first description of MLA it remains the least well characterized of the trigger-related asthma phenotypes.[29] It was not methodologically possible in this study therefore, to utilize a validated case definition for MLA, as no such case definition exists. To minimize the potential effects of ascertainment bias, which has heavily influenced contemporary MLA literature (Table 4), a significant objective of this study was to evaluate the clinical characteristics of MLA in a large female asthma cohort. Self-report was an efficient method to complete the study in a cohort of this size. More importantly a majority of published clinical studies have used self-report as a method for identifying women with MLA, and a review of that literature suggests that it is a valid method to define MLA. In Table 4 we identified five studies that measured physiologic parameters in self-identified MLA cohorts confirming non-parallel changes in premenstrual PEF that discriminated MLA from non-MLA.[1,3,4,7,12] Despite these reassuring findings, we cannot exclude the possibility that we misclassified some subjects by utilizing self-reported MLA as our case definition.

We also used patient self-report to collect outcome measures including B_2-agonist utilization and urgent health services utilization. Although self-reported health services utilization is common in the chronic disease management literature, and although self-report has been validated against administrative databases in other settings, utilization in this study was not validated against an administrative dataset.[30–32] We did, however, utilize methods to increase the accuracy of the self-reported data including measuring acute events that are easily understood by the subject (exacerbations requiring urgent care), and utilizing the shortest meaningful reporting interval (4 weeks) for B_2-agonist use.[33]

Defining the clinical characteristics of women with MLA is required to build upon our understanding of this entity and is a requisite first step toward the development of an accurate phenotypic description or validated case definition. We define the clinical characteristics of MLA in a large cohort of women from primary and specialty care practices. Women with MLA should be identified as a component of health risk stratification and MLA should be considered by healthcare providers when developing an individualized asthma management plan. We identify the following research needs: formal validation of a case definition for MLA that includes clinical, physiologic, and psychophysical measures; and to explore the hormonal influences on B_2-receptor responsiveness and symptom perception throughout the menstrual cycle.

Conflict of interest statement

(1) JT has no conflict of interest to disclose.
(2) JL has received honoraria has for speaking engagements for GlaxoSmithKline, AstraZeneca, and Boehringer Ingelheim.
(3) CML has no conflict of interest to disclose.
(4) CJL has received honoraria for speaking engagements and / or participated on advisory boards for GlaxoSmithKline, AstraZeneca, Novartis, and Merck. CJL has received honoraria from the Ontario Lung Association for continuing education program development and presentations.

Funding

The University of Western Ontario Academic Development Fund — New Research and Scholarly Initiative Award, The Ontario Thoracic Society Block Term Grant Program, The Fowler Kennedy Sport Medicine Clinic Fund, The Ontario Women's Health Scholars Doctoral Award Research Allowance, The University of Western Ontario Graduate Thesis Research Award, and The Kinesiology Graduate Student Research Fund.

Author contributions

JT and CJL contributed to the concept and design of the study, to the analysis and interpretation of data, and drafted the paper. CJL is the guarantor. All authors were involved in critically revising the article for important intellectual content and gave final approval of the version to be published.

Acknowledgements

The authors would like to thank the following individuals who contributed to this project: the University of Western Ontario/St. Joseph's Health Care Asthma Centre and the Asthma Research Group — Windsor Essex County, the participating physician and asthma educator group in London and Windsor, Ontario, The University of Windsor — Centre for Smart Community Innovation; Mr. Jason West for his research assistance; Ms. Kathy Colledge for preparation of the manuscript; and Mr. Larry Stitt for biostatistician support.

