Chapter 15
Women and Asthma

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Introduction

This chapter focuses on women who have asthma, the factors that influence the onset and exacerbation of asthma in women, and the resulting health consequences of the disease and its treatments. Research on women's health is frequently deficient because we fail to separate out the effects of sex, defined as female biology, and gender, the socially constructed roles and behaviors that women perform (Krieger 2003); thus many studies use the terms "sex" and "gender" interchangeably (Krieger 2003; Phillips 2005). Few researchers have successfully wrestled with how to measure the social construct of gender and how it affects women's health and their coping responses to disease states (Phillips 2005). This is particularly important because of the vast political, economic, and social power differentials between women and men that affect women's access to health care and contribute to the feminization of poverty (Phillips 2005; World Health Organization 1998). Both sex and gender have a significant influence on women's exposure to disease risk factors, disease outcomes, health seeking behaviors, and the ability to follow treatment regimens (Krieger 2003). These issues make sex and gender particularly relevant with respect to asthma in women (Clark et al. 2008; McCallister and Mastronarde 2008; Melgert et al. 2007; Postma 2007).

We attempt to distinguish, whenever possible, whether a body of literature is referring to either sex effects or to gender effects. The chapter is organized along the following lines: the epidemiology of women and asthma; asthma over the life course as it relates to changes in sex-steroids (puberty and menopause); asthma and the menstrual cycle; asthma during pregnancy; and women's utilization of health care resources for asthma. We conclude with a discussion of methodological issues and directions for future research.

Asthma Prevalence, Morbidity, and Mortality Among Women

In the United States, 24 million people are affected by asthma (Pleis and Lethbridge-Cejku 2007). Though the prevalence of asthma has increased for both men and women, women have experienced the greatest increase. Among the United States women, the prevalence of asthma increased 82% from a prevalence rate of 2.9% in 1982 to 5.4% in 1992 (Weiss et al. 1992). During the same time frame, prevalence rates for men increased 29% (4.0–5.4%). More recent national data from 2006 indicate that among the women who are the age group of 18 and above, 12.5% reported ever having physician-diagnosed asthma and 8.9% reported that they are still suffering from asthma (Pleis and Lethbridge-Cejku 2007). In comparison, 9.5% of men reported ever being diagnosed with asthma and only 5.6% reported that they still have asthma.

An increase in asthma morbidity and mortality has accompanied the increased prevalence of asthma. Annually there are approximately 11 million medical visits for asthma (Cherry et al. 2008), including over 200,000 emergency department visits related to asthma (Pitts et al. 2008). Women with asthma have hospitalization rates 2.5–3.0 times that of men (Skobeloff et al.

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1992) and report a lower quality of life than men (Bousquet et al. 1994). In addition, women have higher asthma-related mortality rates than men. Approximately 16 deaths per million population are attributed to asthma for women versus 10 deaths per million population for men (Minino et al. 2007). In 2004, nearly 64% of asthma deaths occurred in women (Minino et al. 2007).

Epidemiologic Studies of Asthma

Defining asthma in the context of an epidemiologic study can be challenging. Consequently, many studies rely on self-reported information including self-reports of physician diagnosed asthma, the presence of asthma symptom(s), and the severity of asthma (Eder et al. 2006). The use of different definitions for asthma makes it difficult to compare studies and to generalize results to other populations. Though clinical objective measures for pulmonary function, such as spirometry, can be used, they are costly, and unavailable for large-scale or community-based studies.

In addition to problems with defining asthma, many studies also consider sex to be a confounder of exposure-asthma associations. While sex may be a confounder of some associations, it is also likely that sex is an effect modifier of many of the observed exposure-asthma associations. When associations are not separated out by sex, many important relationships can be obscured. To date, epidemiologic investigations on risk factors for asthma among women are sparse.

Studies that have been conducted among cohorts of women have found that obesity is associated with an increased risk of asthma (Camargo et al. 1999; Coogan et al. 2009; Romieu et al. 2003). Specifically, overweight and obese women have nearly twice the risk of asthma as compared to women with a normal body mass index (BMI). In addition, an increase in body silhouette after menarche has also been found to be related to an increased risk of asthma in adulthood (RR = 1.6; 95% CI: 1.18–2.32).

Studies conducted with populations of men and women indicate that socioeconomic, lifestyle, and environmental factors are associated with an increased risk of asthma. Specifically, low income, lower education level, and non-Hispanic black race/ethnicity have been found to be associated with an increased risk of asthma (Arif et al. 2003; Bandiera et al. 2008; Drake et al. 2008; Grant et al. 2000; Litonjua et al. 1999). Though it has been suggested that associations that have been seen between race/ethnicity and asthma may be largely explained by factors like income, area of residence, and education level, researchers have found race/ethnicity to be an independent risk factor for asthma (Litonjua et al. 1999). However, data from the 2006 National Health Interview Survey did not indicate that the prevalence of ever having physician-diagnosed asthma differed considerably between non-Hispanic black women and non-Hispanic white women (Pleis and Lethbridge-Cejku 2007). Specifically, 12.8% of non-Hispanic white women reported ever having asthma as compared to 13.9% of non-Hispanic black women. Hispanic women had the lowest asthma prevalence (10.8%).

A family history of asthma (Lugogo and Kraft 2006; Sunyer et al. 1997) and diet have also been implicated as risk factors for asthma in populations of men and women. In particular, low dietary intakes of Vitamin E and n-3 polyunsaturated fatty acids (found in oily fish and leafy, green vegetables) and high dietary intakes of n-6 polyunsaturated fatty acids (found in vegetable oils) are associated with an increased risk of asthma (Black and Sharpe 1997; Hodge et al. 1996; Raper et al. 1992; Seaton et al. 1994). Environmental factors such as secondhand tobacco smoke and exposure to chemicals, and materials used in home improvement activities or industries, including beauty salons, also affect asthma risk (Arif et al. 2009; Becklake and Kauffmann 1999; Chan-Yeung and Malo 1995; Delclos et al. 2007; Gold et al. 1996; Masi et al. 1988; Xu and Wang 1994; Xu et al. 1994).

