REVIEW
OF
LITERATURE
"Bronchial asthma is a chronic inflammatory disorders of the airways in which many cells and cellular elements play a role. The chronic inflammation causes an associated increase in airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. These episodes are usually associated with wide spread but variable airflow obstruction that is often reversible spontaneously or with treatment\textsuperscript{28}."

Airway hyper-responsiveness (prevalence of an exaggerated bronchoconstrictor response i.e. at least 20% fall in FEV\textsubscript{1}, to a wide variety of exogenous and endogenous stimuli) and acute airflow limitation are the two predominant manifestations of disordered lung function in asthma\textsuperscript{28}.

Although about 8-11% of children and 6-7% of adults have current asthma, about 4% of all age groups have moderate to severe persistent asthma that requires regular medication\textsuperscript{29}. The cost of asthma treatment in India is 9% of per capita annual income\textsuperscript{30}. 
Bronchial asthma is clinically diagnosed by recurrent occurrence of episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning. Seasonal variability of symptoms and a positive family history of asthma and atopic diseases are also helpful diagnostic guides\textsuperscript{28}.

The most usual abnormal physical finding is wheezing/ rhonchi on auscultation.

On the basis of lung function tests, at least 12 percent improvement in FEV\textsubscript{1} either spontaneously, after inhalation of a bronchodilator or in response to a trial of glucocorticosteroid therapy favours a diagnosis of asthma\textsuperscript{31}.

Also, at least a 15 percent improvement in PEF after inhalation of a bronchodilator or in response to a trial of glucocorticosteroid therapy\textsuperscript{32} or a diurnal variation in PEF of more than 20 percent is considered to be diagnostic of asthma\textsuperscript{33}. However, in mild intermittent asthma or in severe intractable disease, variability in PEF may not be present or may be lost\textsuperscript{28}. 

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Although, etiological and one based on pattern of airflow limitation classifications exists, clinically, asthma can be best classified on the basis of severity into following groups\(^2\)\(^8\):

1. Intermittent Asthma.
2. Mild Persistent Asthma.
3. Moderate Persistent Asthma.
4. Severe Persistent Asthma.

Chronic airway inflammation is invariably associated with injury and repair of the bronchial epithelium, which results in structural and functional changes, known as remodeling.

Airway remodeling is a heterogeneous process leading to changes in connective tissue deposition and to altered airway structure\(^2\)\(^1\). Principal features of airway remodeling are\(^3\)\(^4\):

a) Sub-epithelial fibrosis.

b) Myofibroblast hyperplasia.

c) Airway smooth muscle hypertrophy/ hyperplasia.

d) Mucus gland and goblet cell hyperplasia.
e) Epithelial disruption.

A recent report has added that perhaps perichondrial fibrosis should be added to this list\textsuperscript{35}.

In the bronchi, the sub-epithelial basement membrane is of normal thickness, but thickening and an increase in the density of the lamina reticular is typically occurs early in the disease process of asthma\textsuperscript{28}. It is brought about by a plexiform deposition of interstitial collagens I, III, V and fibronectin\textsuperscript{36} and also tenascin\textsuperscript{37}. This thickening of airway wall characteristic of remodeling, takes place in both cartilaginous (large) and membranous (small) airways\textsuperscript{38}.

The airway wall thickening leads to increased bronchial wall/luminal ratio causing an increased airway resistance and maximal expiratory flow is reduced at all lung volumes. Narrowed peripheral airways close at higher lung volumes, causing marked increase in residual volume, leading to lung hyperinflation. Also contributing to thoracic hyperinflation is the tendency to breathe at a higher lung volume. These changes greatly increase the work of breathing: resistive work is increased due to narrowing of airways and elastic
work is increased due to hyperinflation of the lung. This increased work of breathing and the loss in muscle efficiency causes fatigue and can lead to exhaustion and respiratory failure\textsuperscript{28}.

