
Review article

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The impact of estrogen and progesterone on asthma

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Objective: This paper describes evidence of a positive effect of both endogenous and exogenous estrogen and progesterone on lung function across the life span in women.

Data Sources: Articles were identified using the keywords *asthma*, *pulmonary function*, *menarche*, *menopause*, *estrogen*, *progesterone*, *hormone replacement therapy*, *oral contraceptives*, and *menstrual cycle* from years 1966 to 2001 in MEDLINE. Additional studies were identified from article reference lists.

Study Selection: Relevant, peer-reviewed original research articles in the English language were selected.

Results: Estrogen and/or progesterone may alter pulmonary function and asthma. Premenopausal women experience decreases in pulmonary function and increases in asthma exacerbations and hospitalizations during the premenstrual and menstrual phases. Oral contraceptives and hormone replacement therapy are associated with improved pulmonary function and decrease in asthma exacerbation. Some asthmatic patients experience improved pulmonary function and reduced asthma medication requirement during pregnancy.

Conclusions: Estrogen and progesterone modify airway responsiveness. Further research is needed to elucidate the clinical relevance of estrogen and progesterone in the pathophysiology and therapy of asthma.

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INTRODUCTION

Approximately 15 million United States adults and children suffer from asthma.¹ Asthma causes significant morbidity, accounting for 10.4 million office visits per year, more than 1.8 million emergency room visits, and 466,000 hospitalizations per year.² In 1998, the estimated cost of asthma was \$11.3 billion. Among the general population, the prevalence of asthma is higher among women than men.¹ Thus, the identification of factors that influence the course of asthma among women may significantly reduce associated morbidity.

Evidence suggests that estrogen and progesterone may influence pulmonary function and asthma. This review will address the potential impact of both endogenous and exogenous estrogen and progesterone on pulmonary function and asthma, critically appraise the strengths of weakness of individual reports, and suggest future directions for research.

MECHANISM

Effects on Smooth Muscle

In vitro animal models. The distribution of progesterone receptor expression in the lung, esophagus, proventriculus,

liver, spleen, pancreas, and heart suggests that progesterone may potentially affect organs outside the genital tract.³ A number of animal models suggest that both progesterone and estrogen may directly affect the lungs by reducing contractility and increasing relaxation of bronchial smooth muscle.^{4–8} Further, estrogen withdrawal increases bronchial contractility.⁹ Progesterone, which is responsible for maintaining relaxation of uterine smooth muscle, has been found to impart similar effects systemically. In addition to reducing the contractility of bronchial smooth muscle, progesterone has also been shown to reduce contractile responses in animal gallbladder, esophageal, antral, colonic, arterial, and aortic smooth muscle.^{10–18}

Human models. Similarly, addition of progesterone inhibits contraction of human colon, stomach, and ureter smooth muscle *in vitro*.¹⁹ Synthetic progesterone may also have androgenic properties. Because testosterone has also been found to relax bronchial tissue and depress response to histamine,^{8,20} improvements in pulmonary function among oral contraceptive users^{21–24} may also be influenced by the androgenic properties of progestins. Therefore, considerable evidence suggests that progesterone and estrogen may improve lung function through relaxation of bronchial smooth muscle and reduction in contractile response.

Effects on Inflammation

In vitro and in vivo animal models. Animal models have shown that estrogen stimulates whereas progesterone and

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androgens suppress the immune system.^{25–28} Specifically, progesterone promotes the development of T-helper 2 cells, triggering antibody production and antagonizing the emergence of T-helper 1 cells and proinflammatory cytokines.²⁹

Human models. Both estradiol and progesterone have been found to significantly inhibit human peripheral monocyte production of interleukin-1, a strong mediator of inflammation.³⁰ Estradiol has also been found to exhibit anti-inflammatory properties in human leukocyte studies.^{31,32}

Effects on Skeletal Muscle

Estrogen and progesterone may also improve pulmonary function by strengthening airway muscle or the skeletal and muscular integrity of the thoracic spine. Women in the luteal phase of the menstrual cycle have been found to have better upper airway dilator muscle activity (as measured by awake genioglossus electromyogram) than women in premenstrual phase of the menstrual cycle or postmenopausal women.³³ Additional research on hormones and upper airway strength is needed to further substantiate this hypothesized biologic mechanism.