Concluding Remarks

Women are more likely to report adult onset of asthma than men (Becklake and Kauffmann 1999; Caracta 2003; De Marco et al. 2000; Flattery et al. 2001; Janson et al. 2001; Nicolai et al. 2003; PausJenssen and Cockcroft 2003), and demonstrate higher asthma-related hospitalization and mortality rates than men (Kochanek et al. 2002; McCaig and Burt 2005; Minino et al. 2007; Pitts et al. 2008; Skobeloff et al. 1992). One explanation for these observations relates to the hormonal changes that affect asthma risk in women. In particular, women's

airways are subject to cyclical variations in sex hormones which occur in relation to circadian rhythms, menstrual cycles, hormonal contraceptive use, pregnancy, and menopause (Alberts 1997; Chandler et al. 1997; Edwards et al. 1996; Eliasson et al. 1986; Lieberman et al. 1995; Murphy and Gibson 2008; Schatz et al. 1988; Shanies et al. 1997; Skobeloff et al. 1992; Stenisu-Aarniala 1996; Tan et al. 1997; Troisi et al. 1995). Despite the indication that asthma risk is quite different for men and women, many studies of adulthood asthma treat sex as a confounder of any observed associations. Future studies need to investigate possible risk factors for asthma separately for men and women.

Asthma and Changes in Female Sex-Steroid Hormones Over the Life Course

Asthma in women has been hypothesized to be related to natural changes in sex-steroid hormone levels during a woman's life course; thus, the onset of puberty, the beginning of perimenopause, and the completion of menopause are biological transition points when asthma may begin or change. Whether these transition points trigger the onset of asthma, exacerbate existing asthma symptoms and severity, or relieve asthma is still being researched. It is clear that for many women with asthma, fluctuations in endogenous hormone levels are correlated with changes in their asthmatic condition.

Puberty

The onset of puberty potentially plays a critical role in the development of asthma and its symptoms in females. Observational evidence supporting this are the differences in prevalence rates of asthma between boys and girls prior to puberty, with boys having a significantly higher prevalence of asthma than girls (9.6% vs. 7.4%). This trend then reverses post-puberty with women having a significantly higher prevalence than men in the age group of 18 and above (8.4% vs. 4.9%) (Centers for Disease Control and Prevention 2003). Researchers suspect that hormonal factors are the dominant determinant of the asthma prevalence seen in adult women (Becklake and Kauffmann 1999). Young girls have lower rates of asthma as compared to boys, and around the time of puberty asthma rates are essentially equal in boys and girls. However, after puberty, women have increased rates of developing asthma as compared to men. When considered in 5-year intervals, this reversal is first seen in the 15–20 year age group when women have 1.38 times the rate of asthma as compared to men (95% CI: 1.02–1.88), and becomes more dramatic as age increases (De Marco et al. 2000). Among adults 40–45 years of age, women have nearly six times the rate of developing asthma when compared to men (95% CI: 2.31–15.26). Testosterone appears to have an anti-inflammatory effect, whereas estrogen has a pro-inflammatory effect (Osman 2003). However, researchers are not in agreement on whether puberty is associated with increased risk of asthma, with some supporting an association (Haggerty et al. 2003) and others refuting it (Zannolli and Morgese 1997). There is some suggestion that social and cultural factors may play a role, resulting in girls being under-diagnosed with asthma (Haggerty et al. 2003) and boys being more likely to be diagnosed because they have increased severity of asthma at younger ages resulting in hospitalizations (Balzano et al. 2001; Haggerty et al. 2003).

The actual biological mechanism by which puberty in girls would influence asthma onset and severity has not been explored, although we can infer from studies of asthma and the menstrual cycle that increasing levels of estradiol, follicle stimulating hormone (FSH) and luteinizing hormone (LH) related to menarche and other bodily changes would have some effect. Women who experienced menarche before age 12, had twice the risk of experiencing asthma post-puberty (Salam et al. 2006). Increasing rates of obesity in children may also be a factor that needs to be examined in the future since BMI and asthma are associated in women (Camargo et al. 1999; Romieu et al. 2003).

Menopause

Onset of Asthma

At the other end of the reproductive life cycle, if increasing levels of estradiol precipitate the onset of asthma during puberty, then logically we should see a reversal in asthma severity as women go through

menopause (Balzano et al. 2001; Barr and Camargo 2004); but this has not proved to be the case (Gómez Real et al. 2006).

Prevalence of asthma in women continues to increase with age as 9.2% of women in the age group of 45–64 report having asthma and these rates do not decline until women are over 65 (6.8%) (Centers for Disease Control and Prevention 2003). Postmenopausal women have significantly lower levels of sex-steroid hormones than pre-menopausal women, but asthmatic postmenopausal women have even lower levels of estradiol and estrone than non-asthmatic women in menopause (Haggerty et al. 2003). Research on postmenopausal women and asthma has not examined the natural transition into menopause with concomitant tracking of clinical measures of reproductive hormones and clinical measures of pulmonary function in asthmatic and non-asthmatic women who are not taking hormone replacement therapy (Haggerty et al. 2003). Rather, the tendency has been to examine how hormone replacement therapy (HRT) affects asthma symptoms and severity; thus HRT and asthma have become entwined without first examining the main effects of changes in endogenous sex steroids and its association with pulmonary functioning. A recent study examining this issue, has included only the women who are not HRT users (Gómez Real et al. 2008). This cross-sectional study revealed that menopausal women had decreased lung function (as measured by FEV_1 and forced vital capacity) and increased respiratory symptoms (OR = 1.82; CI: 1.27–2.61) as compared to women who were still menstruating. These results were especially pronounced among lean women with BMI <23 kg/m^2. This analysis underscores the need for a prospective epidemiology study to address this tremendous gap in the science on asthma and menopause.

While there have been no prospective studies examining the natural transition to menopause and pulmonary function, studies that have considered the relationship between asthma and HRT use in relation to menopause are revealing. Four studies have been made and they have concluded that users of HRT have a higher risk of asthma than never users of HRT (Barr et al. 2004; Gómez Real et al. 2006; Lange et al. 2001; Troisi et al. 1995). In a preliminary analysis from the Nurses Health Study, postmenopausal women who had never taken HRT had a statistically significantly lower, age-adjusted risk of asthma than pre-menopausal women. When duration of HRT use was considered, women who had ever used HRT for 10 or more years had twice the risk of asthma as compared to never users of HRT (Troisi et al. 1995). A subsequent analysis controlled for differences in current versus past hormone use in postmenopausal women and found that current estrogen use and current estrogen and progestin use are each associated with increased rates of asthma in comparison to women who have never used hormones (Barr et al. 2004).