Asthma remains one of the most common chronic diseases with trends towards increasing prevalence and severity. While the precise reasons for this trend are unclear, the task of identifying high risk subgroups remains an important focus in the evolving understanding of asthma and the management of the patients with the disease.

Sex difference may be an important determinant in the natural history of asthma. While the prevalence of asthma prior to the onset of puberty is greater in males, females appear to ‘catch up’ after puberty suggesting a possible influence of the onset of menstruation\textsuperscript{39}. The female to male ratio was found to be 1:3 at age 10 while it was 1:1 at age 14 in a study\textsuperscript{9}. In general, the prognosis for asthma in women is worse than for men with increased asthma – associated hospitalization and morbidity after age 40 in women. Women often experience changes in the character of asthma symptoms during early reproductive years, pregnancy and menopause. A subset of asthmatic
women experience significant exacerbations of their asthma at or near the time of menses termed 'menstrual asthma'.

Termed interchangeably\textsuperscript{40} as menstrual linked asthma (MLA), premenstrual asthma (PMA), circamenstrual asthma, menstrual asthma, the condition was first described by Frank\textsuperscript{27} in 1931 in one the original accounts of premenstrual tension. Premenstrual asthma (PMA) is a clinical picture with worsening of asthmatic symptoms and pulmonary functions in the late luteal phase of the menstrual cycle.

Although the exact prevalence of PMA is unclear, it has been estimated to affect at least 40% of females with asthma. In a study by Aggarwal and Shah\textsuperscript{41} conducted in 100 Indian females, it was found that 23% of the patients had asthma exacerbations near menses. Rees\textsuperscript{14} in 1963 reported that 37% of female asthmatics had PMA. This was the first study based on questionnaire limited by recall bias and lack of objective data or spirometry. Other studies reported occurrence of 35\%\textsuperscript{17}, 40\%\textsuperscript{18}, 33\%\textsuperscript{19}, 28.2\%\textsuperscript{42} except for a South African study\textsuperscript{15} which reported 74\% incidence of PMA. The details of prevalence of PMA has been summarized in table I\textsuperscript{14,17-19,41-43}. Large scale community
based studies are required to estimate its true prevalence. Although
awareness of PMA is increasing, there is surprisingly little research into
the condition.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Study designs</th>
<th>Prevalence of PMA</th>
<th>Objective meant</th>
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<tr>
<td>Rees(^{14})</td>
<td>81</td>
<td>Questionnaire retrospective</td>
<td>33%</td>
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<td>Hanley(^{17})</td>
<td>102</td>
<td>Questionnaire retrospective</td>
<td>35%</td>
<td>PEF in selected patients</td>
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<td>Gibbs et al(^{18})</td>
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<td>Questionnaire retrospective</td>
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<td>Questionnaire retrospective</td>
<td>23%</td>
<td>PEF in selected patients</td>
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<tr>
<td>Shames et al(^{42})</td>
<td>32</td>
<td>Questionnaire prospective</td>
<td>28%</td>
<td>PEF and nethacetive challenges of all patients</td>
</tr>
<tr>
<td>Forbes et al(^{43})</td>
<td>481</td>
<td>Questionnaire retrospective</td>
<td>8%</td>
<td>None</td>
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</tbody>
</table>

PEF = Peak expiratory flow
A majority of patients with PMA have worsening of asthma symptoms during the premenstrual week\textsuperscript{41}. In some worsening extends to the menstrual week also. A rare patient may complain of worsening after menstrual cycle was over\textsuperscript{41}. In contrast, a large multicenter study\textsuperscript{44} of 288 women found that greatest number of emergency visits (33\%) occurred prior to ovulation. Only 21\% visits occurred in the premenstrual period. A few patients may have seasonal variation also\textsuperscript{41}. Female sex hormones play an important role but the exact mechanism is still unknown.