MENSTRUAL CYCLE

Women experience large fluctuations in hormonal levels across the menstrual cycle. The follicular phase of the menstrual cycle begins with the onset of menstruation, when the secretion of the ovarian steroids estradiol and progesterone are low. During this phase, follicular growth causes a rapid rise in estradiol. After ovulation, the follicle develops into an endocrine gland, the corpus luteum, which produces progesterone and estradiol. If the ovum becomes fertilized, the corpus luteum maintains elevated progesterone and estradiol levels until the placenta becomes established. Otherwise, the corpus luteum will die at the end of 2 weeks, and estradiol and progesterone levels will drop.

Thus, levels of estrogen and progesterone fluctuate substantially over the menstrual cycle. Asthma symptoms and pulmonary function also seem to vary cyclically. An estimated 33 to 52% of asthmatic women report premenstrual worsening of asthma symptoms.^{34–38} An additional 22% report asthma that is worse during menses.³⁷ These women experience significantly higher rates of hospitalization (mean 1.3 vs 0.6, $P = 0.01$) and office visits (mean 4.6 vs 3.0, $P = 0.03$) per year.³⁵ Women with premenstrual worsening of asthma report significantly higher rates and severity of premenstrual syndrome and dysmenorrhea scores than women without premenstrual worsening of asthma.^{34,35,39} Almost 50% of women admitted to the hospital for asthma have been identified as perimenstrual.⁴⁰ Numerous case studies suggest that premenstrual declines in hormonal levels worsen asthma symptoms, and that exogenous hormone therapy, in reducing hormonal fluctuation, eliminates premenstrual asthma exacerbations and potentially reduces or eliminates corticosteroid dependence.^{22–24,41–45} Further, serum progesterone measured over the menstrual cycle has been positively correlated with peak expiratory flow rate (PEFR).²⁴

Studies that examine changes in asthma symptoms and pulmonary function over the menstrual cycle are limited but generally support the notion that falling estrogen and progesterone are associated with worsening of pulmonary symptoms. Among a group of 16 healthy women (mean age 22.9 years) not using oral contraceptives, total lung capacity has been found to be significantly higher in the luteal phase compared with the follicular phase.²¹ Small studies of women with asthma reported significant deterioration of asthma symptoms (shortness of breath, cough, wheeze, and chest tightness)⁴⁶ and significant decreases in PEFR (range 15 to 25%)^{38,46,47} from the late follicular, the period of highest estrogen concentration, to the late luteal phase, the period before menstruation characterized by declining estrogen and progesterone. Women who report regularly experiencing asthma exacerbations premenstrually have significantly lower premenstrual PEFR compared with midcycle,^{36,47} and report increased bronchodilator use and decreased PEFR when perimenstrual.⁴⁸ However, among nonasthmatic women and asthmatic women who report that they do not experience worsening of asthma premenstrually, no significant changes in PEFR occur over the menstrual cycle.^{36,47,49} A small study of 11 asthmatic patients identified a nonsignificant trend toward a decrease in spirometric values from the midluteal to late luteal phase.⁴⁶ Similarly, among a small sample of nine women who reported regularly experiencing perimenstrual asthma exacerbation, the percent predicted forced expiratory volume in 1 second (FEV₁) was found to be nonsignificantly lower in the luteal phase (70.7%) compared with the follicular phase (75.4%).⁴⁸ Among a group of nine women not using oral contraceptives, a significant increase in airway hyperresponsiveness to adenosine monophosphate (AMP) occurred during the luteal phase of the menstrual cycle (4.0-fold difference in geometric mean PC₂₀ (the provocative concentration that causes a 20% decline in FEV₁), 95% confidence interval [CI] 1.25 to 13.03).⁵⁰ However, several other small studies^{46,51,52} found no change in bronchial hyperresponsiveness over the menstrual cycle among women not taking oral contraceptives. One explanation for the discrepancy in these study results may be the stimulus used to evaluate airway responsiveness. Increased hyperresponsiveness occurred after challenge with AMP,⁵⁰ an indirect measure of airway responsiveness, but not after administration of histamine⁵² or methacholine,^{46,51} direct measures of airway responsiveness. Indirect and direct stimuli elicit different responses,⁵³ and further studies using both type of stimuli may provide some biologic insight into how estrogen and progesterone influence airway hyperresponsiveness. Also, history of premenstrual exacerbation of symptoms was not evaluated in two of these studies,^{46,52} and only one of the 10 participants in the airway responsiveness study by Juniper et al⁵¹ reported previous premenstrual asthma exacerbation.