In a similar analysis of postmenopausal women in the Copenhagen City Heart Study (Lange et al. 2001), there was a significantly higher prevalence of asthma ($p = 0.004$) and the need to use asthma medication ($p = 0.018$), in never smokers who used HRT than in current smokers. Overall, the association between HRT use and self-reports of asthma (OR = 1.42; 95% CI: 0.95–2.12), asthma symptoms (wheezing [OR = 1.29; 95% CI: 1.02–1.64] and coughing upon exertion [OR = 1.34; 95% CI: 1.01–1.77]), and medication use (OR = 1.45; 95% CI: 0.97–2.18) were categorized as "consistent but weak" and the authors concluded that no change in HRT protocol was necessary. In a recent study that examined the interaction of HRT and BMI with asthma in perimenopausal women, Gómez Real et al. (2006) found that in women aged 46–54 who were not taking exogenous hormones, increasing BMI was associated with a greater risk of asthma, supporting the findings of Camargo and colleagues (1999). In women taking HRT, there was a significant increased risk of asthma (Barr et al. 2004). Thus, both HRT and BMI have significant and independent associations with increased risk of asthma. However, when the HRT users are stratified by BMI, the increased risk of asthma is only significant for lean women (Jarvis and Leynaert 2008); thus BMI may act as an effect modifier of the HRT-asthma association. Gómez Real et al. (2006) hypothesize that the pro-inflammatory effects of insulin resistance, which is associated with BMI, may be an important factor in explaining the HRT and BMI interaction.

These findings suggest that physiologically natural low levels of estrogen may be protective against asthma. Thus, lean women, who often tend to be White, wealthier and more educated, should theoretically have reduced rates of asthma. However, these are the same women who are likely taking HRT (Troisi et al. 1995), either because of concerns about reduced bone density (prevalent in lean women), or because they suffer from

menopausal symptoms because of their reduced fatty tissue and reduced estrogen levels. These data suggest that research should examine hypotheses relating to whether women with low body fat percentages such as athletes and dancers, women who are excessively thin, or women with amenorrhea, have lower rates of asthma. Similarly, girls with low body fat and delayed onset of puberty might experience delayed onset of asthma.

Hormone Replacement Therapy and Pulmonary Function

Given the recent controversial findings about HRT and its effects in women in relation to heart disease, breast cancer and stroke (Cauley et al. 2003; Chlebowski et al. 2003; Rossouw et al. 2002), a renewed interest in examining HRT and its effects on asthma in women should be a key priority. Early studies examining the association between estrogen replacement therapy and respiratory function revealed a statistically significant reduction in peak expiratory flow (PEF) in postmenopausal asthmatic women and a self-reported increase in bronchodilator inhaler use (Lieberman et al. 1995), but no corresponding decrease in women's subjective measures of well-being. Thus, the authors concluded that there were sub-clinical effects, but that these effects were not sufficient to influence women's well-being. These findings do not take into account the cumulative long term effects of these sub-clinical markers. In addition, this study did not control for confounders such as tobacco exposure, allergy status, pollution, and respiratory infection among others (Haggerty et al. 2003). In a later study, designed to duplicate the research of Lieberman et al. (1995), Hepburn and colleagues (2001) found no significant changes in forced expiratory volume at 1 s (FEV_1) or use of β-agonist bronchodilators in postmenopausal asthmatic women who ceased HRT and then re-initiated it after 28 days.

In contrast, more recent studies have shown that asthmatic postmenopausal women have significantly lower levels of estradiol and estrone concentration than non-asthmatic women (Kos-Kudla et al. 2000); adjusting these levels through the introduction of exogenous hormones may alleviate asthma symptoms. Kos-Kudla et al. (2000) found that a 6-month intervention with HRT increased estrogen and estrone levels in lean, postmenopausal, non-smoking women. Participants reported decreased psychosomatic symptoms of menopause, reductions in the use of inhaled glucocorticoids, and improved spirometry during the HRT intervention (Kos-Kudla et al. 2001).

These positive effects of an HRT intervention on asthmatic women are supported by other observational studies. In a German study examining HRT use with bronchial hyper-responsiveness (BHR) in postmenopausal women (Mueller et al. 2003), HRT users are significantly less likely to demonstrate BHR in comparison to non-HRT users, suggesting that HRT may relax bronchial smooth muscle. This confirms a large scale cross-sectional analysis of 2,353 postmenopausal HRT users and non-users, who are 65 years and older, which has found that current HRT users have higher FEV_1 than former or never users, and less pulmonary obstruction (Carlson et al. 2001). This study has been able to control for several confounding variables including: smoking status, BMI, other respiratory problems, race, age, years of education, and dose and formulation of HRT; however, the study was limited by the small number of asthmatic women in the project. Additionally, the duration of current or former HRT use, which may be a confounding factor, was not considered. While this study had a sample that was 17% non-White, it is important to remember that Black women with asthma are more likely to die before ever reaching age 65; thus, in this cross-sectional study a survival bias may have occurred.

Despite these studies, no definitive, consistently replicable results have been found (see Haggerty et al. 2003 for a brief review) and BMI may be an effect modifier on the association between HRT and asthma (Gómez Real et al. 2006). Similarly, estrogen dosage in HRT is much less than that found in oral contraceptives and may not be sufficient to demonstrate a dose–response relationship with pulmonary function. The other elements complicating these findings are the various formulations of estrogen therapy and asthma severity. Early studies were conducted using only estrogen therapy while later studies used formulations including progesterone. Early HRT interventions were also of short duration (14–28 days) versus later studies that evaluated HRT duration of 6 months (Kos-Kudla et al. 2000).

Greater efforts to enroll asthmatic, postmenopausal women of all races and of younger ages should be a top priority in future studies of HRT use. Studies also need to be prospective and of sufficient length to examine

long term effects and trends of respiratory function and duration of HRT use. As we have seen from the Women's Health Initiative study (Chlebowski et al. 2003; Cushman et al. 2004; Rossouw et al. 2002), duration of HRT use is particularly important in evaluating disease risk.

