IJMS 2022 9(1): 88 - 102

International Journal of Multidisciplinary Studies (IJMS)
Volume 9, Issue I, 2022

Comparison of lung function during different phases of the menstrual cycle among young female asthmatics and non-asthmatics

Atukorala K.R.[1], Silva W.A.N.Y.[1], Amarasiri W.A.D.L.[2] and Fernando D.M.S.[1]

[1]Department of Physiology, Faculty of Medical Sciences, University of Sri Jayewardenepura

[2]Department of Physiology, Faculty of Medicine, University of Colombo

ABSTRACT

Bronchial asthma is a chronic lung disease that causes significant morbidity and poor quality of life. The incidence of asthma is higher in boys before puberty and higher in females following puberty. Female preponderance is maintained into adulthood and morbidity due to asthma is greater in females. With this background we assessed the lung function with spirometry parameters of young asthmatic and non-asthmatic healthy females during different phases of the menstrual cycle. A case control study was conducted among well controlled asthmatic (N=60) and comparable (age and BMI matched) non – asthmatic healthy females (N=60) between 19 -25 years from June 2017- June 2020. The asthmatics were recruited from the asthma clinic, National Hospital of Sri Lanka, the Family Practice Centre and the medical Centre, University of Sri Jayewardenepura (USJ) while the non-asthmatic females (controls) were recruited from volunteering undergraduates of the university. Although ethnicity was not a criterion for recruitment of participants, the final recruited participants were all from the Sinhalese ethnicity. The sociodemographic data and the relevant information on asthma were obtained through an interviewer administered questionnaire. Forced Expiratory Volume in the first second (FEV_1), Forced Vital Capacity (FVC), FEV_1/FVC ratio, Peak Expiratory Flow Rate (PEFR) and Forced Expiratory Flow Rates, were measured during menstrual, follicular and luteal phases of the menstrual cycle. Spirometry parameters (means), were compared in asthmatics and non-asthmatics, with independent sample t-test. Analysis of variance (ANOVA) was used to analyze differences within the menstrual cycle within the groups. In all three phases, all spirometry parameters (except FVC) were lower in asthmatics ($p<0.05$). The spirometry parameters showed a cyclical pattern but did not change significantly between the three phases of the menstrual cycle in both groups. In asthmatics, the mean values of FEV_1, FEV_1/FVC%, FEF_{25-75}, FEF_{50}, FEF_{75} were lowest in the menstrual phase and highest in the luteal phase and in non-asthmatics, the FEV_1 was lowest in the menstrual phase and highest in the luteal phase.

KEYWORDS: *menstrual cycle, lung functions, spirometry, asthma, young females*

Corresponding author: Atukorala K.R, Email: kushani@sjp.ac.lk

1 INTRODUCTION

Bronchial asthma is a chronic lung disease which causes significant morbidity and mortality worldwide (Global Initiative for Asthma 2021). The population affected by bronchial asthma in different countries varies from 1-18% (Global Initiative for Asthma 2021). Asthma is a significant public health issue in Sri Lanka (Ministry of Health 2018) with more than 20% of children aged 13 to 14 living with symptoms of asthma and more than 7.5 % of them having severe disease (Lai et al. 2009; Mallol et al. 2013). According to reports published in 2018, there were 811 asthma related hospital admissions and 2.6 deaths per 100,000 reporting a case fatality rate of 0.33 (572 deaths for 175,937 cases) (Ministry of Health 2018). Sri Lanka is ranked fourth among the countries with highest mortality from asthma (World health rankings, 2021). In 2019, asthma was reported as the fourth leading cause of death among all ages in Sri Lanka (Institute of Health Metrics and Evaluation 2021).

During childhood, the incidence of asthma is greater in boys. At puberty, the gender distribution of asthma changes with an increase in the ratio of females in comparison to males (Sears et al. 2003; Tollefsen et al. 2007). This difference is maintained into adulthood and morbidity due to asthma is more prevalent in females (Skobeloff 1992), with females experiencing increased emergency department visits, hospitalizations and death from asthma (Baibergenova et al. 2006; Moreno et al. 2012; To et al. 2019). The reasons for the gender differences are not clear but have been linked to immunological and hormonal factors (Almqvist et al. 2008; Melgert 2007; Vink et al. 2010).

