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REVIEW ARTICLE

Sex Differences in Asthma

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Asthma is a common chronic pulmonary disease whose prevalence varies greatly with the sex and age of the patient. Research has shown that men and women may experience this disease differently, although these sex-related differences have not routinely translated into differences in clinical care for patients with asthma. This review explores some of the major differences in asthma between men and women and some of the main hypotheses developed to explain them.

INTRODUCTION

Asthma is a common disease with increasing prevalence worldwide, affecting an estimated 300 million people (1) and resulting in approximately 250,000 deaths per year (2). Surveillance data in the United States has shown that more than 20 million people report a diagnosis of or symptoms consistent with a diagnosis of asthma and nearly 4,000 people die each year from complications of the disease (3). Epidemiologic studies of asthma prevalence, morbidity, and severity seem to illustrate a sex difference that varies with age. This review explores the different susceptibility of men and women to asthma and some of the hypotheses that have been raised to explain this.

ASTHMA PREVALENCE

A review of asthma epidemiology shows some striking differences in asthma prevalence and severity between the sexes that are closely associated with age. Until puberty, asthma is more common and more severe in boys. After puberty, asthma becomes more common in women (3–8). This trend continues until menopause when the differences between the sexes narrow but never completely reverse (5, 9, 10). According to the National Health Interview Survey in 2001–2003, male children in the United States had a higher prevalence of asthma (9.6%) than female children (7.4%), but male adults had a lower prevalence (4.9%) than female adults (8.4%) (3). Analysis of data from the European Community Respiratory Health Survey revealed similar results (6). In this population, girls had a significantly lower risk of developing asthma than did boys in childhood (relative risk [RR]: 0.74 and 0.56 in age groups 0 to 5 years and 5 to 10 years, respectively), with nearly equal risks between the sexes around puberty (RR = 0.84; confidence interval [CI] 0.65 to 1.10 in 10- to 15-year olds). After puberty, the risk in women was significantly higher than that in men (RR: 1.38 to 5.91).

PERCEPTION OF SYMPTOMS AND QUALITY OF LIFE

In addition to the obvious differences in asthma prevalence between the sexes, current data support the notion that men and women experience asthma differently. Using standardized questionnaires, studies have shown that women with asthma tend to describe more asthma symptoms and poorer quality-of-life than men (11, 12) at baseline, despite having comparable or better pulmonary function (13–15). Compared to males, females with asthma report greater healthcare utilization with unscheduled doctors' visits (12–14), the need for more frequent courses of oral corticosteroid therapy (13), and a greater use of rescue medications (12, 14, 15). Similar trends have been identified in patients presenting to the emergency department with acute asthma exacerbations, where women are more likely than men to characterize their symptoms as severe despite having less evidence of airflow obstruction on peak flow monitoring (16, 17).

It has been suggested that women may actually perceive air-flow obstruction differently than men (14, 18), resulting in a greater impact on their daily living. Significantly more women than men have improper techniques when using metered-dose inhalers (19), possibly contributing to the above-reported differences in asthma symptoms. Interestingly, Weiner et al. (18) have shown in a small cohort of mild-to-moderate asthmatics that inspiratory muscle strength as assessed by the maximal inspiratory mouth pressure (P_{Imax}) is significantly higher in male subjects than in female subjects and is associated with less perception of dyspnea and less short-acting beta-agonist use. Through inspiratory muscle training, asthmatic women were able to achieve the same level of strength as their male counterparts, and with equal P_{Imax} , the sex differences in perception of dyspnea and mean daily beta-agonist use disappeared.

ASTHMA MANAGEMENT

Despite the differences noted in perception of asthma symptoms and the associated impact on quality of life, it does not appear that women receive inferior asthma care. Evaluation of asthma management and adherence to national guidelines suggests that women with asthma are more likely to recognize their symptoms and seek treatment (20–22) but differences in the care they receive are small when compared with men. A survey of 237 adults with asthma showed that women were more likely to have been seen by their primary

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care physician for asthma in the preceding 6 months and were five times more likely to have received oral steroids in that same time period than their male counterparts (22). It is unclear whether the increased use of oral steroids in these women was a result of physician tendency to preferentially prescribe these agents to women or simply a consequence of their increased physician visits in response to altered perceptions of asthma symptoms. The use of inhaled corticosteroids was similar between men and women.