Consequences of Asthma in Postmenopausal Women

One-third of the published research on menopause and asthma has examined the effects of corticosteroid use on bone mineral density (BMD) and fractures in perimenopausal and postmenopausal women. The prevalence of this condition has resulted in the term "corticosteroid-induced osteoporosis" (Saag et al. 2006; Tsugeno et al. 2002; Walsh et al. 2002). Typically, this condition is associated with the use of oral glucocorticoid steroids such as prednisone or its equivalents. As inhaled corticosteroids (ICS) have more recently become the "gold standard" treatment for asthma (Dahl 2006) and other lung diseases, and as asthma is a chronic condition, the long term, cumulative effects of ICS usage are a significant health issue. Similarly the use of oral corticosteroids, while no longer the primary/daily form of treatment for asthma, has also been examined for its long term effects, including its well-established negative effects on BMD and fractures (Angeli et al. 2006; National Institutes of Health Osteoporosis and Related Bone Diseases ~ National Resources Center 2005; Walsh et al. 2002).

Both oral and inhaled corticosteroids are absorbed systemically into the circulation system with the former occurring through the gastrointestinal tract and the latter being absorbed through the lung. However, some percentage of ICS are swallowed and the level of absorption of inhaled medications are dependent upon the particular agent, the inhaler device, and inhaler technique (Tattersfield et al. 2004). Drug absorption is particularly salient for women, as they metabolize drugs differently than men (Gandhi et al. 2004; Jochman et al. 2005; Martin 2006; Morris et al. 2003).

Multiple empirical studies of varying designs and sample sizes have found a statistically significant, inverse association between ICS use and BMD (Israel et al. 2001; Langhammer et al. 2004; Toogood et al. 1995; Wong et al. 2000) and this finding is further supported in review articles (Dahl 2006; Tattersfield et al. 2004). However, the specific biological mechanism, dosage, particular drug used, duration of use, cumulative dosage, age of participants, and other factors are not consistent across these studies and no clear dose–response relationship has been established or replicated.

Earlier studies found no significant reduction in BMD with inhaled corticosteroid use (Laatikainen et al. 1999; Luengo et al. 1997) and other reviews have also concluded that ICS use is generally safe with respect to bone density (Jones et al. 2002; Peters 2006). Two recent, separate meta-analyses examining use of inhaled corticosteroids and BMD (Halpern et al. 2004; Sharma et al. 2003) also concluded that use of ICS for asthma was not associated with significant decreases in BMD. The two studies had no overlap between the articles included in their respective meta-analyses and had small sample sizes ($n < 10$). The Cochrane Review article (Jones et al. 2002), while not finding any statistically significant negative effects, did indicate that their conclusions were very narrowly defined to conventional doses of ICS and over the short or medium term (2–3 years) in younger adults (i.e., premenopausal women). More prospective, randomized clinical trials are needed with attention to specific factors related to bone density such as diet and time of assay collection. Studies with postmenopausal women will be complicated by HRT use, which appears to counteract the potential negative effects of ICS on BMD (Toogood et al. 1995). HRT use has been shown to increase BMD in osteoporotic women, although it is not recommended for treatment of existing disease because of the other health risks associated with it (Cauley et al. 2003).

To summarize, no definitive conclusions can be reached about the long term effects of inhaled corticosteroids on BMD and risk of fracture. While there does appear to be a decrease in BMD with possible increase in risk of fracture, findings do not consistently achieve clinical or statistical significance. The role of HRT appears to modify the risk of ICS, but HRT is no longer recommended as a disease preventative and should only be used in cases of severe menopausal symptoms and for the shortest possible duration.

Summary

Evidence exists that changes in sex steroid levels in women are associated with changes in asthma; however,

the direction and magnitude of change is inconsistent. Interaction effects between asthma and weight, and asthma and use of exogenous hormones, complicate comparisons between studies. While changes in endogenous hormone levels are related to biology and life course transitions, the use of exogenous hormones is often related to gender, thus sex and gender need to be examined separately. The need for prospective cohort studies to examine the natural transition points of puberty and menopause are crucial to understand the sex-related issues with asthma in women.

Asthma and the Menstrual Cycle

The exacerbation of asthma in women associated with the menstrual cycle has been explored by researchers beginning as early as 1931 (Tan 2001). Several of these studies have been able to demonstrate that asthma exacerbation related to the menstrual cycle, particularly the perimenstrual phase of the cycle, can be a severe and life threatening event (Martinez-Moragon et al. 2004; Nakasato et al. 1999; Oguzulgen et al. 2002). Because of the potential severity of the phenomenon, it is important that asthma etiology and pathology are understood in order to effectively treat the condition. Most of the studies had small sample sizes and explored this association using retrospective study designs in which asthma severity was self-reported through questionnaires. Objective measures of pulmonary function and airway inflammation have been used in these studies only with in the last 30 years. Although asthma associated with the menstrual cycle has been known to affect women for over 70 years, the prevalence, etiology, and pathology of the association remain unclear (Vrieze et al. 2003).

Prevalence

Estimated prevalence rates of menstrual cycle linked asthma have varied across studies, as the timing of the menstrual cycle phase has been more related to the asthma exacerbation. Zimmerman et al. (2000) were able to demonstrate that only 13% of women reported reproductive factors as triggers of their asthma. A number of studies have demonstrated no significant differences in asthma exacerbation rates across the various intervals of the menstrual cycle, while others were able to demonstrate that the perimenstrual phase of the menstrual cycle can be associated with up to 46% of the cases of asthma exacerbation (Agarwal and Shah 1997; Brenner et al. 2005; Martinez-Moragon et al. 2004; Skobeloff et al. 1996; Zimmerman et al. 2000). Gómez Real et al. (2007) found that irregular menstrual cycles are associated with asthma exacerbation based on self-reports. Despite the variance that can be found in the prevalence and timing of menstrual cycle linked asthma, the most consistent finding is that asthma exacerbations most often occur during the perimenstrual phase of the menstrual cycle, followed by the periovulatory phase (Vrieze et al. 2003).