In a study\textsuperscript{44}, hormonal fluctuations during the menstrual cycle are hypothesized to influence the course the asthma among women. A recent study found that almost 50\% of emergency department (ED) visits occur during the premenstrual phase. The prospective cohort study in 64 EDs examines 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 interview and medical record review after excluding subjects who were pregnant, on hormonal therapy, postmenopausal, status post hysterectomy, had incomplete reproductive data, or whose ED visit fell more than 28 day
after their last menstrual period. Only 13% reported reproductive factors as a personal asthma trigger. For all subjects, ED asthma visits were classified by menstrual phase: 33% were preovulatory (Days 5 to 11), 26% were periovulatory (Days 12 to 18), 20% were postovulatory (Days 19 to 25), and 21% were premenstrual (Days 26 to 4), \( p = 0.008 \). There was no significant association between phase of menstrual cycle and asthma severity. The data indicate that ED visits for acute asthma among women are more frequent during the preovulatory phase in contrast to other studies reporting more visits in the premenstrual phase.

Previous studies of women with stable asthma reported 30-40% had worsening of symptoms immediately prior to or at times of menstruation\(^{17-19,41}\). In another study which noted an increased frequency of ED asthma visits by women during premenstrual phase\(^{20}\).

Hospital based emergency visit was significantly higher in MLA asthmatic patients. Skobeloff and Colleagues\(^{13}\) 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.

Accurate diagnosis is dependent on a detailed history and the demonstration of premenstrual dip in peak expiratory flow. Exacerbations in the majority will response to the usual treatment of bronchial asthma. However, a few women will experience significant morbidity or treatment related adverse effects. PMA has been described as a cause of repeated hospitalizations, recurrent respiratory
failure and even death\textsuperscript{44}. Patients with PMA are significantly older and have a longer duration of asthma compared with other women\textsuperscript{42}. But study by Aggarwal and Shah\textsuperscript{41} indicated that asthma in this subgroup appears earlier and that the duration of illness was longer. This study also suggested that asthma in this group had an onset nearer to their puberty. Also asthma tends to be severe in them. There has been debate whether PMA represents a true “physiologic” event or a “psychologic” phenomenon as part of the spectrum of premenstrual syndrome. In a study by Shames et al\textsuperscript{42}, there was no significant differences between the groups in menstrual cycle length, age at menarche, duration of menses, self reported premenstrual syndrome and self reported psychologic depression.

In a exploratory analysis by Shames et al\textsuperscript{42}, women with or without self-reported perimenstrual exacerbations of asthma (PMA) were examined prospectively to determine the association between asthma and the menstrual cycle and to characterized association clinical factors. Thirty-two adult asthmatic women with regular menstrual periods recorded daily asthma symptoms, medication use and peak expiratory flow rate (PEFR) over six consecutive menstrual
cycles, and underwent spirometry and methacholine bronchoprovocation during the luteal and follicular phases of 2 cycles. Nine of 32 subjects (28.2%) reported PMA. Daily means of rescue medication use and AM peak flow computed for each perimenstrual day demonstrated significant non-parallelism of group profile; subjects with PMA had increasing inhaled short acting beta 2-agonist use and decreasing AM peak flow rates during the perimenstrual interval. Luteal-follicular phase differences in FEV$_1$ or methacholine bronchoprovocation between the groups were not detected. Subjects with PMA were older ($p = 0.007$), had longer duration of asthma ($p = 0.039$), and increased baseline asthma severity ($p = 0.076$) compared with subjects without PMA. The findings of this study suggest that women with self-reported perimenstrual asthma demonstrate perimenstrual differences in rescue bronchodilator use and AM peak flow and appear to constitute a distinct subset of women with asthma who are older, have longer duration of asthma, and increased severity of asthma compared with women without self-reported perimenstrual asthma. These factors identify women who require close monitoring of their asthma during their menstrual cycles.
Several studies have attempted to use objective data to study the problem. Some studies have noted worsening symptoms and decreases in peak expiratory flow rate (PEFR) in the premenstrual and menstrual period whereas others found no changes in symptoms or spirometric parameters. Hanley\textsuperscript{17} as well as Gibbs et al\textsuperscript{18} noted a significant reduction in PEFR at the time of menstruation in those female asthmatics whose symptoms had worsened at the time of menstruation as compared to those who did not experience any cyclic aggravation of asthma symptoms. Studies have also shown a significant fall in the morning as well as evening PEFR in the menstrual and pre-menstrual weeks compared to the midcycle week in patients with PMA\textsuperscript{41}. One report found a marked decrease in PEFR coinciding with ovulation\textsuperscript{45}. Women with PMA experience increased severity of asthma during perimenstrual interval marked by increasing rescue medication and decreasing PEFR, although perimenstrual changes in spirometry or airway responsiveness have not been demonstrated. A recent study concluded increased baseline asthma severity, significantly increased asthma symptoms, increased rescue bronchodilators use and decreased morning and evening PEFR in PMA
patients compared to those who don’t have PMA$^{42}$. But this study failed to detect a luteal follicular phase difference in forced expiratory volume in one second (FEV$_1$) or methatholone bronchoprovocation in patients with PMA and in patients without PMA$^{42}$. The plots of medication use and PEFR on a standardized cycle calendar suggest that the largest increases in medication use and decreases in PEFR occur immediately after the onset of menses (approx. days +1 to +4)$^{42}$.

