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It's all about sex: male-female differences in lung development and disease

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Abstract

Accumulating evidence suggests that gender impacts the incidence, susceptibility and severity of several lung diseases. Gender also influences lung development and physiology. Data from both human and animal studies suggests that sex hormones may contribute to disease pathogenesis or serve as protective factors, depending on the disease involved. In this review, the influence of gender and sex hormones on lung development and pathology will be discussed, with specific emphasis on pulmonary fibrosis, asthma and cancer.

Introduction

Lung disease kills over 349,000 Americans every year and more than 35 million Americans have chronic lung disease [American Lung Association (ALA) lung disease data 2006; www.lungusa.org]. Substantial epidemiological evidence suggests that gender impacts the incidence, susceptibility and severity of several lung diseases. Many studies have addressed the role of hormones in the gender disparities of pulmonary conditions. Some studies point to developmental and physiological differences as playing roles. We will first review evidence for gender differences in lung development and then address gender differences in the prevalence and severity of several lung diseases utilizing data from both human and animal studies.

Lung Development

Sex hormones appear to exert regulatory effects on human lung development before and during the neonatal period. The androgen receptor is expressed in mesenchymal and epithelial cells of the lung throughout the human lifespan [1], and branching morphogenesis of human lung may be regulated in part by androgens [1]. Estrogen receptors α and β (ER α and ER β) are also expressed in human lung [2]. Sex differences are also manifested in expression of key genes. For example, surfactant production appears earlier in female than in male neonatal lungs [3]. The earlier appearance of surfactant in female neonatal lungs favors patency of small airways and airspaces and may contribute to their higher airflow rate and lower airway resistance compared to neonatal males [4]. In preterm infants, surfactant deficiency is a major contributor to the development of respiratory distress syndrome (RDS) [3]. Male neonates have an elevated risk of developing RDS and of mortality due to RDS compared to female neonates [5]. Female lungs tend to be smaller and weigh less than those of males and, on average, may contain fewer respiratory bronchioles at birth [6]. The number of alveoli per unit area and alveolar volume do not differ between boys and girls, but boys have larger lungs than girls [6]. Thus, the total number of alveoli and alveolar surface area are larger for boys than for girls of a given age.

Whereas large airways tend to grow faster than parenchymal tissue in young females, the growth of large airways tends to lag behind that of the parenchyma in young males in a phenomenon known as dysanaptic growth, resulting in relatively narrower airways in young males than in young females [7]. Maturation of the airways and lungs continues through childhood and into adolescence during which time, for the most part, males continue to have larger lungs than females. Further, the conducting airways of adult males are larger than those of adult females, even when lung or body sizes are equivalent [8]. Minor changes in lung structure and development can have a major impact on respiratory health in later life. As sex and sex hormones are critical modulators of normal human lung development and maturation, greater emphasis should be placed on further understanding the processes involved.

Considerable experimental animal data support a role for sex hormones in regulating lung development. Androgens and estrogens have been shown to exert inhibitory and stimulatory effects, respectively [9]. Androgens inhibit fetal lung surfactant production in a variety of species [9] by a mechanism involving alteration of epidermal growth factor and transforming growth factor- β (TGF- β) signaling events [10]. Adult female mice and rats have more and smaller alveoli than males of the same species [11] thereby providing them with larger alveolar surface area to body mass ratios, whereas adult male mice have larger absolute lung volumes than females but smaller volume to body mass ratios [12].

The formation and maintenance of a full complement of alveoli in females dependent on estrogens and has been shown in mice to be mediated by ER α and ER β [12]. Genetic deletion of ER α or ER β decreases the number and increases the size of alveoli in mice [12,13], and these changes are more prominent in females than in males [12]. In particular, the alveolar abnormalities in ER β -deficient mice have been proposed to be mediated by alteration of platelet derived growth factor (PDGF) and granulocyte macrophage colony stimulating factor (GM-CSF) activity [13], resulting in defects in alveolar structure and surfactant production. Thus, gender and sex hormones influence lung development and the implications are particularly significant for preterm infants. Estrogen and both ER α and ER β are critical for alveolar development, and studies support an inhibitory role for androgens in surfactant production.

Fibrosis, Other Interstitial Lung Diseases and Idiopathic Pulmonary Arterial Hypertension

Gender differences exist in the prevalence of interstitial lung diseases. Idiopathic pulmonary fibrosis is more prevalent in men than in women [14,15] (Figure 1A), but whether this difference is directly due to or modified by sex hormone effects is unclear.

Lymphangiomyomatosis (LAM) is a rare pulmonary condition affecting primarily young women of childbearing age [16]. Various anti-estrogen strategies have been used in the treatment of LAM and, currently, progesterone is the most commonly used hormone treatment for LAM [17]. Chronic obstructive pulmonary disease (COPD), which may display features of chronic bronchitis and/or emphysema, is characterized by airflow limitation that is not fully reversible. Historically, COPD has been more prevalent in men than in women due at least in part to the higher smoking rates in the former. However, the recent increase in smoking trends in women throughout the world has resulted in increased numbers of women with symptoms of COPD [18]. Interestingly, there is also a preponderance of women in the small percentage of people with COPD that are nonsmokers [19], indicative of a potential predisposition to this disease in females. One contributing factor could be increased environmental tobacco smoke exposure in women which has been reported in different populations [20,21].