Analysis of data from two large managed-care organizations suggests that adherence to current asthma guidelines (23) by asthma care providers may actually favor female patients (20, 21). In these populations, women were more likely to regularly use a peak-flow meter (21), have a written asthma management plan (20, 21), and have a regular clinician for asthma care (21). While the prescription of inhaled corticosteroids was similar for both sexes in these two studies (20, 21), compliance with prescribed therapies was not. Krishnan et al. (20) reported that men with asthma were more likely than women to use prescribed inhaled corticosteroids on a daily basis. A study of adherence to inhaled corticosteroid treatment in southeast Michigan found similar results, with significantly better compliance with prescribed regimens in white men when compared with white women ($p = 0.008$) (24). In contrast, a study of self-reported compliance with asthma medications in Sweden found that women were more likely to adhere to their prescribed regimens than men (25).

EXACERBATIONS AND HOSPITALIZATIONS

Sex differences in asthma morbidity have also been described (26–30) (Table 1). In a year-long study to evaluate the effects of four treatment regimens on asthma exacerbations, the only risk factor identified for the development of a severe exacerbation was being female (odds ration [OR], CI 1.37–2.6) (28, 30). In population-based studies, the risk of asthma exacerbations requiring admission to the hospital varies with the age and sex of the patient. Skobeloff et al. (29) reviewed the records of 33,269 patients admitted for asthma treatment in 67 hospitals in Southeastern Pennsylvania. In children (0- to 10-year-olds), boys were admitted nearly twice as often as girls, but in adolescents and young adults (11- to 20-year olds), the rates of admission were nearly equal in men and women. From 20 to 50 years of age, fe-

males were admitted nearly three times as often as their male counterparts. Although the female-to-male ratio for hospital admission decreased somewhat to 2.5:1 after age 50, women continued to be admitted to the hospital more often than men for asthma treatment. Similar trends in hospital admissions for asthma exacerbations have been described in Canada and Europe (26, 27).

Women presenting to the emergency department for treatment of asthma symptoms are more likely to be admitted to the hospital than men despite presenting with better pulmonary function (17, 31) and less hypercapnea (32), even after correcting for differences in asthma prevalence and smoking (33). In addition, the length of hospital stays for asthma exacerbations has been shown to be longer in women (29, 32, 34) than in men.

INTENSIVE CARE UNIT ADMISSIONS

A small subset of women seems to be particularly at risk for severe asthma exacerbations. In most series in the literature (32, 34, 35) minority women account for the majority of intensive care unit (ICU) admissions for status asthmaticus. Two single-center reports have described the authors' experiences with predominantly African American cohorts (34, 35). Afessa et al. (35) prospectively studied 89 individuals during 132 intensive care unit (ICU) admissions. In this cohort, 67% of patients were African American and females accounted for 79% of admissions. Although not statistically significant, all asthma-related deaths ($n = 11$) occurred in the female subset. Gehlbach et al. (34) retrospectively reviewed the first ICU admission for 78 patients with status asthmaticus. Nearly all (96%) of the patients were African American, and 72% were female. Only three deaths were reported.

MORTALITY

Sex differences in asthma mortality have been more difficult to characterize. The introduction of the tenth revision of the International Classification of Diseases (ICD-10) in 1999 (37) has resulted in a decline in asthma mortality as a result of coding changes(3) and has made comparison with data coded according to the ninth revision of the ICD difficult. Studies using panels of experts assessing death certificates have suggested that the sex of the deceased may influence the determination of the ultimate cause of death in respiratory diseases (38–40). Under-coding of asthma deaths occurs more commonly in males (39), where deaths due to asthma may be incorrectly attributed to chronic obstructive pulmonary disease (COPD) or cardiovascular causes (40). This misclassification seems to increase with the age of the subject (40). Along the same lines, deaths due to COPD in women may be incorrectly attributed to asthma, resulting in over-coding

TABLE 1.—Sex differences in asthma morbidity.