In asthmatics, the reported spirometry parameters at different time points of the menstrual cycle are not uniform. Deterioration in lung function has been more frequently described in the pre or peri - menstrual phase (Arora et al. 2015; Kaur, N et al. 2019), which is described as pre- or perimenstrual asthma (PMA) (Vrieze et al. 2003). Nearly 30% of women with asthma, are thought to have worsening of symptoms of asthma just before menstruation (Pereira Vega et al. 2010, Vrieze et al. 2003). However, there are other studies that report worsening of lung functions closer to ovulation (Brenner et al. 2005; Wegienka et al. 2012) and during the luteal phase (Farha et al. 2009; Wegienka et al. 2012) while others report no significant changes (Nittner-Marszalska et al. 2018).

Similar to asthmatics, previous studies have assessed lung function parameters during the menstrual cycle of healthy females and the findings reported are not consistent. Lung function parameters have been reported to be highest in the luteal phase (Ameen et al. 2014; Bhirange and Jajulwar 2019; Goyal et al. 2017; Handergulle and Sommani 2018; Hebbar 2013; Kaur, H et al. 2015; Kavitha and Chris 2017) while some have reported no significant variation during the menstrual cycle (Pauli et al. 1989; Timon et al. 2014). A disparity between spirometry parameters and respiratory symptoms during the menstrual cycle has also been reported (Pauli et al 1989). Most studies have assessed only Peak Expiratory Flow Rate (PEFR) using peak flow meters which largely reflect the large airways but not small airways which are also affected in asthma. Further, assessment of PEFR by peak flow meter is known to greatly depend on the voluntary effort and muscular strength of the subject, which diminishes its reliability, hence considered to be not as reliable as spirometry.

With this background, the current study was planned to assess the lung function parameters during different phases of the menstrual cycle in a cohort of asthmatics and in a comparable group of non-asthmatics, with the aim of comparing the changes in lung function parameters more objectively (using spirometry). The current study was designed to address some of the shortcomings of previous published study designs as practically as possible, like increasing sample size, having a case control approach and sampling of parameters at three points in the menstrual cycle.

2 RESEARCH METHODOLOGY / MATERIALS AND METHODS

A case control study was conducted with well controlled female asthmatics (n=60) and non-asthmatic healthy females (n=60), aged between 19 - 25 years. The sample size for this study was determined by the equation used to calculate sample size for matched samples with continuous outcome with the goal of comparison between matched groups (Charan and Biswas 2013; Sullivan 2013) Only unmarried nulliparous females with regular menstrual cycles who were not on hormonal contraceptives were included in the study. The asthmatics were recruited from the asthma clinics of National Hospital of Sri Lanka (2), Medical Centre University of Sri Jayewardenepura (USJ) (54) and Family Practice Centre of USJ (4), while healthy volunteers were recruited among the undergraduates of USJ who served as the non-asthmatic control group. Diagnosis of asthma was confirmed by demonstration of a reversible obstructive defect by spirometry on females with a suggestive clinical history. Well-controlled asthma was identified using Global Initiative of Asthma (GINA) criteria (Global Initiative for Asthma 2016).

Sociodemographic data and asthma related information were obtained using an interviewer administered questionnaire. The interviews were conducted in the English or Sinhala languages and those who could not speak either language were excluded. At the interview, the menstrual history was also obtained, and appointments were made to assess the lung functions by spirometry, in all the recruited participants. The interviews, measurement of anthropometric parameters and spirometry were carried out by the principal investigator after obtaining informed consent from the recruited participants. The standing height was measured using a portable Stadiometer (Seca Stadiometer-213, Seca Ltd, Birmingham, UK) and recorded to the nearest centimeter. Participants were asked to stand with their backs straight, with the head held in the Frankfort horizontal plane and feet flat and arms hanging loosely by their sides. Body weight was measured to the nearest 0.1 kg using calibrated (digital flat) electronic weighing scale (Seca 770, Digital Scales, Seca Ltd, Birmingham, UK).