Etiology and Pathophysiology

There are several hypotheses relating to the etiology and pathophysiology of menstrual cycle related asthma exacerbations. The most common of these hypotheses relates asthma exacerbations to the cyclical changes in sex hormone levels in women, including significant decreases in estrogen, progesterone and estradiol levels during the follicular and luteal phases of the menstrual cycle. Findings from human and animal models suggest that progesterone and estrogen may improve lung function in women, by reducing contractility of bronchial smooth muscle and by strengthening airway muscles (Matsubara et al. 2008; Popovic and White 1998; Skobeloff 1995). It has also been demonstrated that estrogen withdrawal causes an increase in bronchial smooth muscle contractility, thereby decreasing lung function (Haggerty et al. 2003). Sex hormone levels in women have also been thought to be associated with lung inflammation, which increases the risk of asthma exacerbation. Morishita and colleagues (1999) found that estradiol and progesterone inhibit human peripheral monocyte production of interlukin-1. Interlukin-1 has been found to be a mediator of inflammation. Other studies have also been able to demonstrate that estradiol exhibits anti-inflammatory properties (Litonjua et al. 1999).

Other hypotheses relating to the pathophysiology of menstrual cycle related asthma exacerbations center around mediators and manifestations of airway inflammation in asthma. Previous research has demonstrated

that prostaglandins are mediators of airway inflammation (Smith et al. 1992). Metabolites of prostaglandins have been found to increase in women during ovulation and pre-menstrually. The peaking of the metabolites of prostaglandins is important to the pathology of asthma exacerbations related to the menstrual cycle because they have been shown to be effective bronchoconstrictors that may trigger or at the very least increase the risk of asthma exacerbations (Koullapis and Collins 1980).

Bronchial hyperresponsiveness (BHR) is a manifestation of the airway inflammation process and triggers much of the symptomatology of asthma exacerbation (Tan 2001). Studies examining the presence of BHR among women with menstrual cycle related asthma have found varying results. Tan et al. (1997) found that BHR increased during the luteal phase of the menstrual cycle. Other studies have found that there are no cyclical changes in BHR (Juniper et al. 1987; Weinmann et al. 1987).

Additional hypotheses refer to the effects that endogenous female sex steroids have on the vasorelaxant and bronchorelaxant effects of catecholamines (Tan 2001). Many of the studies exploring these hypotheses have focused on β_2-adrenoceptor function and regulation. It has been demonstrated that women have more β_2-adrenoceptor responses to β_2-agonists than men, suggesting that female sex hormones may facilitate β_2-adrenoceptor function and regulation (Rahman et al. 1992). It has also been demonstrated that there are cyclical changes in β_2-adrenoceptor function. A study by Wheeldon et al. (1994) found that there is greater β_2-adrenoceptor density during the luteal phase of the menstrual cycle when the sex hormone levels are high.

Psychological factors may also influence physiological reactivity in women with menstrual cycle related asthma. The results of studies exploring potential psychological factors have varied (Dorhofer and Sigmon 2002; Mirdal et al. 1998). Dorhofer and Simon (2002) explored the relationship between anxiety and other psychological symptoms and the menstrual cycle in women with and without a diagnosis of asthma. While the investigators did not find any significant differences in psychological measures with menstrual cycle phase as a factor, they did find that women with asthma and a history of panic attacks typically experienced more psychological distress than did the other women in the study. Experiencing more psychological distress has been suggested to be a factor in the exacerbation of asthma during the perimenstrual phase. Mirdal and colleagues (1998) were able to demonstrate a relationship between lower resistance to stress and infections and increases in bronchial hyperresponsiveness during the perimenstrual phase. These findings suggest that in addition to the physiological changes that occur during the menstrual cycle, psychological factors can also play a role in increasing risks of asthma exacerbation related to the menstrual cycle.

Oral Contraceptives

Because it has been demonstrated that some female asthmatics experience menstrual cycle related asthma exacerbation as a result of cyclical changes in female sex hormone levels, the way in which exogenous female sex hormones influence asthma and asthma-like symptoms is important, particularly in the case of oral contraceptive use. In non-asthmatic women, using oral contraceptives increased risk of current wheeze (OR = 1.75; 95% CI: 1.15–2.65) (Salam et al. 2006), but in contrast, a study of Tasmanian women found that each year of oral contraceptive use decreased the risk of current asthma by 7% (95% CI: 0–13%) (Jenkins et al. 2006). Oral contraceptives reduce the amount of fluctuations in female sex hormone levels throughout the menstrual cycle (Forbes 1999). Consequently, it is easy to hypothesize that the use of oral contraceptives would reduce the presence of menstrual cycle related asthma exacerbations (Forbes 1999). Studies investigating the relationship between the use of oral contraceptives and asthma exacerbations, however, have found varying results.

Of the studies that have explored the relationship between the use of oral contraceptives and asthma, only some were able to demonstrate significant differences in asthma symptoms, and severity between women taking oral contraceptives and those who did not take them. However, even among the studies that found significant differences between groups, there is some variance in the specific findings (Forbes 1999). One such study was able to demonstrate that there is an increase in airway reactivity and in peak expiratory flow rates during the luteal phase of the menstrual cycle among women not receiving oral contraceptives (Tan et al. 1997). The participants that received the oral contraceptives did not have significant increases

in airway reactivity or in peak expiratory flow rates during the luteal phase, suggesting a decrease in asthma symptoms as a result of oral contraceptive use (Tan et al. 1997). Other studies demonstrating improvements in asthma symptoms as a result of oral contraceptive use in women with more severe menstrual cycle related asthma exacerbations have also been reported (Matsuo et al. 1999; Salam et al. 2006).

In contrast to the studies mentioned above, Forbes et al. (1999) were able to demonstrate that the use of oral contraceptives can have either a negative or positive influence on asthma symptoms. The results of their study demonstrated that only 6% of women taking oral contraceptives reported that their use of contraceptives influenced asthma severity. Surprisingly, of those women stating that their use of oral contraceptives influenced asthma severity, nearly two-thirds stated that their symptoms worsened as a result of the contraceptives. The remaining women reported improvements in their asthma symptoms.