Sex differences in asthma morbidity
Women with asthma describe more asthma symptoms and worse asthma-related quality of life than men [11,12] despite comparable pulmonary function[13–15].
Women with asthma report more frequent unscheduled doctors' visits [13–12].
Women with asthma report the need for more frequent courses of oral corticosteroid therapy [13] and greater use of rescue medications[12, 14, 15].
In patients presenting to the emergency department with asthma, women are more likely than men to complain of severe symptoms despite having less evidence of airflow obstruction [16,17].
Female sex is an independent risk factor for suffering severe asthma exacerbations [28,30].
Women presenting to the emergency department with asthma symptoms are more likely to be admitted to the hospital than men despite having better pulmonary function[17, 31] and less hypercapnea [32].
The length of hospital stays for asthma exacerbations has been shown to be longer in women than in men [29, 32, 34].

TABLE 2.—Hypotheses for sex differences in asthma.

Hypotheses for sex differences in asthma
Altered perception of air-flow obstruction in women
Improper technique in metered-dose inhaler use in women
Decreased inspiratory muscle strength in women
Increased bronchial hyperresponsiveness in women
Increased susceptibility to tobacco smoke in women
Female sex hormones (including effects of menstruation, pregnancy, and menopause)

of asthma deaths in some situations (38). Nonetheless, some interesting trends in asthma mortality exist.

For the 3-year period 2001–2003, data from the National Vital Statistics System in the United States revealed that females had a higher at-risk–based death rate from asthma than males (2.3 and 1.8, respectively) (3). However, when individual age groups were examined, males had higher rates than females in all subsets except in people ≥ 65 years of age. Evaluation of mortality data for asthma in Chicago from 1990–1997 showed a strong interaction between age and sex (41). In this population, for patients less than 35 years of age, mortality rates were higher in males than in females. For people ≥ 35 years of age, women had higher mortality rates than men. When reviewing data from the National Hospital Discharge Survey Database in the United States from 1995 to 2001, Getahun et al. (42) found a similar trend. In subjects younger than 35 years of age, the asthma mortality rate was higher in males than in females, but reversed in those over 35 years of age.

OCCUPATIONAL ASTHMA

Sex differences in the susceptibility and expression of occupational asthma have been reported, but clear patterns have been difficult to establish. In some series the prevalence of occupational asthma is higher in men (43–45), whereas in others there does not appear to be a difference between the sexes (46, 47). Meredith (48) noted that the rate of occupational asthma in the general population of the United Kingdom was similar between men and women when adjusted for occupation. However, the risk of work-related asthma and its relation to sex has been shown to be occupation specific in some instances (49, 50). In a recent review by Camp et al. (51), it is suggested that factors such as gender segregation in the workplace may contribute to observed differences where employees with the same job title may actually perform different tasks according to gender. Finally, Kogevinas et al. (47) have proposed that occupational asthma may be underreported in some women who may experience unrecognized exposures at home (such as household cleaners) in addition to those identified in the workplace. Although the available literature raises some interesting questions, further research is needed to clearly establish a relationship between sex and the risk of developing occupational asthma.

HYPOTHESES

As outlined above, obvious differences exist between men and women in the prevalence and severity of asthma. Women describe more asthma symptoms and poorer asthma-related quality of life than men and as a result have as associated increase in health-care utilization. While no clear explanation has been found for these differences, there are several factors that may contribute to their development (Table 2).

Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness (BHR) to nonspecific stimuli such as methacholine or histamine is one of the key features of asthma. Many, but not all (52, 53), population studies have shown a higher prevalence of BHR in women than men (54–57). It has been suggested that the excess in bronchial responsiveness in women may be a result of their

having a smaller airway caliber than men (52, 54, 58). Airway flow depends on the fourth power of the airway radius so that any stimulus that causes obstruction creates more turbulence in smaller airways than larger ones (59). Accordingly, it has been shown that a low forced expiratory flow in one second (FEV_1) (% predicted) is associated with an increased risk of BHR (54, 60, 61). Britton et al. (54) evaluated 2,415 adults from the general population and found a nearly twofold increase in the risk of airway hyperresponsiveness ($PD_{20} \leq 12.25 \mu\text{mol}$) in women (OR: 2.05, CI: 1.58–2.66) that lost significance (OR: 1.59, CI: 0.89–2.81) when adjusted for FEV_1 (% predicted). In contrast, data from the European Community Respiratory Health Survey (ECRHS) (55, 57) found that BHR was more common in women in populations in France ($n = 799$) and Sweden ($n = 1448$) even when adjusted for FEV_1 (% predicted). Manfreda et al. (56) confirmed these findings in a large ($n = 2,962$) Canadian population.

Effects of Tobacco

Bronchial hyperresponsiveness. Other authors have suggested that the increased rate of bronchial hyperresponsiveness in women can be attributed to their increased susceptibility to tobacco smoke (55), which seems to begin during childhood. In a study of 1,215 school-age children (7 to 11 years of age), girls seemed to be more susceptible to the effects of passive smoke exposure than did boys of the same age (62). In those children that exhibited a strong response to methacholine inhalation ($PC_{20} \leq 4 \text{ mg/mL}$) the OR for BHR in girls for maternal and paternal smoking in the home when compared with boys in a similar environment were 2.29 and 2.59, respectively. The results were confirmed after adjustment for airway caliber.

Using data from two French centers in the ECRHS described above, Leynaert et al. (55) showed the risk of BHR in a general population was greater in women than men (OR: 2.3, CI: 1.9–3.6). After excluding subjects with asthma and adjusting for lung function, BHR was still significantly more frequent in women (OR: 1.9, CI: 1.1–3.4) and was primarily related to smoking (55, 63). Interestingly, the amount of tobacco exposure had a greater impact on the prevalence of BHR in women than it did in men. In women, the OR for BHR in heavy versus nonsmokers was 2.0 (CI: 0.99–4.1) and in heavy versus moderate smokers was 2.8 (CI: 1.3–6.4). In men, the corresponding odds ratios were 1.1 (0.4–2.7) and 0.8 (0.3–2.3), respectively. Paoletti et al. (64) found a similar relationship in an evaluation of 1,694 subjects from a general Italian population.

In some studies (65, 66) a sex difference in the susceptibility to tobacco smoke and its relationship to bronchial hyperresponsiveness is less clear. Methacholine challenge testing was performed in 5,877 current smokers with mild-to-moderate airflow obstruction ($FEV_1/FVC 63.0 \pm 5.5$) in the Lung Health Study (66). In this population, BHR was significantly more frequent in women than in men (85.1% vs. 58.9%). In addition, nearly twice as many women as men (46.6 and 23.9%, respectively) responded to less than or equal to 5 mg/mL of methacholine. In men, BHR was not significantly associated with current or lifetime tobacco use, and in women the association between BHR and cigarette pack-years was relatively weak ($p = 0.044$). When 3,993 participants from the ECRHS were followed longitudinally,

BHR increased over time in continuing smokers and in those restarting smoking (65). Although BHR was greater in women at baseline, no differences in the change of BHR were found between men and women.

Effects of smoking on pulmonary function. There is a growing body of evidence that suggests that female smokers may be at a higher risk for tobacco-related loss in pulmonary function than men (67–72). Similar to the data described with tobacco exposure and bronchial hyperresponsiveness, the accelerated effects of tobacco exposure on lung function in females can be seen in children and adolescents. During childhood, girls experience a larger reduction in lung function when exposed to environmental tobacco smoke compared with boys (67, 71). A longitudinal study of 10,060 adolescents suggested that girls may be more vulnerable than boys to the effects of smoking on growth of lung function (69). Gold et al. (69) showed that girls who smoked five or more cigarettes per day demonstrated slower growth in their FEV₁ and FVC compared with girls who did not smoke (–1.09%/year FEV₁ and –0.76%/year FVC). In contrast, smoking five or more cigarettes per day in boys was not associated with a significant alteration in growth of FEV₁ or FVC.

