DISCUSSION
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The etiopathogenesis of bronchial asthma is obscure, the pathophysiologic mechanism are multiple. The essential feature of the disease is hyperreactivity of airway in inflammation. The stimuli provoking bronchoconstriction, may include a variety of allergens infections, emotional stresses, physical irritants provoking bronchoconstriction is hormonal change in premenstrual and menstrual period. The relationship of asthma with menstruation has been known since ages. The exact pathophysiology of MLA, which occurs in a subset of female asthmatic patients, remains largely unknown. A number of factors, including premenstrual syndrome, dysmenorrhoea, increased bronchial mucosal hydration, and increased autonomic liability have been postulated as a cause but no consistent association has been recorded. Premenstrual asthma is a problem that may last for a long time in some asthmatic women. It is a clinical picture with worsening of asthmatic syndromes and pulmonary functions in the late luteal phase of the menstrual cycle. Most existing literature suggests that this worsening is caused by the sudden fall in plasma progesterone level, as progesterone has a role in smooth muscle
relaxation and β-adrenoceptor regulation. Certain asthmatics who exhibit cyclical relationship of symptoms with menstrual cycle are known to do better with hormonal therapy.

Menstruation exacerbation of asthma has long been reported to be a common finding in women with asthma. Previous studies, however, have failed to examine this pheromones in women who specifically reports these symptoms, but rather, have examined the relationship of asthma to the menstrual phase in asthmatic women in general. The studies have largely been retrospective, short term, have failed to demonstrate objective changes in airway function during the premenstrual period and have not convincingly demonstrated a consistent association between asthma symptoms and menstrual cycle. The current study is prospective evaluation about MLA and objective measurement of peak expiratory flow rate in relation to MLA.

The exacerbation of asthma in the premenstrual period has been of interest. As number of studies have investigated that prevalence of premenstrual asthma which ranged from 8% to 40%\textsuperscript{14,17-19,41-43}. Most research has been questionnaire based and therefore limited by recall
bias and the use of leading questions which may result in false positive reporting. The first study of this kind was undertaken in 1963 by Reeds\textsuperscript{14} who concluded that 33\% of a group of women with asthma attending a hospital chest clinic has premenstrual asthma. The study of limited by each of objective data such as peak expiratory flow (PEF) measurements or Spirometry. Two decades later, three questionnaire based studies found a prevalence of 33 to 40\%\textsuperscript{17-19}. In our study, the prevalence of MLA was 34\% which is as western data. The duration of illness was longer in these patients. The presented at later stage of reproductive life. Hanley\textsuperscript{17} and Gibbs et al\textsuperscript{18} also asked symptomatic patients to keep daily PEF diaries. Although statistically significantly lower PEF occurred premenstrualy, the amplitude of change was small enough to be doubtfull significance.

Recent research has found that prevalence of menstrual asthma to be slightly lower at 23 to 28\%\textsuperscript{41,42}. Shames et al\textsuperscript{42} carried out a detailed prospective study of 32 women with asthma over six consecutive menstrual cycles. Self reported worsening of symptoms premenstrualy were associated with significantly reduced PEF readings and increased $\beta_2$ agonist requirement which has be seen in our
patients also. The use of $\beta_2$ agonist was increased during these periods. In our study also there was increase use of $\beta_2$ agonist. Aggarwal and Shah\textsuperscript{41} carried out a retrospective questionnaire evaluation of 100 women with asthma of whom 23 reported premenstrual asthma exacerbation. In a recent report using self completed questionnaire among women with asthma in primary case found a much lower prevalence of premenstrual asthma of only 8.2%\textsuperscript{43}. Whether this reflects a group with milder disease compared with the previous hospital based studies is unclear.

Hospital based emergency visit was significantly higher in MLA asthmatic patients indicating severity of disease. A significant association between emergency visit and hospitalization has observed in two groups, indicating severity of disease to be more in MLA patients. Skobeloff and Colleagues\textsuperscript{13} estimated that 75% of adults admitted to hospital for asthma were females and that these patients required longer hospital stays than age matched males. The authors concluded that hormonal changes might be responsible and went on to demonstrate, in a prospective study of 182 females patients with asthma, that presentation to the emergency department for acute
asthma was greater during premenstrual period\textsuperscript{20}. In contrast, a longer multicentric study of 288 women\textsuperscript{44} found that the greatest number of emergency visit (33\%) occurred prior to ovulation. Only 21\% of visit occurred in premenstrual period. In addition 13\% of women with asthma reported that menstrual cycle influence exacerbation. Although, both the groups of female who had PMS and others have significantly high emergency visit but patients having PMA had significantly higher emergency visit than other group. The discrepancy between these studies could be accounted for by differences in simple selection and methodology.