Other studies have been able to show that there are no significant differences between women receiving oral contraceptives and those not receiving them and their resulting asthma severity. These studies, however, explored a limited subset of asthma symptoms and they did not investigate differences between women receiving monophasic and triphasic oral contraceptives (Lange et al. 2001; Murphy and Gibson 2008; Tan et al. 1998). Tan et al. (1998) investigated β_2-adrenoceptor regulation and function without examining other asthma symptoms. In a similar manner, Lange and colleagues (2001) questioned their participants on the presence of wheeze, cough on exertion, and use of asthma medication without exploration of the underlying causes of these asthma symptoms. These limitations in the methods may have influenced the researchers' ability to demonstrate any differences in asthma symptoms and severity among the study groups.

Summary

While there have been several studies examining the association between asthma exacerbation and the menstrual cycle throughout the last 70 years, the details regarding the phenomenon remain unclear (Chhabra 2005). Despite the inconsistent findings of studies investigating asthma and the menstrual cycle, the results of studies that demonstrate an association between the menstrual cycle and asthma exacerbations suggest that the menstrual cycle can be a factor in asthma exacerbation in some women, although the exact prevalence, etiology, and pathophysiology is still uncertain (Tan 2001). The inconsistencies in the results of these studies also suggest that menstrual related asthma exacerbations may be dependent upon other non-menstrual related factors in the individual female, particularly with regards to the use of oral contraceptives, which have been shown to have varying effects on asthma exacerbations (Forbes et al. 1999).

It is possible that much of the confusion about asthma and the menstrual cycle results from the limitations of the studies exploring the disease. These studies often had small sample sizes that may not have allowed for enough power to identify any significant differences. In addition, many of the studies used participant self-report to measure asthma symptoms and severity which may not have allowed for full exploration of the disease. Also, the limitations in the measures used may have allowed for some important underlying causes of asthma exacerbations to be ignored.

Asthma and Pregnancy

Because this chapter is focused on women *with* asthma, the relationship between asthma and pregnancy is considered from the perspective of the effect of asthma on pregnant women and subsequent maternal outcomes (preeclampsia, gestational hypertension, oligohydramnios, etc…), but not fetal outcomes. There are several excellent recent articles on the subject of maternal asthma and fetal outcomes (Dombrowski 2006; Hanania and Belfort 2005; Rudra et al. 2006; Sheiner et al. 2005), but these will not be discussed here.

The prevalence of asthma among pregnant women in the U.S. is estimated to be between 3.7% and 8.4% based on self-reports in national datasets (Kwon et al. 2003). African Americans have a 38% higher prevalence of asthma than do Whites (American Lung Association 2005), and thus we should expect a higher prevalence among pregnant women as well. Parity may play a role in the onset of asthma. Risk of current asthma has been found to increase with each birth (OR = 1.50; 95% CI: 1.01–2.23) (Jenkins et al. 2006). However, in the same study, women with a solo birth

had a lower risk of current asthma than nulliparous women (OR = 0.46; 95% CI: 0.2–1.06).

Based on empirical studies, there is a direct relationship between a woman's asthma severity classification and her experience of severe asthma exacerbations during pregnancy (Murphy et al. 2005, 2006; Schatz et al. 2003). In a recent meta-analysis, 20% of pregnant women experienced an asthma exacerbation requiring medical intervention (Murphy et al. 2006). In both the Asthma During Pregnancy Study (ADPS) (Schatz et al. 2003) and an Australian study (Murphy et al. 2005), modeled on the ADPS, the percentage of asthmatic women experiencing severe asthma exacerbations (as defined by hospital admission, emergency department visit, unscheduled physician visit or treatment with oral steroids for asthma) increased with increasing asthma severity classification. In women with mild asthma, 8% and 12.6% experienced exacerbations (ADPS study and Australia study respectively). Severe exacerbations during the course of pregnancy were experienced by 25.7% (ADPS) to 47% (Australia) of women with moderate asthma and by 51.9% (ADPS) to 65% (Australia) of women with severe asthma. There were some slight differences between the study protocols and the proportions of women in the various asthma severity categories. Overall, 36% of women in the Australia study experienced severe exacerbations versus only 20% in the ADPS. Notably, the ADPS had a large percentage of African American participants (55%), who typically experience a higher prevalence of asthma and more severe asthma. Differences in the health care systems of Australia and the U.S. may also explain variation in the findings. Australia has a government financed, universal health care system; in the U.S., women may underutilize health care depending upon their health insurance status.

The Yale Asthma Study enrolled 873 pregnant asthmatic women and 1,333 women with no asthma history (Bracken et al. 2003). In women with diagnosed asthma, 49% were classified as mild severity, 24.6% had mild persistent asthma severity, 15.2% had moderate persistent severity, and 11.2% had severe persistent asthma severity. In addition, 34% of non-asthmatic women experienced asthma symptoms or used asthma medication during pregnancy. Severe asthma during pregnancy was associated with younger age, unmarried, Hispanic and black ethnicity, lower education, higher prepregnancy weight, smoking during pregnancy, and consuming 150 mg or more of caffeine during pregnancy.

A recent and comprehensive retrospective chart review of pregnant white and black women enrolled in Medicaid in Tennessee (Carroll et al. 2005), found that in comparison to white women, black women had a significantly higher risk of asthma exacerbations including: emergency room visits for asthma (adjusted RR = 1.89; 95% CI: 1.57–2.27), hospital admission (adjusted RR = 1.73; 95% CI: 1.34–2.24), or filling a rescue corticosteroid prescription (adjusted RR = 1.35; 95% CI: 1.14–1.61). In this study, Blacks were more likely to be single, urban, non-smoking and to receive substandard pre-natal care.

Asthma Improvement During Pregnancy

In the ADPS, some women experienced improvements in their asthma during pregnancy (23%), whereas 30% demonstrated increasing asthma severity (Schatz et al. 2003). In a subset analysis of the ADPS using data from the San Diego site, 33.6% of pregnant women experienced improvements in their asthma during the course of pregnancy based on self-assessments and 36.4% experienced worsening of their asthma (Kircher et al. 2002). Changes in asthma were directly related to self-reported changes in rhinitis. A recent study prospectively measured peak flow values in 43 racially and ethnically diverse, asthmatic pregnant women (Beckmann 2008) and found a statistically significant increase in peak flow between the first and third ($p < 0.005$) and second and third trimesters ($p < 0.01$).