In a large (n = 4,554) longitudinal study of the general population in the Netherlands, Xu et al. (72) demonstrated that women smokers had a more rapid decline in FEV₁ than men who smoked over a 24-year observation period. Compared to lifetime nonsmokers, the estimated excess decline in FEV₁ for light, moderate, and heavy continued smokers was 4.4, 9.5, and 13.5 ml/year for men and 6.1, 10.8, and 18.8 ml/year for women, respectively. These sex differences seemed to continue even after smoking cessation. Former female smokers had a more rapid decline in FEV₁ than lifetime nonsmokers, while former male smokers actually had a slower rate of decline than lifetime nonsmokers.

In a cross-sectional study of 13,897 subjects, Prescott and associates (70) showed that smoking had a greater impact on the lung function of females than of males in two independent adult populations. In the Copenhagen City Heart Study and in the Glostrup Population Study, female smokers had a faster decline in FEV₁ when compared to men with similar smoking habits: –7.4 ml/pack-year in women versus –6.3 ml/pack-year in men and –10.5 ml/pack-year in women versus –8.1 ml/pack-year in men, respectively. Similar results were reported by Dransfield and colleagues (68) who showed that when adjusted for pack-years of smoking, female smokers had a greater loss in FEV₁ than male smokers (–1.21%/pack-year in women vs. –0.98%/pack-year in men; p = 0.001).

Interestingly, when women stop smoking, they seem to recover more lung function than do male ex-smokers (73). In the Lung Health Study, in the first year after smoking cessation, women showed greater improvements in both FEV₁ and FEV₁% predicted than men (3.7% predicted in women vs. 1.6% predicted in men; p = < 0.001). In sustained quitters, women gained more FEV₁% predicted than men across the five-year follow-up period.

Obesity

Epidemiologic studies have shown an association between obesity and asthma (74–80), but the role of sex in this

relationship has remained controversial. Some authors have shown that the effects of obesity on asthma are significant only in women (67, 74, 81, 82) while others have demonstrated a stronger association between obesity and asthma in men (83, 84). In a recent meta-analysis of prospective series evaluating body mass index (BMI) and the incidence of asthma, Beuther and Sutherland (85) concluded that increasing BMI, in a dose-dependent fashion, was associated with an increased incidence of asthma in both men and women. While no clear conclusions can be reached on this increasingly important issue, clinicians should consider the possible impact of obesity on the incidence and course of asthma in both men and women until more definitive data are available.

Menstrual-Linked Asthma

Asthma symptoms. Given the trends in asthma prevalence and severity, which seem to coincide with key transition points in a women's reproductive life, it has been hypothesized that the female sex hormones influence the development of asthma and its severity. Women often experience changes in the character of asthma symptoms during the early reproductive years, pregnancy, and menopause. A subset of asthmatic women experience exacerbations of their asthma which seem to be linked to the phase of their menstrual cycle (86–90). Fluctuations in levels of estrogen and progesterone during the menstrual cycle are believed to influence the course of asthma; however, current data have been inconclusive in defining a specific period during the menstrual cycle at which time women subject to perimenstrual asthma exacerbations are at the greatest risk (91–94).

Small studies in unselected series of women of reproductive age with asthma suggest that 30 to 40% of these women experience premenstrual worsening of asthma symptoms (87, 88, 95). Gibbs et al. (88) surveyed 91 women with asthma with a questionnaire and reported that 36 (40%) described worsening of their asthma before menstruation. Similarly, Eliasson et al. (87) found that 19 (33%) of 57 women with asthma reported significant worsening of pulmonary symptoms during the premenstrual period, the menstrual period, or both. Hanley (89) surveyed 102 female asthma patients and found that 36 (35%) had worsening of their asthma just before or at the onset of menses. Daily monitoring of peak expiratory flow rates (PEFR) showed a significant reduction at the time of menstruation in those women who described premenstrual worsening in asthma symptoms when compared with those subjects who were unaffected. A similar finding was noted in the study of Gibbs et al. (88). However, in both studies, clinically significant deterioration was infrequent, leading the authors to speculate that a heightened awareness of asthma symptoms during the premenstrual period may play more of a role than a demonstrable reduction in pulmonary function. In contrast, Agarwal and Shah (86) documented that menstrual-linked asthma was associated with a significant reduction in PEFR in the premenstrual and menstrual weeks in female asthmatics who reported subjective worsening of their asthma symptoms in the perimenstrual period when compared to those who did not and reported that the reduction in PEFR was associated with more frequent emergency room visits and hospitalizations.