In a study by Chong et al$^{46}$ to characterize intrasubject, intersubject, and diurnal variability in peak expiratory flow rates (PEFR) of healthy nonasthmatic women over at least one complete menstrual cycle; to determine whether a relationship exists between PEFR and premenstrual symptoms in these women; and to provide a forum to educate women pharmacy students by interactive study participation. A longitudinal, investigator-blinded study in University of British Columbia and Children’s and Women’s Health Centre forty healthy nonasthmatic female pharmacy students were enrolled, and 31 (aged 22.1 ± 1.5 yrs) completed the study. Women were followed for at least one menstrual cycle during which they recorded premenstrual
symptoms questionnaire scores daily (15 mood and physical symptoms, graded 0-3 in severity). They also measured a recorded PEFR (3 consecutive attempts) every morning and every evening. A feedback survey was later administered by electronic mail. Thirty-one women, 28 of whom were of Asian descent, completed the study. Over half of them (58.1%) showed classic patterns of premenstrual symptoms, whereas PEFR fluctuated randomly over the course of the cycle. Average coefficients of variation (CVs) were 4.17 ± 2.09% for morning PEFR, 3.97 ± 2.25% for evening PEFR and 3.72 ± 2.55% for mean daily PEFR. Average absolute diurnal variation was 17.13 ± 12.46 L/ minute, and relative diurnal variation was 3.98 ± 2.52%. Intersubject variability for morning, evening, and mean daily PEFRs yielded low CVs of 13.7%, 14.3%, and 13.9% respectively. Only 14 (11.3%) of 124 correlations between PEFR and premenstrual symptoms were significant (p < 0.05). Most participants responded positively (mean score 3.87 on a 5-point scale) to the survey on the impact of this study. It concluded intrasubject and diurnal variability is relatively low. The menstrual cycle appears to have little effect on PEFR in healthy nonasthmatic Asian women. Pharmacy student who
take part in serial PEFR monitoring gain new appreciation for asthma and asthmatic patients.