Forced Expiratory Volume in the first second (FEV1) which is the volume of air exhaled in the first second during forced exhalation after maximal inspiration, (Normally at least 80% of the FVC is exhaled in the first second), Forced Vital Capacity (FVC)- which is the total amount of air exhaled during forced exhalation, FEV1/FVC ratio (%), Peak Expiratory Flow Rate (PEFR) which is the maximal flow rate generated during a forceful expiration and Forced Expiratory Flow Rates (FEF25-75, FEF50, FEF75) which measure the airflow in the mid portion of the vital capacity, i.e. forced expiratory flow between 25% and 75% of FVC , 50% of FVC and 75% of FVC were measured by the spirometer MicroQuark (Cosmed, Italy). The above were measured at three points; menstrual, follicular and luteal phases of a single menstrual cycle in accordance with the American Thoracic Society / European Respiratory Society spirometry guidelines (Graham et al., 2019). The spirometry maneuvers were repeated up-to eight attempts until three acceptable maneuvers with two largest values for FVC and FEV1 possessed repeatability with a value 150mL of each other. The first day of menstruation was considered as day 1 of the menstrual cycle. Accordingly, Day 1-2 was defined as menstrual phase, Day 7-10 as follicular phase and Day 21-24 as luteal phase. Participants were instructed to report on the above defined dates to assess the lung function. Data were analyzed using SPSS 20 software. Mean values of spirometry parameters, at each of the three points in menstrual cycle were calculated and were compared between groups, using paired sample t-test. Analysis of variance (ANOVA) was used to analyze differences between different phases within the same menstrual cycle.

Ethical clearance was obtained from the ethics review committee of the Faculty of Medical Sciences, University of Sri Jayewardenepura (No-26/17) and institutional approvals were taken from the relevant institutions.

3 RESULTS & DISCUSSION

Socio-demographic and other characteristics of the study population

The two groups (asthmatic and non-asthmatic) were comparable in terms of age, height, weight and BMI. The demographic and other characteristics of asthmatics and non-asthmatics are given in Table 1. All the asthmatics and non-asthmatics of the study were from the Sinhala ethnicity which was an incidental occurrence. Both groups were comparable in their level of education and were not employed. All asthmatics and non-asthmatics were residing in Western Province at the time of data collection.

Out of the 13 asthmatics with allergies, two had known food allergies, one had drug allergy and eight had allergic skin conditions (contact dermatitis, eczema). There was no difference between asthmatics and non-asthmatics in exposure to allergens such as cigarette (tobacco) smoke, outdoor air pollution, fumes (including cooking fumes and other fumes) ($p = 0.619$) and animal fur / animal dander ($p = 0.439$).

Table 1: Characteristics of the asthmatics and non-asthmatics

	Asthmatics [Mean (SD)] (n=60)	Non asthmatics [Mean (SD)] (n=60)	*p* value
Age (years)	22.2 (1.6)	22.3 (1.6)	0.869$^{\varphi}$
Height (cm)	158.6 (6.7)	156.8 (5.9)	0.137$^{\varphi}$
Weight (kg)	53.1 (8.3)	52.5 (8.6)	0.684$^{\varphi}$
BMI (kg/m^2)	21.1 (4.0)	21.3 (2.6)	0.367$^{\varphi}$
History of allergies n (%)	13 (12.5)	12 (12.5)	0.822^{ŧ}
Exposure to allergens n (%)			
Smoke/fumes	3 (5)	1 (1.7)	0.619 $^{ŧ¥}$
Animal fur	22 (36.7)	18 (30)	0.562^{ŧ}

$^{\varphi}$ Independent sample *t* test
^{ŧ} Chi-square test $^{¥}$ Fisher exact test

Characteristics of the menstrual cycles of asthmatics and the non -asthmatics

Characteristics related to the menstrual cycles of the study participants are given in Table 2. The mean (SD) age of menarche was delayed in asthmatics; 12.8 (1.0) years compared to non-asthmatics; 12.0 (1.1) years (*p* <.001). The length of the menstrual cycles, the duration of bleeding and pain during menstruation (dysmenorrhea) were comparable in the two groups.