Two cases reports have highlighted that premenstrual asthma can be associated with serious morbidity and rarely mortality. Barkman\textsuperscript{21} reported that two sisters, aged 13 and 14 years, died during acute asthmatic attaches the day before the expected date of menstruation. Three women with severe acute asthma associated with menstruation required ventilatory support until the end of their periods\textsuperscript{23}.


Discussion

After observing three cases of severe recurrent exacerbations of asthma in relation to menstruation, we conducted a survey among women with asthma inquiring about the relationship of asthma symptoms to the menstrual cycle. Of 57 women with asthma, 19 (33%) had significant worsening \( (p = 0.006) \) of total pulmonary symptom scores during the premenstrual period, the menstrual period, or both with maximum increase in dyspnea, wheezing and chest tightness during the premenstrual period \( (p = 0.002) \). The other 38 (66%) women noted no such changes in their asthma. Logistic regression analysis comparing women with and without worsening of their asthma around menstruation revealed that the former group reported significantly more severe wheezing in general \( (p \text{ less than } 0.05) \). Of the women whose asthma was affected by menses, 13 (68%) had been hospitalized for asthma but only 10 (26%) of the women who were unaffected \( (p = 0.002) \). Both dysmenorrhea scores and premenstrual syndrome scores correlated significantly with baseline pulmonary symptom scores in the premenstrual asthma group. It appears that asthma morbidity is affected by the menstrual cycle in a subgroup of women with asthma\(^{19} \). In our study cough, sputum
production, breathlessness, wheeze, chest tightness was more in MLA group of patients, suggesting more severe form of disease in this group of patients.

To characterized and compare premenstrual symptoms (mood, physical) throughout two menstrual cycles with and without estradiol administration, in women with premenstrual asthma (PMA), and to examine relationships between asthma symptoms versus premenstrual symptoms and pulmonary function versus premenstrual symptoms in these women. Open-label, longitudinal, 9-week study (consisting of two complete menstrual cycles). Clinical study at the University of Kentucky; data analysis at the University of British Columbia and Children’s and Women’s Health Centre of British Columbia. Fourteen women (age 35.6 ± 6.6 yrs) with mild to moderate asthma with a baseline ratio of forced expiratory volume in 1 second: forced vital capacity of 0.72 ± 0.12. Women were followed for two complete menstrual cycles. During the second complete cycle (i.e., cycle 3), they received estradiol 2 mg orally between days 23 and 28 (premenstrual). Throughout both cycles 2 and 3, each subject recorded premenstrual symptom questionnaire scores (15 mood and
physical symptoms, graded 0-3) every morning on awakening. Peak expiratory flow rates (PEFR) and visual analog scales of asthma symptoms (cough, wheezing, breathlessness, chest tightness) were recorded daily at the same time. Seven subjects showed a classic pattern of premenstrual symptoms. Four of the five subjects who complained of PMA symptoms at study enrollment also demonstrated this classic pattern of premenstrual symptoms. After estradiol administration, four women had lower symptom scores, eight had high scores, and two had the same scores. Overall, estradiol had no significant effect on symptoms (mean area under the curve 18.9 ± 14.8 day (-1) vs 20.3 ± 14.8 day (-1), p > 0.05). Ten subjects had significant relationship between asthma symptoms and premenstrual symptoms, whereas six had significant relationship between PEFR and premenstrual symptoms. Exogenous estradiol administration had no significant effect on premenstrual symptoms in women with PMA. The lack of a significant effect allows for patient blinding in a placebo-controlled, crossover study of exogenous estradiol in PMA that is currently under way. Clinical implications of relationships between
asthma symptoms versus premenstrual symptoms and pulmonary function versus premenstrual symptoms may warrant further study\textsuperscript{65}.

Our data suggest that ED visit for asthma exacerbation in women are more frequent during the menstrual phase. There was total of 36 emergency visits in case of MLA group patients as compared to non MLA group who had 12 visits in two months. Some women reported that menses were important triggers of their asthma exacerbation. Previous survey studies of women with stable asthma reported 30 to 40\% had worsening of symptoms immediately prior to or at the time of menstruation\textsuperscript{17-19,41}.