Idiopathic pulmonary arterial hypertension (IPAH), a pulmonary vasculopathy of unknown etiology, predominantly affects females [22]. Recent therapies such as epoprostenol, bosentan and sildenafil have been directed at the arterial vascular bed to induce vasodilatation and reduce

pulmonary vascular resistance. A recent review by Smith and colleagues suggests that sex hormones, in particular testosterone which has known vasodilatory effects in both the coronary and pulmonary circulation, should be considered as potential treatments for IPAH [23].

While a reliable animal model that displays the morphological and functional aspects of COPD has not yet been established, female mice exposed to cigarette smoke have been shown to develop emphysematous-like changes in alveolar structure and related alterations of pulmonary function more rapidly than males [24]. Rodent models of pulmonary fibrosis have been studied for years, and a gender difference in experimental pulmonary fibrosis in rats was recently reported in that females displayed greater fibrosis than males in response to intratracheal bleomycin [25]. In a bleomycin model, ovariectomized female rats displayed less fibrosis than sham-operated controls and estradiol replacement restored the fibrotic response to that of the intact female mice [25]. Lung fibroblast studies suggested that the pro-fibrotic effect of estradiol was mediated by increased procollagen 1 and TGF- β 1 mRNA expression [25]. Contrary to these findings, a greater degree of pulmonary fibrosis has been observed in male than in female C57BL/6 mice in response to bleomycin as determined by histological assessment, although a thorough analysis of other fibrotic endpoints was not performed in this study [26]. These sex-specific differences in bleomycin-induced fibrosis potentially result from differential expression and/or activity of bleomycin hydrolase, a fibrosis susceptibility candidate gene expressed in lungs [26]. In our laboratory, we have observed gender differences in lung function decline in bleomycin-treated C57BL/6 mice in that males display greater declines in static compliance than females (Voltz, Card, Carey and Zeldin, unpublished observation). Whether these observations are the result of androgenic, estrogenic or a combination of sex hormone effects remains to be elucidated. To the best of our knowledge, no clinical studies to date have addressed the therapeutic potential of hormonal manipulation in fibrotic lung disease.

Asthma

Evidence from several studies suggests a role for sex hormones in the pathogenesis of asthma. Among the general population, asthma prevalence is higher in women than men [27]. However, several clinical studies point to distinctive changes in the prevalence and severity of asthma with age. Male children have asthma more frequently [28,29]. However, in and around the time of puberty, there is a reversal of this incidence and a female predominance exists [29]. Later in life around the 5th or 6th decade, the differences between the sexes disappear and some reports suggest an increase once again in male prevalence [28,30]. An examination of data from the third National Health and Nutrition Examination Survey (NHANES III) illustrates the interaction between sex and age in the prevalence of current asthma (Figure 1B) [28]. Researchers conducting observational or experimental studies in asthma should take into consideration the sex-age interaction. For example, an environmental intervention study that follows young children into the teen or early adult years could be affected by the natural rise of asthma incidence in females or fall of asthma incidence in males. Thus, the sex-age interaction adds a further layer of complexity to the study of effects of sex and sex hormones in asthma.

Female reproductive processes such as pregnancy and menstruation impact asthma suggesting a major role for the female sex hormones. Studies have suggested that respiratory function is influenced by female sex hormones and menstrual cycle phase [31,32]. As many as 20% of women with asthma have exacerbations which require medical intervention during pregnancy [33]. Up to 40% of female asthmatics report perimenstrual worsening of asthma [34]. Many studies link deviations in levels of progesterone and/or estrogen to premenstrual asthma. For example, Rubio and colleagues examined the blood concentrations of estradiol, progesterone and cortisol on the 5th day and 21st day of the menstrual cycle and found that at least one

hormone was out of range in 80% of the asthmatics [35]. Other studies have linked sex hormones with premenstrual asthma via their effects on cells and cytokines involved in inflammation and the asthmatic response [36]. A limited number of studies have associated oral contraceptive or exogenous estrogen use with improvement in lung function and asthma symptoms [37]. One theory suggested to explain this beneficial effect is that hormonal contraceptives reduce the degree of hormonal fluctuation during the menstrual period thereby eliminating the cyclical fluctuations in lung function and symptomology [38]. Conclusions are divided on the effects of hormone replacement therapy (HRT) in asthma. It has been shown that postmenopausal hormone therapy increases subsequent risk of asthma [39,40]. On the otherhand, studies have demonstrated that HRT is associated with better lung function [41, 42]. Girls with Turner's syndrome, which is characterized by low circulating estrogen levels, have increased airway responsiveness, which is significantly reduced after estrogen therapy [43].

There is a strong association between pre-existing obesity and the risk of adult onset asthma with the effects being greater in females than males [44,45]. Obesity is associated with higher estrogen levels and this is thought to occur as adipose tissue contains the aromatase enzyme which converts androgens to estrogens. The increased estrogen levels associated with obesity are thought to be one mechanism to explain the strong association between female obesity and adult onset asthma [45].