Investigations of premenstrual asthma (PMA) have been based on studies of asthmatics already aware of a deterioration of asthma premenstrually. Little is known, therefore, about relationship between the menstrual cycle and airway function in asthmatics who do not complain of PMA or in normal subjects. The author investigated airway function in both of these groups of three or four consecutive menstrual cycles. Daily records of asthma symptoms and peak expiratory flow rates were maintained by 11 asthmatics and 29 normal control subjects. Standard spirometry and serum estradiol and progesterone levels were measured during the follicular, midluteal, and late luteal phases of the menstrual cycle. Airway reactivity to methacholine was tested during the follicular and luteal phases. The normal group showed no significance changes in symptoms, peak flow rates, spirometric parameters, or airway reactivity. Although the asthmatic group also demonstrated no significant changes in spirometry and airway reactivity, asthma symptoms (shortness-of-breath, cough, wheeze, and chest tightness) deteriorated significantly
(p less than 0.001) from the follicular to the luteal phase, as did the morning peak flows of the asthmatics (p = 0.045). Airway function and reactivity were not related to hormone levels in either group. This study indicates that asthmatics not previously aware of PMA will record a premenstrual worsening of asthma symptoms and peak expiratory flow rates. These changes are not related to deterioration in spirometry and airway reactivity or to the absolute levels of circulating progesterone and estradiol.

PMA has also been defined as a complex state with worsening of airway inflammation. In a study done to demonstrate increase airway responsiveness, daytime symptom scores, sputum eosinophilia and fractionated exhaled NO (FE\textsubscript{NO}) were significantly higher in PMA patients\textsuperscript{47}. Thus, PMA is a condition associated not only with decreased airway caliber but also increased airway inflammation. The increased levels of (FE\textsubscript{NO}) before menstrual cycle were significantly correlated with the increased sputum eosinophilia\textsuperscript{47}.

In a study\textsuperscript{47} to evaluate the inflammatory changes in asthmatic women who complain of PMA. Forty asthmatic women attending
outpatient clinic were questioned about worsening of their asthma
before menstruation. Eleven women (aged 17-40) who complained of
PMA participated in the study. Subjects were asked to record peak
expiratory flow rates, symptoms scores, and β-agonist use daily. After
the first menses on the seventh day of their cycle, and before the
onset of the next menstruation, on the 26 ± 3rd day of the cycle,
patients were evaluated with pulmonary function tests, methacholine
challenge test, and fractionated exhaled nitric oxide (FE\textsubscript{NO}) levels.
Eosinophils in peripheral blood and induced sputum were also
evaluated. When comparing the two groups of results, the significant
changes were in FE\textsubscript{NO} levels, day time symptom scores, and
eosinophils in induced sputum (29.25 ppb/ 9.16 ppb p < 0.05, 1/0.45
p < 0.05, %6.63/ %4.09 p < 0.01, respectively, before and after
menstruation). These results show that PMA is not only a clinical
picture with a decrease in airway caliber that can be related to the
regulation of 2 receptors, but also a complex state with worsening of
airway inflammation.

The physiological changes that lead to these severe clinical
conditions in PMA are evaluated in many clinical and in vitro studies.
The most accounted factor is the sudden fall in progesterone in the late luteal phase of menstruation. Progesterone has been shown to potentiate the effects of endogenous catecholamines on airway smooth muscle and cause bronchodilation\textsuperscript{48}. Progesterone was also shown to up-regulate the $\beta_2$ adrenoceptors, an effect that was not shown with estrogens in human studies\textsuperscript{49}.

In some reports, therapies with high doses of progesterone were found to be successful in improving PMA symptoms, supporting the role of progesterone in PMA, but it was of no benefit in some cases\textsuperscript{24,50}. Gonadotropin-releasing hormone analogs have been introduced as a novel treatment for PMA, supporting the role of both progesterone and estrogen\textsuperscript{51}.

It has been suggested that premenstrual exacerbation of asthma is part of the premenstrual syndrome. Rees\textsuperscript{14} found that more patients with premenstrual asthma had symptoms of premenstrual syndrome compared with those without. Another small study suggested that psychological factors might play an important role\textsuperscript{52}. Eliasson et al\textsuperscript{19} also found an association between premenstrual asthma and symptom
scares for premenstrual syndrome and dysmenorrhoea. Although neither study included an objective measurement of asthma control, they suggest that mood changes, which occur in some women premenstrually, may give rise to the subjective feeling that stable asthma is worse even though physiologically it is not altered. Alternatively, low mood may be a consequence of the morbidity associated with poor asthma control.