Table 2: Characteristics of the menstrual cycles of the asthmatics and non-asthmatics

Characteristics	Asthmatics [Mean (SD)] (n=60)	Non asthmatics [Mean (SD)] (n=60)	*p* value
Age of onset of menarche (years)	12.8 (1.0)	12.0 (1.1)	<0.001***
Cycle length (days)	29.5 (2.8)	29.3 (2.1)	0.671
Duration of bleeding (days)	4.5 (1.1)	4.3 (.9)	0.123
Presence of dysmenorrhea n (%)	35 (58.3)	26 (43.3)	0.144$^{\#}$

Independent sample *t* test
#Chi square *p<0.05 ***p<0.001

Features related to asthma

The asthmatics in the study were classified based on the treatment they were on at the time of recruitment according to GINA criteria and their features are given in Table 3.

Of them, 15 (25%) were categorized as having intermittent asthma, 15 (25%) as having mild persistent asthma, while 30 (50%) had moderate persistent asthma. None of the asthmatics were diagnosed with severe asthma as none were on high dose of inhaled corticosteroids (ICS). None were on anticholinergics.

None of the asthmatics were obese or had obstructive sleep apnoea. Majority (n=41, 68.3%) had symptoms suggestive of allergic rhinitis with some having symptoms suggestive of concomitant allergic conjunctivitis (n=4, 6.67%) and rhinosinusitis (n=4, 6.67%). Symptoms suggestive of gastro oesophageal reflux disease (GORD) was present in 29 asthmatics (48.3%). Other trigger factors included exercise, emotions, weather / climate changes (Table 3).

Only one asthmatic noticed menstruation related worsening of symptoms. History of asthma among close family (parents and siblings) was present in 46 (76.7%).

Spirometry parameters of asthmatics and non-asthmatics

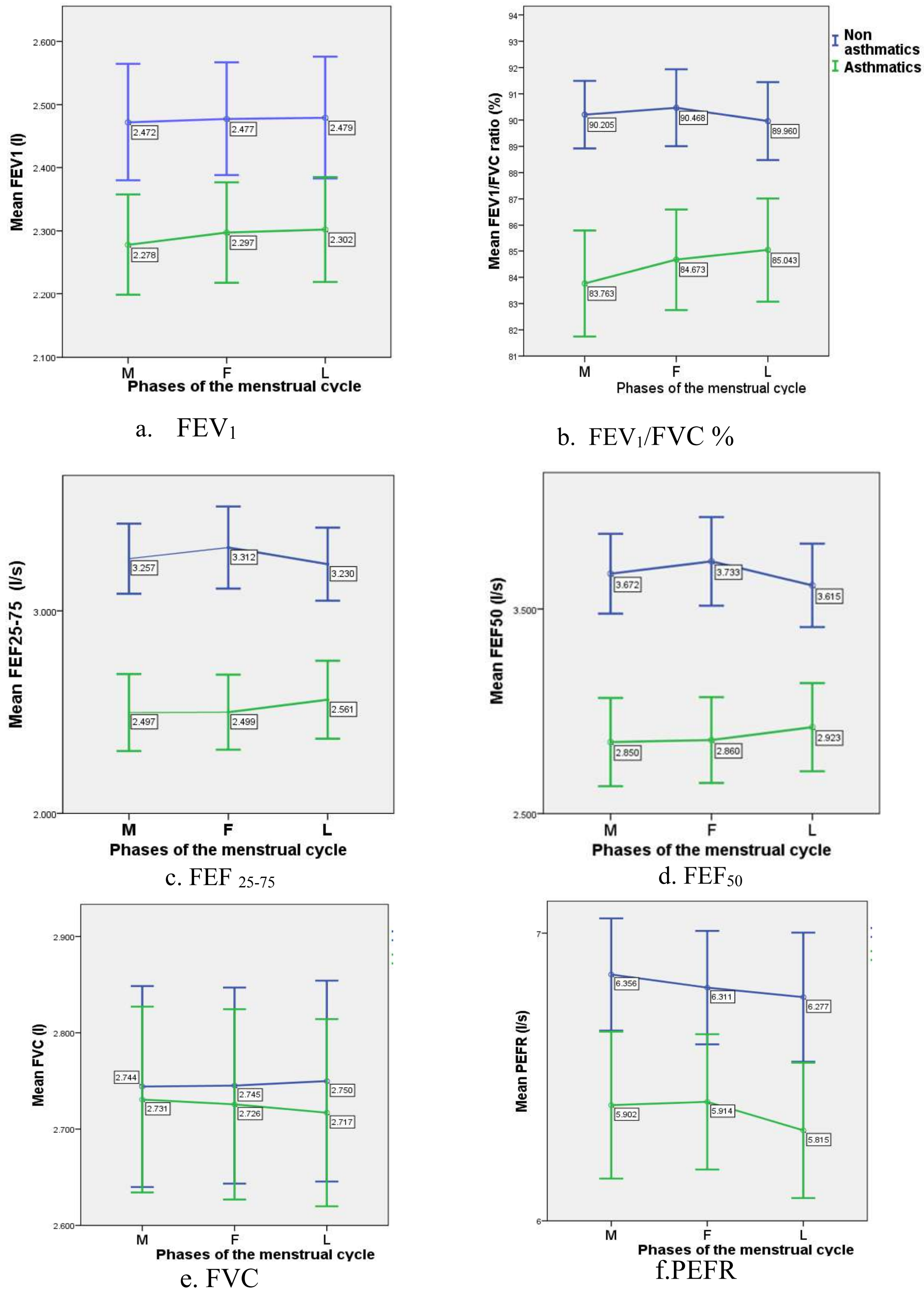
All spirometry parameters (means) assessed, other than FVC, were significantly lower in asthmatics compared to non-asthmatics during all three phases of the menstrual cycle (p<0.05) as shown in Figure 1. Predicted values for spirometry parameters were generated using regression equations for Sri Lankan females of 19-29 years (Udupihille M., 1988).