Studies examining the underlying causes of asthma exacerbation during pregnancy have investigated the following factors: sex of the infant (Bakhireva et al. 2008; Firoozi et al. 2009), maternal weight gain, maternal pre-pregnancy BMI, maternal smoking during pregnancy, panic-fear hypotheses, infant birth weight, use of corticosteroids, and seasonality. There are conflicting results for all of these variables. For example, Kircher and colleagues (2002) analyzed a subset of ADPS data ($n = 568$) and found no association between pre-pregnancy weight and asthma exacerbations during pregnancy, whereas Hendler et al. (2006), analyzing the full ADPS data set ($n = 1{,}699$) found that obesity was significantly related to asthma exacerbations during pregnancy (OR = 1.3; 95% CI: 1.1–1.7).

It has been hypothesized that many asthma exacerbations during pregnancy are the result of women not adhering to their asthma drug therapy for fear of harming the fetus. Non-adherence is a distinctly gendered response by women based on the medicalization of pregnancy and social norms about motherhood. Enriquez et al. (2006) in a retrospective review of Medicaid claims data of over 8,000 pregnant women with asthma, found that women decreased asthma medication use in the first trimester (23% decrease in ICS, 13% decrease in β-agonists and 54% decline in rescue therapies). These findings are similar to patients of a managed care organization (Chambers 2003). If true, health care providers require training to educate women about the course and progression of asthma during pregnancy and the safety of ICS.

Adverse Maternal Outcomes in Pregnant Women with Asthma

Obesity is associated with pregnancy complications (gestational hypertension, gestational diabetes and caesarean section), regardless of the presence of asthma (Hendler et al. 2006). But in a recent analysis of the ADPS and an additional dataset for an asthma medication randomized control trial, lower FEV_1 in asthmatic women during pregnancy was significantly associated with increased gestational hypertension, gestational diabetes and premature birth (Schatz et al. 2006b). Similarly, pregnant women with moderate-to-severe asthma have an increased risk of caesarean delivery as compared to nonasthmatic controls (adjusted OR = 1.4; 95% CI: 1.1–1.8) (Dombrowski et al. 2004).

Treatment of Asthma During Pregnancy

There are two consistently definitive findings in studies on asthma and pregnancy: first, inhaled corticosteroids are safe to use during pregnancy and there are no significant adverse maternal, fetal or infant outcomes as a result of ICS use; second, use of oral steroids increases adverse perinatal outcomes. In the Yale Asthma Study (Bracken et al. 2003), pregnant women with and without asthma and pregnant women without a diagnosis of asthma but with asthma symptoms were prospectively monitored from weeks 20 through postpartum. There was no increased risk of pre-term delivery or intrauterine growth restriction (IUGR) with ICS use. Preterm delivery was 50% more likely in asthmatic women, however, there was no increased risk of preterm delivery associated with increasing levels of asthma severity as determined by the Global Initiative for Asthma criteria. A recent review of ICS use during pregnancy concluded that ICSs were safe to use, but the authors noted the low statistical power of the current published studies (Breton et al. 2008).

Summary

Based on the few available studies, pregnancy does change the severity of asthma in many women, but the direction of the change is not predictable. Those women experiencing an asthma exacerbation during pregnancy may be at increased risk for adverse maternal outcomes. Increased exacerbations of asthma may be due to reduced use of asthma medications, even though evidence-based research supports the safety of inhaled corticoid steroids during pregnancy with no significant adverse maternal or fetal outcomes.

Women and Health Care Utilization

Although gender differences in the incidence and prevalence of asthma among children have been recognized throughout the last 20 years, gender differences among adults have not been explored as thoroughly. Most studies that have explored gender differences among adults with asthma have focused on the use of health care due to asthma exacerbations. These studies have demonstrated that women are more likely than men to present to the emergency department with complaints of asthma exacerbation and to be admitted to the hospital, despite similar prevalence rates of asthma among both groups (Cydulka et al. 2001; DiMarco 1989; Prescott et al. 1997; Rowe et al. 2009). These findings agree with the results of previous research exploring gender differences in health care utilization. Bertakis and colleagues (2000) were able to demonstrate that women tend to utilize health care

services more than men, particularly emergency room, primary care, and diagnostic services. The gender differences that have been shown in health care use related to asthma are thought to be caused by differences in severity of the disease and symptom experience (Prescott et al. 1997; Schatz et al. 2006a).

Upon presentation to the emergency room, women have been found to report more severe symptoms in terms of symptom frequency, intensity, and resulting activity limitations than do men (Cydulka et al. 2001). While self-reports of symptoms indicate that women experience more severe asthma than men, analysis of objective measures of asthma severity such as forced expiratory volume in 1 s and peak expiratory flow rates demonstrate that men more often present to the emergency room with more clinically severe asthma exacerbations (Awadh et al. 1996; Cydulka et al. 2001; Schatz et al. 2006a; Singh et al. 1999). In particular, women with clinically moderate asthma exacerbations were found to be much more likely than men to report severe activity limitations. In males and females reporting to the emergency department for acute asthma, women were more likely than men to report an ongoing asthma exacerbation or relapse (Rowe et al. 2008; Singh et al. 1999).

The differences found in self-report of symptoms and objective clinical measures indicate that differences in symptom experience between men and women may explain the differences in health care use (Cydulka et al. 2001). Gender differences in symptom experiences that result in differences in health care utilization for asthma exacerbations may be due to several factors including clinical factors (e.g., the natural history of asthma), and psychosocial issues (Cydulka et al. 2001), and education related to sex and gender and asthma (Clark et al. 2008).

Studies exploring clinical factors that may influence gender differences in symptom experience have varied in their results. Burden and colleagues (1982) were able to demonstrate that asthmatic patients with a longer history of airflow obstruction were more likely to have a lower awareness of airway obstruction. These findings were found to occur independently of gender, suggesting that the propensity for women to develop asthma at a later age then men may cause them to have a higher perception of airway obstruction during an exacerbation (Burdon et al. 1982). Other studies have shown that female sex, along with younger age and more severe airway responsiveness, is associated with an increased perception of airway obstruction (Brand et al. 1992). In contrast, Boulet and colleagues (1994) found that high or low perception of obstruction and breathlessness were similar across age, gender, and baseline level of airway obstruction and responsiveness.