Studies of pulmonary function and asthma across the menstrual cycle are limited by small sample sizes and unadjusted comparisons. Collectively however, these findings suggest that in an identifiable subset of asthmatic patients, low hor-

monal levels may be associated with an increase in asthma symptoms. It is possible that low hormonal levels were associated with increased asthma symptoms among all asthmatic women, but these small studies may have lacked statistical power to find the overall association.

ORAL CONTRACEPTIVES

Oral contraceptives smooth hormonal fluctuations. In this way, they may diminish the cyclic exacerbation of symptoms that results from airway hyperresponsiveness. In a study of 18 women with asthma, women taking oral contraceptives experienced no significant cyclic change in airway hyperresponsiveness to adenosine monophosphate, whereas women not taking oral contraceptives experienced a significant increase in airway hyperresponsiveness during the luteal phase.⁵⁰

In a study of 30 healthy nonasthmatic women, women using oral contraceptives were found to have significantly higher mean total lung capacities compared with non-users during the follicular but not the luteal phases of their menstrual cycles (25.3 mL/L vs 21.15 mL/L).²¹ Therefore, when endogenous hormone levels were high among naturally menstruating women, total lung capacity was increased and equaled that of oral contraceptive users. Asthma symptoms (cough, wheezing, breathlessness, chest tightness) and dyspnea index scores improved significantly after estradiol administration in a study of 14 women with mild to moderate asthma.³⁸

Overall, the studies of oral contraceptive use among asthmatic women are sparse, have small sample sizes, and do not properly control for potential confounders such as medication use, allergic status, or exposure to allergens. There are no studies comparing symptoms or pulmonary function by dose or type of oral contraceptive. However, they do suggest that oral contraceptive use may eliminate menstrual fluctuations of both pulmonary function and symptomatology, perhaps by delivering a constant hormonal milieu.

PREGNANCY

Pregnancy is a time of marked estrogen and progesterone elevation. After ovum fertilization, the follicle develops into an endocrine gland, the corpus luteum, producing elevated amounts of progesterone and estradiol until the placenta becomes established. Progesterone is at an elevated, stable rate through the first trimester of pregnancy. At 3 months, progesterone levels rise linearly and are approximately 900% higher by the end of gestation. Similarly, estrogen levels rise at a significant and linear rate over pregnancy. By the end of gestation, estrone and estradiol levels are 100 times higher and the level of estriol is 1,000 times higher. Progesterone levels decrease dramatically immediately before parturition, increasing uterine contractility. After delivery, both estrogen and progesterone drop to prepregnancy levels.

Estrogen and progesterone are therefore highly elevated during pregnancy, reaching their greatest concentrations during the final trimester. Parallel to these changes in hormonal

levels, pregnant asthmatic women report improvements in asthma symptoms from preconception to pregnancy, with the lowest rates of symptoms occurring during the last 4 weeks.⁵⁴ Improvements include significantly reduced wheezing, sleep interference, and activity interference.⁵⁴ Up to 70% of women with asthma report improvement in symptoms during pregnancy. However, the rates of change vary substantially from study to study: 12 to 71% of women report improvement, 6 to 43% report no change, and 3 to 43% report worsening of symptoms.^{37,54–56} Large differences are likely attributed to the subjectivity of outcome measures. Additionally, none of the prospective studies followed women from preconception through delivery.^{54–56}

Few studies have objectively examined asthma during pregnancy. Over one-third of a cohort of 31 pregnant women experienced increased PEFR and reduction in bronchodilator use in the last trimester, with a deterioration postpartum in 42% of the women.⁵⁵ Among 17 asthmatic women followed prospectively from preconception through delivery, airway responsiveness improved and medication requirements decreased significantly over the pregnancies, returning to prepregnancy levels after delivery.⁵⁷ Spirometry was stable over pregnancy, but medication requirements were less.⁵⁷ Similarly, a study of 27 asthmatic women reported no statistically significant change in FEV₁/forced vital capacity (FVC) or percent predicted FVC during pregnancy (measured at 20, 34, and 38 weeks gestation).⁵⁸ However, this study did not examine pulmonary function before pregnancy or medication use. Among a subgroup of 11 women in whom the FEV₁/FVC was less than 70% on at least one occasion during gestation, the percent predicted FVC decreased 8% between week 38 and 48 hours postpartum. Although objective studies of asthma during pregnancy are sparse, they suggest an improvement of clinical asthma through reductions in asthma control medication and bronchodilator use, with stable or improved PEFR and spirometry.