The changes in lung function parameters during different phases of the menstrual cycle are given in Figure 1.

In asthmatics, the mean values of FEV_1, FEV_1/FVC %, FEF_{25-75}, FEF_{50}, FEF_{75} were lowest in the menstrual phase while FVC and PEFR were lowest in the luteal phase. FEV_1 and FEV_1/FVC%, $FEF_{25-75,}$ FEF_{50} were highest in the luteal phase in the asthmatics. In non- asthmatics, the highest mean FEV_1, FVC were recorded in the luteal phase while highest mean FEV_1/FVC%, $FEF_{25-75,}$ FEF_{50} were recorded in the follicular phase. However, with repeated measures ANOVA there was no significant effect of the phase of menstrual cycle on the lung function parameters measured in either of the groups (p>.05).

Table 3: Features related to asthma of the participants (n=60)

Characteristics related to asthma	n	%
Asthma severity		
Intermittent	15	25
Mild persistent	15	25
Moderate persistent	30	50
Severe	-	-
Trigger factors (multiple responses allotted)		
Exercise	2	3.3
Respiratory infections	32	53.3
Emotions/laughter	7	11.7
Weather (changes in temperature/humidity)	6	0.1
Dust/fumes/smoke/air pollutants	5	8.3
Menstruation	1	1.67
Asthma comorbidities		
Allergic rhinitis / rhino sinusitis/rhino conjunctivitis	41	68.3
Gastro oesophageal reflux disease (GORD)	29	48.3
Treatment		
Short Acting Beta Agonists (SABA) only	15	25
Inhaled corticosteroids (ICS) / SABA+ICS	15	25
Long-Acting Beta Agonists (LABA)+ICS	30	50
Leukotriene antagonists	1	1.7
Nasal steroids	3	0.05
Antihistamines	1	1.7
Family history of asthma	46	76.3
Age of onset /diagnosis		
Early childhood	38	31.7
Since adolescence	18	15.0
Recent (within 1-2 years)	4	3.3



M- Menstrual phase F- Follicular phase L- Luteal phase

Figure 1. Spirometry parameters (mean ± SD) during different phases of the menstrual cycle in asthmatics (n=60) and non-asthmatics (n=60)

This study was conducted among females between 19 and 25 years and asthmatics and non-asthmatics were comparable in age, height, weight and BMI. The characteristics of the menstrual cycles were similar although the age of menarche was significantly delayed in the asthmatics. Delayed age of menarche in asthmatics has been reported previously (Moudiou et al. 2003, Gaudino et al. 2021). The well accepted phenomenon of chronic illness delaying puberty in girls (Pozo and Argente 2002) and/or due to the effects of long term inhaled corticosteroids (Zhang et al. 2019) could be the possible reason for the delayed menarche in the asthmatics.