Bronchial hyperresponsiveness. Several authors have investigated the influence of the menstrual cycle on airway responsiveness (96–98). Juniper et al. (96) evaluated 17 well-controlled asthmatics and examined changes in methacholine responsiveness at 1 week before and 1 week after the start of menses. There were no differences in PC_{20} or FEV_1 when the values for the week before menses were compared to those obtained the week after the start of menstruation. However, symptoms were worse during menstruation, again raising the possibility of an altered perception of asthma symptoms as a factor in perimenstrual asthma. In a similar study, Weinmann et al. (98) evaluated 9 women with asthma and found no significant differences in FVC, FEV_1 , or histamine responsiveness when compared at two points in the menstrual cycle (days 7 and 24). However, none of these women reported cyclic asthma symptoms at baseline. Pauli et al. (97) studied 11 asthmatic women who had not previously noted a relationship between asthma symptoms and their menstrual cycle and compared them with 29 healthy control subjects. They found no changes in airway function over the menstrual cycle in normal women. Although the asthmatic group also did not demonstrate significant changes in spirometry or airway responsiveness to methacholine, asthma symptoms deteriorated significantly from the follicular to the luteal phase ($p = 0.001$) as did the morning PEFr ($p = 0.045$) in this group. Only Tan et al. (99) have documented a significant increase in airway responsiveness during the premenstrual period. In a small series of 15 well-controlled female asthmatics without prior history of subjective premenstrual deterioration in asthma control, they documented a significant increase in bronchial hyperresponsiveness to adenosine 5'-monophosphate (AMP). In this population, the PC_{20} AMP decreased significantly from 19.0 mg/mL to 7.6 mg/mL during the follicular (days 1 to 6) and luteal (days 21 to 24) phases, respectively ($p < 0.05$).

The studies described above evaluated women without self-reported menstrual-associated asthma symptoms; results may be different when a symptomatic population is selected for review. In a study of 11 women with self-reported premenstrual asthma, Oguzulgen et al. (100) evaluated pulmonary function and airway inflammation at two points in the menstrual cycle (day 7 and day 26 ± 3 rd days). In this small sample, PEFr, FEV_1 (% predicted), and PC_{20} methacholine were worse during the premenstrual period but did not achieve statistical significance. In contrast, fractionated exhaled nitric oxide (Fe_{NO}), sputum eosinophilia, and day-time symptom scores were significantly altered in the premenstrual period.

Exacerbations. Regardless of the true prevalence of menstrual-linked asthma, the literature seems to support its clinical importance. Eliasson et al. (87) described three patients with repeated hospitalizations for worsening of asthma in relation to menstruation, two of whom had recurrent respiratory failure without evidence of other obvious precipitating etiologies. In a population of 182 nonpregnant women of reproductive age (ages 13–menopause) presenting to the emergency department with acute asthma symptoms, Skobeloff et al. (93) found that 46% of these women presented during the perimenstrual phase (days 26 to 4 of an idealized 28-day cycle), a period during which serum estradiol levels decrease sharply after a prolonged peak. In contrast, in a prospective

cohort study of 288 women presenting to the emergency department with acute asthma exacerbations, Zimmerman et al. (94) found that more women presented during the preovulatory phase (days 5 to 11) than any other phase (33% for the preovulatory phase compared to 26% in the periovulatory phase [days 12 to 18], 20% in the postovulatory phase [days 19 to 25], and 21% in the perimenstrual phase [days 26 to 4], $p = 0.008$). When limited to the 13% of women who reported phase of the menstrual cycle as a personal asthma trigger, there were no significant associations with the phase of menstrual cycle at the time of ED presentation. In a similar study of 792 women, Brenner et al. (91) found that both the preovulatory and perimenstrual periods were more often triggers for asthma exacerbations than the remaining periods of the menstrual cycle (28% and 27% respectively, compared to 25% in the periovulatory phase and 21% in the postovulatory phase, $p = 0.03$).