Progesterone elevation during pregnancy inhibits the formation of gap junctions in the smooth muscle of the uterus.⁵⁹ The rapid progesterone decline at parturition is responsible for an increase in gap junctions and resulting uterine contractility.⁶⁰ It has been hypothesized that progesterone may have similar effects in the smooth muscle of other organs.^{10–18} This may have two implications for respiratory function during pregnancy. First, bronchial smooth muscle may be relaxed in response to progesterone. Second, relaxation of esophageal smooth muscle and increased intra-abdominal pressure may promote gastroesophageal reflux, which may worsen asthma.^{61,62}

Pregnancy is associated with numerous maternal organ system and physiologic changes. Uterine enlargement restricts diaphragmatic excursion, reducing residual volume and functional residual capacity. These factors may negatively affect pulmonary function during pregnancy, attenuating improvements attributable to increased estrogen and progesterone levels. Controlling for these factors in examinations of asthma and pulmonary function over pregnancy will identify the independent effect of hormones.

MENOPAUSE AND HORMONE REPLACEMENT THERAPY (HRT)

Menopause entails a sharp reduction in hormone levels. Circulating levels of estradiol and estrone are approximately 85 to 93% lower among postmenopausal women compared with premenopausal women who are in days 2 to 4 of the menstrual cycle.⁶³ Few studies have examined the relationship between endogenous hormone level and asthma in menopausal women, but asthmatic women have been found to have significantly lower levels of dehydroepiandrosterone sulfate, dehydroepiandrosterone, estradiol, and estrone than nonasthmatic women in menopause.^{64,65} It may be that asthma is exacerbated or prolonged by these lower endogenous hormone levels.

Similarly, little research has focused on HRT among asthmatic women. In two case reports, steroid-dependent asthmatic women experienced reductions of asthma exacerbations and elimination of prednisone after the initiation of conjugated estrogen therapy.⁴¹

Among 2,353 women in the Cardiovascular Health Study, the prevalence of asthma was similar ($P = 0.589$) among women using HRT (9.4%) and women not currently taking HRT (8.5%).⁶⁶ However, women with asthma who used HRT had an average 8% higher FEV₁ and were less likely to have pulmonary obstruction (crude odds ratio [OR] 0.70, 95% CI 0.33 to 1.49). Statistical significance was limited by the small sample size of women with asthma in the Cardiovascular Health Study ($n = 204$). Among the entire cohort, HRT use was associated with a significantly lower prevalence of pulmonary obstruction (adjusted OR 0.67, 95% CI 0.48 to 0.95) and higher FEV₁ (adjusted mean 1.76 L vs 1.71 L), even after controlling for factors associated with pulmonary function and HRT use.⁶⁶ Cardiovascular Health Study findings were not consistent with those from the Nurses Health Study, which reported that past users of HRT were at an increased risk of self-reported incident asthma compared with women who never used HRT.⁶⁷ However, consistent with the Cardiovascular Health Study, current HRT use in the Nurses Health Study was not significantly associated with asthma onset.⁶⁷ Findings from the Nurses Health Study are limited by recall biases. In a cross-sectional analysis of 3,016 postmenopausal women, investigators from the Copenhagen City Heart Study showed a weak association between HRT and prevalent, self-reported asthma (adjusted OR 1.42, 95% CI 0.95 to 2.12).⁶⁸ These cross-sectional findings do not necessarily show that HRT increases the risk of asthma. Rather, it is possible that women with asthma have increased contact with the health care system and are thus more likely to be prescribed HRT.

Few prospective studies^{69–71} have examined change in pulmonary function over time. None found a positive effect for estrogen replacement therapy (ERT). No significant difference in FEV₁ was found after the initiation of estrogen therapy in a group of 36 nonasthmatic postmenopausal women, although estrogen therapy was associated with a

significantly lower maximal decline of FEV₁ after histamine challenge.⁶⁹ Among a group of 15 asthmatic postmenopausal women, ERT was not associated with change in spirometry or self-rated asthma.⁷⁰ PEFR was significantly decreased (6% lower) and bronchodilator requirements were significantly increased (mean 0.9 inhalations) during ERT, although differences were modest.⁷⁰ Neither ERT discontinuation nor re-initiation was associated with percent predicted FEV₁ or PEFR among a group of 20 postmenopausal asthmatic women.⁷¹ These studies did not control for potential confounders that may influence pulmonary function and rescue medication use such as changes in preventive therapy, allergic status, exposure to allergens, tobacco exposure, air pollution, respiratory infection, or stress.