Psychosocial issues as related to gender differences in symptom experience and health care utilization have not been explored in detail. Studies that have explored these issues in adults with asthma have demonstrated that women, compared to men, more often exhibit elevated levels of psychological distress and anxiety (Belloch et al. 2003; Tovt-Korshynska et al. 2001). These elevated levels of distress occur across all levels of clinical severity and duration of asthma and are often reflected in somatic and psychological complaints, such as dyspnea, insomnia, and lack of energy (Belloch et al. 2003). These findings suggest that women react to the presence of the disease and the somatic symptoms of their psychological distress and not necessarily the severity of the disease. In contrast, levels of distress in men have been shown to increase as the clinical severity and duration of the disease increases, demonstrating that they react to the physiological exacerbation of the disease (Tovt-Korshynska et al. 2001).

Other hypotheses regarding the source of the gender differences in symptom experience and health care utilization have been proposed. One hypothesis is that women are more aware of, and attentive to, bodily changes than men (Redline and Gold 1994) and thus may be more likely to seek clinical help for less severe asthma symptoms. It has also been suggested that gender differences in health care utilization may result from men being more reluctant to seek health care and/or acknowledge symptoms until the severity of the exacerbation has reached a point that it is unable to be ignored (Cydulka et al. 2001). Further investigation of these hypotheses will be important in developing a greater understanding of gender differences in symptom experience and subsequent health care utilization. Clark et al. (2007) have demonstrated that an asthma disease-management program targeted to women with asthma can improve women's quality of life ($p=0.0005$), self-regulation ($p=0.03$), and asthma self-efficacy ($p=0.001$).

Discussion

The majority of asthma research with women, similar to other health research with women, has focused on the biological mechanisms that influence the onset and

course of asthma, primarily changes in sex-steroid levels. These studies have had conflicting findings, but it is clear that fluctuations in sex-steroid levels, whether because of exogenous or endogenous hormones, are associated with changes in asthma severity in many women. However, *the direction* of the change is inconsistent, and thus there may be additional biological factors underlying these relationships that have yet to be determined. The existing research base is limited by the lack of prospective studies examining women at different stages of the menstrual cycle; at all phases of pregnancy, both pre- and postpartum; and at menopause and its transitions.

Given that asthma exacerbations reported during pregnancy may be due to women's decreased medication usage, more research is needed to examine women's gendered responses to motherhood and pregnancy. The increasing focus on in utero influences on fetal development and health can be embodied by women as a "blame the mother" mentality. Medical and societal strictures on women in relation to alcohol use, smoking, food intake, and drug and medication use during pregnancy, and now even pre-pregnancy, are increasing and can carry social stigma and even criminal penalties. These social strictures have resulted in some women being tested for drug use without their knowledge or consent and then being arrested for child abuse (Dailard and Nash 2000). In Oklahoma, the state took custody of a woman's fetus because she was found in an environment where drugs were manufactured. Despite the fact that the woman tested drug free, she was incarcerated where ironically she was denied milk and prenatal vitamins for 2 weeks (Cooper 2003). While these are admittedly extreme cases and focus on women who are poor and often African American, at the other end of the spectrum are upper middle-class White women who continue to drink alcohol during pregnancy (albeit at reduced rates) with the endorsement of their physicians (Moskin 2006). Given these double standards, societal norms about motherhood, and persistence advice from physicians, websites, and pregnancy books to avoid medications that are contraindicated during pregnancy, (Andrade et al. 2004) it is understandable that women may respond in a manner that they perceive to be protective or conservative, with the result that women choose to avoid all medications, even those that may be deemed safe such as inhaled corticosteroids. In that context, the decreased use of asthma medications during pregnancy is a logical gendered response.

Similarly, women's use of HRT has gendered connotations. Many women approach menopause with concerns about their appearance and sexuality deteriorating when they are surrounded by a culture that values youth and beauty. For years, HRT was marketed as the wonder drug to forestall aging and sexual decline. With new research that now highlights the negative effects of HRT on women's health and risk profiles, we have seen large numbers of women stop taking HRT with a corresponding drop in the incidence of breast cancer (Clarke et al. 2006). This decline in HRT use increases the need to understand the relationship between the perimenopause and menopause transition, and asthma, now that these conditions will be uncomplicated by HRT use.

Gender influences how and when women access the health care system. In contrast to other research that demonstrates that women tend to delay seeking health care treatment, such as with myocardial infarction (Rosenfeld et al. 2005; Schoenberg et al. 2003) and stroke (Mandelzweig et al. 2006), where delay is associated with more severe cases of disease and thus the need for hospitalization and emergency care, the research on asthma suggests that women are more likely to seek health care with only mild or moderate asthma flare-ups. However, women are still more likely to be hospitalized than men who have more severe asthma. This finding has gender implications, both on the part of the patients and their symptom interpretation, but also the physicians who admit them. The role of the physician and potential gender bias with respect to asthma has not been studied.

Possibly the most troubling gap in the research on women and asthma is the lack of research on African American women who have asthma mortality rates that are reportedly 2.5 times higher than white women (National Institute on Allergy and Infectious Diseases 2001). The most recent statistics available on asthma mortality rates for black females indicate that black women over age 65 had the highest crude asthma mortality rates (Moorman and Mannino 2001), but these numbers are now over a decade old. Given the number of co-morbidities that African American women have, the low socioeconomic status of many of these women, and lack of health care access, all of which are significantly associated with asthma, this population subgroup deserves special attention in order to reduce the health disparities associated with asthma morbidity and mortality.

Future asthma research needs to address multiple methodological issues such as the reliance on self-reports as opposed to clinical measures of respiratory function; the lack of prospective studies examining natural sex-steroid transition points; and the need to test various formulations of HRT and oral contraceptives including monophasic and triphasic pill formulations (Haggerty et al. 2003); and the myriad hormone delivery mechanisms (pill, patch, and cream) now available to women. In sum, research on women and asthma is still in its infancy with many avenues yet to be explored. These issues are unfortunately becoming more, not less, complicated as we untangle sex differences from gender differences in women's health research.

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