Researchers are slowly piercing together clues as to the aetiology and pathogenesis of the disorder. The cyclical nature of this phenomenon implies that female sex steroid hormones have a pivotal role. The fact that the sex ratio of asthma incidence alters at puberty in females and that asthma control may differ in pregnancy provides further evidence for this. However, the exact mechanism by which these hormones exert their influence an asthma control is unclear. Some of the earliest work centered on the erroneous hypothesis that those with PMA may have been allergic to endogenous hormones because of cutaneous reaction to steroid hormones. With evidence linking sex steroid hormones to PMA, a number of studies investigating a possible pathogenetic mechanism have been undertaken.
Some have suggested that PMA is a part of pre menstrual syndrome (PMS)\textsuperscript{14}. Some have found an association between PMA and symptom scores for PMS dysmenorrhoea. They suggest that mood changes, which occur in some women premenstrually may give rise to the subjective feeling that stable asthma is worse even though physiologically it is not altered. Alternatively, low mood may be a consequence of the morbidity associated with poor asthma control.

No consistent associations have been found between PMA with characteristics of the menstrual period, pregnancy and menopause\textsuperscript{17-19}. Some have postulated that the PMA could be due to withdrawal of relaxant effect on bronchial smooth muscle as progesterone and estrogen decline during the late luteal phase but such relationship was not seen in a later study\textsuperscript{41}. Alternatively, prostaglandin (PG) F\textsubscript{2}α has been found to peak at ovulation and premenstrually\textsuperscript{54}. Being a potent bronchoconstrictor, this could conceivably trigger PMA. However later studies found a dip premenstrually\textsuperscript{55}.

In PMA, heightened bronchial hyper responsiveness (BHR), which is a manifestation of underlying inflammation, is seen. Although a
study\textsuperscript{47} failed to show variation in broncho provocation by methacholine or histamine during luteal and follicular phase, Tan and colleagues\textsuperscript{56} found increased BHR to adenosine monophosphate (AMP) during the luteal phase. Unlike histamine and methacholine, which act directly on smooth muscles, AMP acts indirectly on mast cells and airway sensory nerves and thus AMP challenge is a more sensitive discriminator of airway inflammation. The authors speculated that sex hormones may affect asthma by sensitizing the adenosine receptors on the surface of mast cells but failed to demonstrate significant correlation between hormone levels and degree of changes in airway responsiveness.

Several new studies have tried to elucidate the mechanism of PMA and the role of sex hormones in asthma. Tan et al\textsuperscript{56} discovered cyclical changes in lymphocyte β 2 adrenoceptor function during the menstrual cycle in normal women with greater β 2 receptor density and isoprenaline responsiveness in the luteal phase when sex steroid levels are raised. The up-regulation effect is most probably mediated by progesterone rather than estrogen. This cyclic change is lost in women with asthma. Furthermore, administration of exogenous progesterone
during the follicular phase (when endogenous sex hormones are normally low) resulted in up regulation of lymphocyte $\beta_2$ adrenoceptorus in normal women but paradoxically produced a down regulation in asthmatic women. This phenomenon was not observed with the estrogen administration. The authors suggested that progesterone may play an important role in PMA, with high levels in the luteal phase suppressing the bronchial $\beta_2$ adrenoceptors thereby promoting asthma exacerbation. This hypothesis seems to be in discordance with three earlier reports of therapeutic effect of intramuscular progesterone in patients of severe PMA. It was felt that the precipitous fall of progesterone during the late luteal phase might be responsible for PMA and intra muscular progesterone was given to avoid this fall with benefit$^{42}$.

Other investigators have focused on the impact of estrogen on asthma. Estradiol administration has been demonstrated to decrease symptoms, cyclic variability in PEFR, and airway reactivity in premenopausal asthmatic women. However, estrogen replacement therapy is associated with a greater risk of developing asthma in
postmenopausal non asthmatic women and worsening of disease activity in postmenopausal asthmatics.