In a review of 44 female patients of reproductive age with near-fatal asthma attacks, significantly more near-fatal asthma episodes occurred on the first day of menstruation ($n = 11$, 25%) than on any of the remaining days ($p = 0.022$) (92). Patients whose attacks were noted on the first day of menses used more rescue medication (inhaled salbutamol, $p = 0.003$) on the 7 days preceding the exacerbation than the other women had. Similarly, Shames et al. (90) noted that women with self-reported perimenstrual asthma demonstrated increasing use of short-acting bronchodilators during the perimenstrual period (days -5 to $+5$) than did women who did not report the phase of the menstrual cycle as a personal asthma trigger ($p < 0.005$). In addition, those subjects who reported perimenstrual asthma had significantly increased asthma symptoms and decreased AM and PM peak expiratory flow rates overall when compared to the non-perimenstrual asthma group. However, no significant differences between FEV_1 (% predicted) and methacholine responsiveness were noted between the groups when values obtained during the luteal and follicular phases of the menstrual cycle were compared.

Pathogenesis of menstrual-associated asthma. The pathophysiology of menstrual variability in asthmatic women is not well understood, but several possible mechanisms have been proposed. Current evidence supports a contributory role for the female sex hormones, but it is not possible to determine which hormone is primarily responsible or whether absolute levels or changes in hormone levels are more important (94). However, premenstrual worsening of asthma symptoms coincides with a decrease in progesterone secretion and an increase in the estrogen:progesterone ratio (101). This suggests that progesterone may exert a protective, possibly anti-inflammatory effect in some patients. It has been shown that progesterone receptors interact with the transcription factor nuclear factor- κ B (NF- κ B) in a manner similar to glucocorticoid receptors (102). Accordingly, it has been hypothesized that a decrease in progesterone in the late luteal phase of the menstrual cycle would tend to increase inflammation mediated by an increase in NF- κ B (101, 102), thus contributing to an increase in asthma symptoms.

Another possibility is that there is an abnormality in β -receptor regulation in women with premenstrual

exacerbations of asthma. In normal women, the monthly menstrual variations in progesterone and estradiol appear to affect the regulation of lymphocyte β_2 -adrenoreceptors (β_2 -AR). Predictable post-ovulatory increases in the levels of progesterone and estradiol occur in women, and have been shown to correspond with an increased density of lymphocyte β_2 -AR and cyclic adenosine monophosphate (cAMP) mediated responses to isoproterenol during the luteal phase (103). Despite an appropriate post-ovulatory hormone response, the luteal phase increase in β_2 -AR appears to be absent in women with asthma (104). In addition, in healthy women, the administration of exogenous progesterone, but not estrogen, during the follicular phase produces up-regulation of lymphocyte β_2 -AR (105). In women with asthma, progesterone administration seems to have a paradoxical effect. Tan et al. have shown in these patients that exogenous progesterone, but not estrogen, results in an unexpected decrease in β_2 -AR density and cAMP response in lymphocytes (106).

Other authors have suggested that inflammatory mediators such as the leukotrienes (LT) may contribute to the pathogenesis of premenstrual asthma (107, 108). Nakasato et al. (108) compared five patients with premenstrual asthma to five women with asthma who did not report menstrual worsening in symptoms. In those subjects with menstrual-associated asthma worsening, serum levels of LTC₄ were significantly higher just before or during menstruation compared with mid-cycle values (days 10 to 16). Similarly, PEFR were noted to decrease during the premenstrual or menstrual phase in these patients. Administration of an oral LT receptor antagonist, pranlukast, prevented the premenstrual decrease in PEFR for those with premenstrual asthma symptoms. In contrast, in the women who did not complain of menstrual-linked asthma, no changes in PEFR or serum leukotriene values could be detected between the two points in the menstrual cycle.