Additionally, these prospective studies examined ERT without progesterone. These findings may not be generalizable to current HRT preparations, as estrogen and progesterone are typically prescribed in combination today. The exclusion of progesterone from these analyses may also suggest that estrogen alone is not responsible for the respiratory benefits achieved from exogenous hormones. Alternatively, the doses of estrogen in HRT, which are much less than those in oral contraceptives, may not be great enough to affect pulmonary function.

In a prospective study of HRT in 32 women with moderate asthma, the proportion of women requiring oral glucocorticosteroids for asthma exacerbations decreased from 37.5 to 6.25% during 6 months of combined HRT therapy.⁶⁵ This study did not compare spirometry before and after HRT administration, but did show a positive effect of combined estrogen/progesterone on asthma through a reduction in asthma control medication.

Overall, the research on asthma during menopause is sparse. The analysis of combined HRT and pulmonary function in the Cardiovascular Health Study cohort is the only objective examination conducted to date.⁶⁶ Findings should be replicated in other cohorts of postmenopausal women. Additionally, prospective studies of pulmonary function and asthma change through menopause would further our understanding of the effect of both endogenous and exogenous hormones and pulmonary function.

REFINEMENTS

There are several complexities to the notion that female hormones are protective for asthma. Although both boys and girls with childhood asthma have a 50% likelihood of becoming symptom free during puberty, with no difference in the rate of improvement between the sexes,^{72–75} age-specific prevalence and incidence for asthma peaks in women during their reproductive years. The prevalence of asthma and asthma hospitalization is higher among boys during childhood, but higher among girls after puberty.^{76–82} Case studies suggest that menarche may be associated with asthma onset and increased severity of existing asthma.^{22,43–45}

There are a number of possible explanations for these findings. First, female and male sex hormones may both have

similar beneficial effects on pulmonary function. As mentioned, testosterone has also been associated with relaxation of bronchial tissue and depressed response to histamine.^{8,20} Second, the cyclic hormonal declines associated with menstruation may increase susceptibility for asthma exacerbations or asthma onset in teenage women. Third, asthma may be underdiagnosed in girls compared with boys, but not underdiagnosed in women compared with men. In a study of 4,849 13- to 14-year-old boys and girls, the prevalence of ever-diagnosed asthma was lower in girls (OR = 0.58, P = 0.004), whereas the prevalence of asthma symptoms including wheezing (OR = 1.26, P = 0.029) and night cough (OR = 1.67, P = 0.0001) were higher among girls.⁸³ Finally, menarche may mark the introduction of nonsteroidal anti-inflammatory drugs for menstrual symptoms, which have been associated with bronchial hypersensitivity and asthmatic episodes.^{84,85}

Another complexity is the observation that some women experience premenstrual exacerbations of asthma and changes of asthma during pregnancy whereas others do not. Women who report experiencing asthma exacerbations premenstrually are significantly older, with longer asthma durations and greater baseline asthma severity, and with higher rates and severity of premenstrual syndrome.^{34,35,48} Stress exposure in the premenstrual or menstrual phase was associated with a significant decline in PEFr among a group of asthmatic women, although reactivity was not compared across the menstrual cycle.⁸⁶ These factors might identify the group of women with greater hormonal fluctuations or susceptibility to hormonal fluctuations. Significantly lower levels of progesterone have been identified in women with premenstrual syndrome compared with controls.^{87,88} This may suggest that women with premenstrual syndrome may have inadequate production of progesterone, leading to both psychoneuroendocrine and asthmatic symptoms. It is also possible that a portion of women with asthma may not be aware of cyclic variation in their disease. In a study of 14 women followed over two menstrual cycles, only 36% reported premenstrual worsening of asthma symptoms at enrollment, whereas 100% experienced a 20% or greater PEFr reduction premenstrually.³⁸ Therefore, premenstrual asthma worsening may occur in more women than self-reported estimates of 33 to 52%.^{34–38} Further studies examining objective asthma measurements over the menstrual cycle are needed to better estimate the proportion of women with asthma who experience premenstrual declines.

A final complexity in the literature is the possibility that hormones improve pulmonary function through the relaxation of bronchial smooth muscle but worsen pulmonary function in a subgroup of asthmatic patients with extrinsic asthma by increasing airway hyperresponsiveness to allergens. Estrogen and progesterone have been associated with increased airway hyperresponsiveness, skin prick responses, subjective nasal symptoms, and objectively measured nasal mucosal swelling in a few studies.^{46,50,51,89–91} Women have higher self-reported and diagnosed nasal and skin allergies, suggesting that estro-

gen or progesterone may influence allergic susceptibility.^{92,93} These limited findings do suggest that hormones may affect airway function through a variety of complex mechanisms with both positive and negative effects.