Most patients of PMA are likely to be controlled using standard treatment guidelines. However, there may be a subset of women who experience significant morbidity and treatment related complications. Some of them may respond to intramuscular progesterone and oral estrogens while others may not. There have been case reports of PMA improving\textsuperscript{45} and worsening\textsuperscript{57} with the combined oral contraceptives. A few case reports have demonstrated a marked improvement in PMA with gonadotrophin releasing hormone (GnRH) analogue. Meclofenamate, an NSAID, has been tried with no significant improvement. Other potential strategies have yet to be explored.

In order to properly manage premenstrual asthma, an accurate diagnosis is necessary. A detailed history of timing of exacerbations is essential to this end, and a diary of symptoms of PEF recordings highlighting premenstrual worsening is often invaluable.

Although as many as 40% of female patients may have premenstrual asthma, most are likely to be controlled using standard
treatment guidelines\textsuperscript{58}. Some may require an increased dose of inhaled corticosteroid or the addition of a long acting $\beta_2$-agonist during the second half of the menstrual cycle. However, there may be a subset of women who experience significant morbidity and treatment-related complications\textsuperscript{59}. Evidence based treatment for these individuals are scantily reported with only two randomized controlled trials published on the subject. Studies are largely observational and results anecdotal, making it difficult to draw firm conclusions. The experimental therapies that have been tried are discussed in this section and are summarized in table II.

The exact pathophysiology of MLA, which occurs in a subset of female asthmatics 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\textsuperscript{25}. Juniper et al\textsuperscript{26} examined changes in airway responsiveness to methacholine in 17 well-controlled asthmatics one week prior to and one week after the onset of menstruation but found no significant difference in airway responsiveness, FEV\textsubscript{1} or medication use. In a
similar study, Weinmann et al\textsuperscript{60} found no significant difference in FVC, \( \text{FEV}_1 \) and airway responsiveness to histamine when measured early and again late in the menstrual cycle. Eliasson et al\textsuperscript{61} postulated that MLA could be due to withdrawal of relaxation effect on bronchial smooth muscle as progesterone and estradiol decline during the late luteal phase but such relationship was not seen in a later study\textsuperscript{16}. Alternatively, monthly variations in levels of circulating prostaglandins, especially PGF\(_2\alpha\) have been suggested to modulate the bronchial tone in patients with MLA\textsuperscript{54}. Tan et al\textsuperscript{62} have demonstrated cyclical changes in airway responsiveness to AMP during the premenstrual period along with a loss of normal cyclical pattern of \( \beta_2 \)-adrenoceptor regulation in female asthmatic subjects. The increased response to AMP may be due to regulation of adenosine receptors on airway mast cells under the influence of circulating sex hormones. Tan et al\textsuperscript{63} have also shown that exogenous progesterone, but not estrogen, given during the follicular phase, decreasing \( \beta_2 \)-adrenoceptor and cyclic-AMP response in female asthmatics, which was in contrast to the previous observation of up-regulating effect of progesterone seen in healthy women\textsuperscript{49}. This paradoxical effect of progesterone in female asthmatics might be a
possible mechanism for MLA when progesterone levels are high during the premenstrual period. However, further research using other established measures of airway inflammation are needed to document the pathophysiology.

A remarkable response to intramuscular progesterone was reported in three women with severe premenstrual exacerbations of asthma resistant to systemic corticosteroids. Treatment with intramuscular progesterone eliminated premenstrual PEF dips and allowed a significant reduction in systemic corticosteroid dose. Dosages and frequency (100mg daily in two women and 600mg twice weekly in the order) were greater than those currently licensed. It is not known whether lower and less frequent doses would be as efficacious. Interestingly, two patients were treated previously with the combined oral contraceptive pill, which did not improve asthma control.