In a prospective cohort study\textsuperscript{44} of 64 EDs examined the relation between phase of menstrual cycle and visits for acute asthma. A total of 288 women with acute asthma were evaluated with a standardized patient interviewed and medical record reviewed after excluding subjects who were pregnant on hormonal therapy, postmenopausal. There was no significant association between phase of menstrual cycle and asthma severity. The data indicate that ED visit for acute asthma among women were more frequent during preovulatory phase.
Discussion

Objective evaluation of airway function during the menstrual cycle in women with stable asthma has yielded inconsistent result. Some studies have noted worsening symptoms and decreases in PEFR in the premenstrual and menstrual period\textsuperscript{17,18,26,42,64} whereas others found no changes in symptoms or spirometric parameters\textsuperscript{60}. One report found a marked decrease in PEFR coinciding with ovulation\textsuperscript{45}. Other studies found discordance between symptoms and spirometric measurements during the menstrual cycle\textsuperscript{25,26}. These were premenstrual PEFR fall in MLA. The PEFR recordings revealed a significant fall in morning as well as evening in premenstrual and menstrual week as compared to mid cycle week. This fall was maximal in the premenstrual week. Similar observation was also recorded in earlier studies\textsuperscript{17,18}. Pauli et al\textsuperscript{25} compared PEFR in normal and asthmatic subjects who did not complain of any menstrual linked exacerbation in asthma. The result shows that mean PEFR value over two cycles were significantly lower in MLA patients in all the weeks. The mean PEFR was significantly less in menstrual phase, premenstrual phase as compared to midcycle week. In our study there
was significant fall of PEFR during premenstrual and menstrual phase in group having history of PMA which is same as other studies.

The pathophysiology of menstrual variability in asthmatic women is unknown. The effects of menstrual cycle on the expression of asthma have been attributed to changes in preestradiol and/ or estradiol level that affect airway function or inflammatory processes. Current evidence does not allow identification of the responsible hormone or hormones or whether absolute level or changes in hormone level are most important. Both exogenous progesterone and estradiol administration have been reported to improve asthma in women\textsuperscript{66}. Estrogen replacement therapy is associated with a greater risk of developing asthma in postmenopausal nonasthmatic women and worsening of decrease activity in postmenopausal asthmatics\textsuperscript{69}.

The aetiology and patengenesis of premenstrual asthma are unknown. The cyclical nature of this phenomenon implies that female sex steroid hormone have a pivotal role. The fact that the sex ratio of asthma incidence alters at puberty in female\textsuperscript{61} and that asthma control may differ in pregnancy\textsuperscript{54} provided further evidence for this. However
the exact mechanism by which these hormones exert their influence on asthma control is unclear. Some of the earliest work centered on the hypothesis that these with premenstrual asthma may have been allergic to endogenous hormones because of cutaneous reaction to steroid hormones\textsuperscript{70}. As number of factors including PMS, dismenorrhea, increased bronchial mucosal hydration and increased autonomic lability have been postulated as a cause but no consistent association has been recorded\textsuperscript{16}. The commonly encountered premenstrual symptoms are fatigue, irritability, lack of concentration, backache, vague sensation of pelvic discomfort. Clinic alteration personality is also included in premenstrual syndrome. In our study 90\% of 34 patients complain that they have some form of PMS; the most common was vague abdominal pain (10\%), headache (3\%), backache (8\%), breathlessness (4\%), stomach blotting (2\%), anxiety (9\%), depression (3\%), irritability (9\%), and nausea (4\%). Eliassor et al\textsuperscript{61} postulated that MLA could be due to withdrawal of relaxation effect on bronchial smooth muscle as progesteress and estradiol decline during the late luteal phase.
Hormonal changes in relation to menstrual cycle are thought to be a factor responsible for exacerbation of bronchial asthma during the menstruation and need further analysis which may constitute an important factor in the management of bronchial asthma during this period. Asthma in patients with MLA appears nearer to their puberty and their duration of illness is longer. Patients with MLA are hospitalized more often and have more emergency room visits than those without MLA which suggest that these patients have a more severe form of disease and such patients need to be closely monitored.

In conclusion, this study reveals 34% of Indian females have MLA. The severity of disease is more in case of MLA patients. There is a decrease in peak flow rate during premenstrual and menstrual phase in these patients. They have a longer duration of illness. A large scale prospective study is required to define changes in airway function, underlying mechanism, and specific intervention. Identification of these patients will lead to increased recognition and development of specific interventions for a high risk subgroup of asthmatic women.