AVENUES FOR FUTURE STUDY

Several study designs would clarify our understanding of the role of hormones in asthma. Any of these would need to be of sufficient size, to use both functional and self-reported measures, and to control for potential confounders known to influence asthma frequency and severity such as preventive medication use, baseline asthma severity, allergic status, exposure to allergens, exercise, environmental exposures, smoking, and nonsteroidal anti-inflammatory drug usage. Studies specifically examining the correlation between the age at menarche and age of asthma onset would clarify the impact of the menstrual cycle on the increase in incidence rates among females compared with males after the ages at which puberty occurs. Further, prospective studies are needed of women throughout the menstrual cycle. Supracadian fluctuations in pulmonary function should be examined in both men and women and between premenopausal and postmenopausal women. Additional studies are also needed to investigate the potential effect of both estrogen and progesterone on allergic reaction. Both subjective and objective comparisons between oral contraceptive users and non-users are necessary with particular emphasis before and after oral contraceptive administration. Comparisons should be made between women taking low-dose and high-dose oral contraceptives, between women using triphasic and biphasic oral contraceptives, and by varying ratios of progestin to estrogen. Analyses that include risk factors for premenstrual syndrome as potential risk factors for asthma exacerbation may shed some light on the underlying etiology, the effect of estrogen and progesterone, and the interaction of premenstrual syndrome symptoms and premenstrual asthma exacerbation. Additional studies which control for potential confounders that could influence change in asthma severity during pregnancy such as changes in preventive medication usage, initial asthma severity, or gastroesophageal reflux are necessary to explain the different subgroups of pregnant asthmatic patients. Finally, studies in both healthy and asthmatic postmenopausal populations that consider both estrogen and progesterone therapies are needed to better understand the impact of HRT on asthma and pulmonary function. Prospective observational studies of pulmonary function through menopause are warranted.

CONCLUSION

The evidence presented here suggests that estrogen and/or progesterone may be involved in pulmonary function and asthma symptomatology. During the premenstrual and menstrual phase when hormonal levels are low, asthmatic patients have been found to experience increased asthma exacerbations, increased hospitalizations for asthma, and decreased pulmonary function. Oral contraceptives, which dampen fluc-

tuations in hormonal levels, have been found to improve pulmonary function. Subsets of pregnant asthmatic patients have been found to experience improved pulmonary function, reduced medication requirements, and fewer symptoms.

However, the relationship between hormones and asthma symptoms/lung function is complex. Testosterone, estrogen, and progesterone may each independently affect pulmonary function to varying degrees. Certain subgroups of women may be more susceptible to hormonal cyclicality, and hormones may not similarly affect intrinsic and extrinsic pathways. A further understanding of the role of hormones in asthma may better predict exacerbations and direct therapeutic strategies. Such an understanding may help to improve the quality of life in women who suffer from this often debilitating disease.

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CME Examination

1–5, Haggerty CL, Ness RB, Kelsey S, and Waterer GW. 2003;90:284–291.

CME Test Questions

1. Airway hyperresponsiveness occurs during the luteal phase of the menstrual cycle after challenge with:
 - a. AMP.
 - b. Histamine.
 - c. Methacholine.
 - d. All of the above.
 - e. b and c.
2. Progesterone and estrogen may affect the lungs by:
 - a. Increasing the relaxation of bronchial smooth muscle.
 - b. Inhibiting peripheral monocyte production of interleukin-1.
 - c. Strengthening airway muscle.
 - d. All of the above.
 - e. a and b.
3. Women have higher:
 - a. Rates of asthma in the general adult population compared with men.
 - b. Rates of asthma during childhood compared with boys.
 - c. Rates of asthma hospitalization than men after puberty.
 - d. All of the above.
 - e. a and c.
4. Studies suggest that pulmonary function is lower:
 - a. During the premenstrual phase among premenopausal women not using oral contraceptives.
 - b. Among premenopausal women using oral contraceptives.
 - c. Among postmenopausal women not using HRT.
 - d. a and b.
 - e. a and c.
5. Studies suggest that women who report premenstrual worsening of asthma:
 - a. Have significantly higher rates of hospitalization and office visits compared with women who do not report cyclic variation.
 - b. Experience no change in PEFr premenstrually.
 - c. Have higher rates and severity of premenstrual syndrome.
 - d. All of the above.
 - e. a and c.

Answers found on page 347.