Estrogens have also been shown to be beneficial. In an uncontrolled study, 14 women with asthma, five of whom reported premenstrual asthma exacerbations, were given a single dose of
oestradiol 2mg during the luteal phase. Asthma symptom scores improved compared with the previous natural cycle, although the ‘before and after’ design of the study made it difficult to rule out the possibility that improvements occurred for reasons other than hormone administration. Another uncontrolled study found no benefit with estradiol supplementation. A report of three cases found that the addition of supplemental estrogens improved asthma controlled and allowed the withdrawal of oral corticosteroid therapy. However, two of the women were postmenopausal and the results may not be directly applicable to premenstrual asthma.
### Table II: Trials of treatment for premenstrual asthma (PMA)

<table>
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<th>Reference</th>
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<td>Beynon et al(^{24})</td>
<td>3</td>
<td>Intramuscular progesterone (100mg daily, 600 mg twice weekly)</td>
<td>Uncontrolled</td>
<td>Improvement in PEF reduction in oral corticosteroid dose</td>
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<td>Chandler et al(^{64})</td>
<td>14 (5 with PMA)</td>
<td>Oral estradiol 2mg</td>
<td>Uncontrolled</td>
<td>Improvement in symptoms</td>
</tr>
<tr>
<td>Myers &amp; Sherman(^{66})</td>
<td>3 (2 postmenopausal)</td>
<td>Oral estrogens 0.625mg</td>
<td>Uncontrolled</td>
<td>Improvement in symptoms, discontinuation of oral corticosteroids</td>
</tr>
<tr>
<td>Tan et al(^{67})</td>
<td>18 (not with PMA)</td>
<td>Combined oral contraceptive pill</td>
<td>Parallel group, uncontrolled</td>
<td>Improvement in BHR to AMP, reduction in PER variability</td>
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<tr>
<td>Blumenfeld et al(^{68})</td>
<td>1</td>
<td>Monthly intramuscular GnRH analogue</td>
<td>Uncontrolled</td>
<td>Improvement in symptoms and FEV(_1), reduced oral corticosteroid dose</td>
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<tr>
<td>Murray et al(^{51})</td>
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<td>Monthly intramuscular GnRH analogue</td>
<td>Uncontrolled</td>
<td>Improvement in symptoms, PEF and reduction in oral corticosteroid dose</td>
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<tr>
<td>Authors</td>
<td>Study Duration</td>
<td>Treatment</td>
<td>Design</td>
<td>Outcome</td>
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<tr>
<td>Ensom et al\textsuperscript{55}</td>
<td>14 (7 with PMA)</td>
<td>Oral estradiol 2mg</td>
<td>Uncontrolled</td>
<td>No improvement</td>
</tr>
<tr>
<td>Eliasson et al\textsuperscript{55}</td>
<td>24</td>
<td>Oral meclofenamic acid 100mg daily</td>
<td>Randomised, placebo-controlled, double-blind</td>
<td>No significant improvement in FEV\textsubscript{1} and symptoms</td>
</tr>
<tr>
<td>Eliasson et al\textsuperscript{61}</td>
<td>17</td>
<td>Oral meclofenamic acid 100mg twice daily</td>
<td>Randomised, placebo-controlled, double-blind</td>
<td>No significant improvement in PEF and symptoms</td>
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</tbody>
</table>

AMP = adenosine monophosphate; BHR = bronchial hyperresponsiveness; FEV\textsubscript{1} = forced expiratory volume in 1 second; GnRH = gonadotrophin releasing hormone; PEF = peak expiratory flow.
To sum up, PMA is a clinical entity that affects up to 40% of women with asthma. The aetiology and pathogenesis of the condition are unclear. Symptoms in the majority are treated with conventional regimens. For the few who experience significant morbidity, advice on therapy is inadequate and can only be taken from anecdotal uncontrolled studies. Larger randomized controlled studies are required to glean further information on the pathogenesis and treatment of this intriguing condition. Physicians treating asthma should be aware of this clinical entity as these patients need to be monitored more closely. Proper patient education and initiation of appropriate preventive measures in patient with PMA could lead to better control and decrease in morbidity.