Pregnancy

Asthma is the most common pulmonary disease encountered during pregnancy, affecting approximately 4% to 8% of all pregnancies (109). It has been said (110, 111) that one third of women will experience a decline in asthma control during pregnancy, one third will have no change, and one third will actually notice an improvement in asthma control during pregnancy. A recent review by Murphy et al. (112) found that 20% of pregnant women will experience an exacerbation requiring medical intervention, with nearly 6% needing admission to the hospital. Identification of those factors that lead to a worsening in asthma control in some pregnancies has been difficult, but the available literature suggests that a combination of the expected physiologic and hormonally mediated changes of pregnancy and other mechanisms is at play (112, 113). The underlying severity of asthma seems to be the most important feature, with approximately 40% of severe asthmatics having an exacerbation during pregnancy (114, 115). Concomitant rhinitis (116), gastroesophageal reflux disease (117), and superimposed viral upper respiratory tract infections (112) seem to be important triggers. Interestingly, in a prospective study of 34 pregnant women with asthma, those with female fetuses reported significant worsening in asthma symptoms more commonly than those with male fetuses (118).

Menopause and Exogenous Estrogen Replacement

The hormonal influences on the development and course of asthma in women seem to persist through menopause and beyond (119–121). In an early report from the Nurses' Health Study, Troisi et al. (121) showed that postmenopausal hormone replacement therapy (HRT) was associated with an increase in the number of new physician diagnoses of asthma. In this population, postmenopausal women who had never used HRT had a significantly lower risk of asthma than age-adjusted premenopausal women (RR: 0.65; CI: 0.46 to 0.92). Women with any history of postmenopausal hormone use (past or current) had approximately twice the risk of asthma when compared with postmenopausal women without any exogenous hormone exposure. In a follow-up study, Barr et al. (119) assessed postmenopausal hormone use and new physician diagnoses of asthma. Their findings confirmed the association of postmenopausal HRT and newly diagnosed asthma, with an RR of 2.30 (CI 1.69–3.14) in current users of estrogen when compared with women who had never used replacement hormones. Data from the Copenhagen City Heart Study found similar results, with an increase in self-reported asthma and asthma-related symptoms in postmenopausal women using replacement hormones (120). In contrast, there were no significant associations between self-reported asthma and symptoms in premenopausal women taking oral contraceptives in this population.

Interestingly, the effects of exogenous hormones and asthma in women seem to be related to body mass index, with leaner women having a greater risk. In the Nurses' Health Study, the relative risk for HRT and asthma in women with a BMI >30 was 1.58, compared to 3.09 in women with a BMI ≤25 (119). A follow-up study of participants from the European Community Respiratory Health Survey found similar results (122). In perimenopausal women not taking HRT, an increased BMI was associated with an increased risk of asthma. In contrast, among women taking HRT, the greatest risk was identified in those with a BMI <22.76. In these women, the use of replacement hormones resulted in a risk of asthma that was equal to their obese counterparts (BMI >25.71).

The effects of estrogen replacement therapy in postmenopausal women with existing asthma have been explored, but the results are inconsistent (123, 124). In a small series of 20 postmenopausal women, Lieberman et al. (124) described a significant reduction in PEFR and an increase in short-acting bronchodilator therapy after the initiation of estrogen therapy but failed to show a statistically significant change in FEV₁. In comparison, Hepburn et al. (123) evaluated 20 postmenopausal women with asthma actively taking estrogen replacement. No changes in FEV₁, PEFR, or bronchodilator use were noted with either the discontinuation of estrogen therapy or its reinitiation.

SUMMARY

Sex-related differences in asthma prevalence and morbidity should be considered in the evaluation and management of all patients with asthma and should be the focus of ongoing research efforts. Awareness of these disparities should improve the ability of asthma care providers to deliver quality care and education for these patients and should

stimulate further investigation to explore the underlying mechanisms.

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