The spirometry parameters FEV1, FEV1/FVC%, PEFR, FEF25-75 FEF25, FEF50, FEF75 were significantly lower in asthmatics in all the phases of the menstrual cycle, indicating expiratory air flow limitation and/or airway obstruction which is the hall mark of asthma. All non-asthmatic subjects had normal lung functions which were comparable to the previously reported values for Sinhalese females of similar age groups (Udupihille. 1995) and also comparable to the values reported for Sri Lankan Tamil females (Sooriyakanthan et al. 2019).

The lung function spirometry parameters varied during the different phases of the menstrual cycle in both groups, similar to the studies reported previously, although a significant change between phases was not observed in the current study (Aissani et al. 2019; Pauli 1989; Nittner-Marszalska et al. 2018). The reason for no significant change between phases is probably because the asthmatics in the current study were well-controlled and were asymptomatic at the time of assessment. The pattern of change observed in asthmatics and non-asthmatics was also not similar. In asthmatics, the expiratory flow parameters FEV1, FEF25-75, FEF50, FEF75 were lowest during the menstrual phase and highest during the luteal phase, while PEFR and FVC were lowest during the luteal phase and highest during the menstrual phase. This finding of deterioration of lung function from luteal to menstrual phase has been reported previously (Agarwal and Shah 1997; Aissani et al. 2019; Arora et al. 2011; Chandler et al.1997; Jeon et al. 2009; Kaur, N et al. 2019) and supports the widely accepted premenstrual exacerbation of asthma symptoms. Even though this phenomenon may not be apparent in all asthmatics, it may occur in susceptible females. Most previous studies report a deterioration of lung functions from luteal to menstrual phase in asthmatics. A few studies have conversely reported highest spirometry parameters in menstrual phase (Farha et al. 2009) and lowest parameters in the luteal phase (Farha et al. 2009, Wegienka et al. 2012).

In non-asthmatics of the current study, there was no significant change in the variation of lung functions between the different phases, similar to the studies by Chen and Tang (1989), da Silva et al. (2006), Das (1998) and Timon et al. (2014). However, the mean FEV1, was highest during the luteal phase and was lowest during the menstrual phase similar to the asthmatics. In contrast, some studies conducted in India including young healthy female undergraduates (Arora et al. 2015; Bhirange and Jajulwar 2019; Goyal et al. 2017; Handergull and Sommani 2018; Hebbar 2013; Kaur, H et al. 2015; Kavitha and Chris 2017; Nandhini 2012) found that the spirometry parameters changed significantly during the menstrual cycle with highest values reported in the luteal phase and lowest recorded in the menstrual phase.

The three main sex hormones, oestrogen, progesterone and testosterone are known to have effects on the bronchial smooth muscle and airway inflammation (Fuentes and Silveyra 2018). Oestrogen and progesterone levels decrease to very low levels during the menstrual phase. The lowest FEV1, FEF25-75, FEF50, FEF75, FEV1/FVC seen in the menstrual cycle may be a result of very low levels of sex hormones which are known to have bronchodilatory effects. Further, the same lung function parameters FEV1, FEF25-75, FEF50, FEF75, FEV1/FVC % were highest in the luteal phase and could be explained by high levels of oestrogen and progesterone levels known to peak during the luteal phase. The low concentrations of the same hormones during the premenstrual phase may be contributing to the phenomenon of PMA as evident by the deterioration of lung functions in the asthmatics observed during the menstrual phase in the current study.

This study reports several lung function parameters assessed by spirometry which is the most reliable lung function assessment, in a group of asthmatics and a comparable group of non-asthmatics at three points in the menstrual cycle. Measurements of lung function more frequently would have been useful in assessing a cyclical variation. However, due to practical difficulties in assessing them frequently, this could not be achieved.

4 CONCLUSION & RECOMMENDATIONS

The lung function spirometry parameters assessed were lower in the asthmatics in menstrual, follicular and luteal phases of menstrual cycle compared to matched non-asthmatics. Most lung functions (FEV1, FEV1/FVC %, FEF25-75, FEF50, FEF75) were detected to be lowest in the menstrual phase in asthmatics. The reasons and the mechanism for the changes in lung function during the menstrual cycle needs to be further studied.

ACKNOWLEDGMENTS

The study was funded by University of Sri Jayewardenepura -Research grant ASP/01/RE/MED/2016/68.

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