References

1. Agarwal AK, Shah A. Menstrual-linked asthma. *J Asthma* 1997; **34**(6):539–45.

2. Eliasson O, Scherzer HH, DeGraff Jr AC. Morbidity in asthma in relation to the menstrual cycle. *J Allergy Clin Immunol* 1986; **77**(1 Pt 1):87—94.
3. Gibbs CJ, Coutts II , Lock R, et al. Premenstrual exacerbation of asthma. *Thorax* 1984;**39**(11):833—6.
4. Hanley SP. Asthma variation with menstruation. *Br J Dis Chest* 1981;**75**(3):306—8.
5. Mirdal GM, Petersson B, Weeke B, et al. Asthma and menstruation: the relationship between psychological and bronchial hyperreactivity. *Br J Med Psychol* 1998;**71**(Pt 1):47—55.
6. Oguzulgen IK, Turktas H, Erbas D. Airway inflammation in premenstrual asthma. *J Asthma* 2002;**39**(6):517—22.
7. Shames RS, Heilbron DC, Janson SL, et al. Clinical differences among women with and without self-reported perimenstrual asthma. *Ann Allergy Asthma Immunol* 1998;**81**(1):65—72.
8. Suzuki K, Hasegawa T, Sakagami T, et al. Analysis of perimenstrual asthma based on questionnaire surveys in Japan. *Allergol Int* 2007;**56**(3):249—55.
9. Vrieze A, Postma DS, Kerstjens HA. Perimenstrual asthma: a syndrome without known cause or cure. *J Allergy Clin Immunol* 2003;**112**(2):271—82.
10. Bain BJ, England JM. Variations in leucocyte count during menstrual cycle. *Br Med J* 1975;**2**(5969):473—5.
11. Faas M, Bouman A, Moesa H, et al. The immune response during the luteal phase of the ovarian cycle: a Th2-type response? *Fertil Steril* 2000;**74**(5):1008—13.
12. Nakasato H, Ohrui T, Sekizawa K, et al. Prevention of severe premenstrual asthma attacks by leukotriene receptor antagonist. *J Allergy Clin Immunol* 1999;**104**(3 Pt 1):585—8.
13. Foster PS, Goldie RG, Paterson JW. Effect of steroids on beta-adrenoceptor-mediated relaxation of pig bronchus. *Br J Pharmacol* 1983;**78**(2):441—5.
14. Fox SD, Adams WC, Brookes KA, et al. Enhanced response to ozone exposure during the follicular phase of the menstrual cycle. *Environ Health Perspect* 1993;**101**(3):242—4.
15. Pauli BD, Reid RL, Munt PW, et al. Influence of the menstrual cycle on airway function in asthmatic and normal subjects. *Am Rev Respir Dis* 1989;**140**(2):358—62.
16. Tan KS, McFarlane LC, Lipworth BJ. Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill. *Am J Respir Crit Care Med* 1997;**155**(4): 1273—7.
17. Martinez-Moragon E, Plaza V, Serrano J, et al. Near-fatal asthma related to menstruation. *J Allergy Clin Immunol* 2004; **113**(2):242—4.
18. Rees L. An etiological study of premenstrual asthma. *J Psychosom Res* 1963;**52**:191—7.
19. Skobeloff EM, Spivey WH, Silverman R, et al. The effect of the menstrual cycle on asthma presentations in the emergency department. *Arch Intern Med* 1996;**156**(16):1837—40.
20. Aoyama Y, Toyoizumi K, Fueki R, et al. Relation between bronchial asthma and the menstrual cycle. *Arerugi* 1965; **14**(11):583—9.
21. Magadle R, Berar-Yanay N, Weiner P. Long-acting bronchodilators in premenstrual exacerbation of asthma. *Respir Med* 2001;**95**(9):740—3.
22. Morris JF, Koski A, Johnson LC. Spirometric standards for healthy nonsmoking adults. *Am Rev Respir Dis* 1971;**103**(1): 57—67.
23. Becker A, Berube D, Chad Z, et al. Canadian pediatric asthma consensus guidelines, 2003 (updated to December 2004): introduction. *CMAJ* 2008;**173**(Suppl. 6):S12—4.
24. Boulet LP, Becker A, Berube D, et al. Canadian asthma consensus report, 1999. Canadian Asthma Consensus Group. *CMAJ* 2008;**161**(Suppl. 11):S1—61.
25. Lemiere C, Bai T, Balter M, et al. Adult asthma consensus guidelines update 2003. *Can Respir J* 2008;**11**(Suppl. A):9A—18A.
26. Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. *Ann Intern Med* 2004;**140**(10):802—13.
27. Spitzer WO, Suissa S, Ernst P, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;**326**(8):501—6.
28. Suissa S, Ernst P, Boivin JF, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;**149**(3 Pt):604—10.
29. Wenzel S. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;**368**(9537):804—13.
30. Dubois M, Raiche M, Hebert R, Gueye N. Assisted self-report of health-services use showed excellent reliability in a longitudinal study of older adults. *J Clin Epidemiol* 2007 Oct;**60**(10): 1040—5.
31. Lynne D. Diabetes disease management in managed care organizations. *Dis Manag* 2004;**7**(1):47—60.
32. Ungar WJ, Coyte PC. Health services utilization reporting in respiratory patients. Pharmacy Medication Monitoring Program Advisory Board. *J Clin Epidemiol* 1998 Dec;**51**(12):1335—42.
33. Bhandari A, Wagner T. Self-reported utilization of health care services: improving measurement and accuracy. *Med Care Res Rev* 2006 Apr 1;**63**(2):217—35.