Airway hyperresponsiveness to cholinergic agents is a cardinal feature of asthma. Gender differences exist in airway responsiveness to cholinergic stimulation, with most studies reporting greater sensitivity to inhaled methacholine in females than in males [46,47]. However, it has been suggested that this disparity can be explained, at least in part, by taking the relative differences in lung and airway sizes into account [48,49]. Cholinergic airway responsiveness is markedly different in male and female mice. Males of the C57BL/6 and BALB/c strains are more sensitive than females to inhaled methacholine as determined by greater changes in total respiratory system resistance, elastance and other mechanical parameters [50]. This gender difference appears to be due to in vivo effects of androgens on vagus nerve-mediated reflex pathways and not to differences in innate responsiveness of airway smooth muscle [51].

Several ER gene polymorphisms have been reported to be associated with various diseases including inflammatory diseases, rheumatoid arthritis and coronary heart diseases. Recently, Dijkstra and co-workers reported that ER α polymorphisms are associated with airway hyperresponsiveness and lung function decline, particularly in female subjects with asthma [52]. We recently found that in the absence of immunologic stimulation, ER α deficient (α ERKO) mice exhibit substantially enhanced airway responsiveness to inhaled methacholine compared to wild type mice, suggesting that ER α is a critical regulator of this process [53]. Studies have also revealed a role for male sex hormones in airway hyperresponsiveness. Our laboratory recently demonstrated that following LPS exposure, male mice develop greater airway hyperresponsiveness and airway inflammation than female mice and that these effects were mediated by testosterone [50]. Conversely, studies have also suggested a protective role for testosterone in a mouse model of allergic airway disease [54]. Males showed less airway inflammation than females and castrated males performed like the females. These contrasting findings may be due to differential effects of testosterone on the innate versus adaptive immune system. In summary, it is clear that gender and sex hormones have a major impact on the prevalence and severity of asthma. However, the many discordant results complicate and highlight the complexity of the underlying mechanisms. Further population studies examining the association of ER gene variants, hormone levels or hormone interventions with asthma may yield greater understanding of underlying mechanisms and direct future therapeutic strategies.

More mechanistic animal studies focused on the effector pathways modulated by sex hormones are also prudent at this time.

Lung Cancer

While lung cancer mortality in men appears to have plateaued, the mortality rate in women has skyrocketed in the last 30 years, increasing 4-fold since 1970 [55]. However, rates of diagnoses and deaths from lung cancer are still greater in men than women (Figure 1c). While cigarette smoking is certainly the primary cause of lung cancer, an estimated 15,000 lung cancer deaths per year occur in never-smoking individuals [56]. Among these never-smoking individuals, it was long thought that women were more likely than men to develop lung cancer [57], although recent studies indicate that this may not be the case [56]. As mentioned earlier, one contributing factor could be increased environmental tobacco smoke exposure in women, which has been reported in different populations [20,21]

Epidemiological studies indicate men and women tend to develop different histological types of lung cancer, with squamous cell carcinoma, small cell carcinoma, and adenocarcinoma accounting for between 80-90% of the total lung cancers around the world [58]. Squamous cell carcinoma is the most common type among men in the United States, while adenocarcinoma is the primary type diagnosed in women [59]. The male:female rate ratios for squamous cell carcinomas varies substantially with geography, with males being anywhere from 3-50 times (depending on populations studied) more likely than females to be diagnosed with this particular type of lung cancer [58]. Women are also at higher risk than men of developing small cell carcinomas and bronchioalveolar carcinomas [57].

Since smoking is the overwhelming cause of lung cancer worldwide, in the discussion of lung cancer risk an important question is whether or not women are more susceptible to the damaging effects of tobacco smoke. Despite extensive research into this question, no consensus has been reached. A number of thorough reviews and discussions on this topic have been published recently [59-62], and the findings of those reviews are summarized here. Case-control studies of smokers regularly report that women are more susceptible to the carcinogens in cigarette smoke than men [62]. However, several cohort studies have indicated that there is no sex difference in susceptibility [62]. Furthermore, a large scale study has recently found that no difference in male: female lung cancer rates exists in non-smokers, reviewing nearly 1,000,000 adults enrolled in cancer prevention study cohorts [56]. However, it is likely that many of these studies are confounded by the effects of passive smoking and under-reporting of smoking habits, thus the question of whether there are sex differences in lung cancer risk is still an open one.

Other than smoking, factors that vary with regard to gender may impact the susceptibility of men and women to lung cancer. A recent meta-analysis reveals higher rates of human papillomavirus (HPV) infection in women versus men [63]. HPV is a well known critical factor in the development of cervical cancer, but recent evidence indicates HPV may also be involved in the development of lung cancer. HPV infection of lung tissue was found to be associated with increased rates of lung cancer in distinct populations, including Iran [64], China [65], Latin America [66], and Taiwan [67]. These findings, along with the potential impact of the HPV vaccine on lung cancer development, warrant further investigation.

Despite the uncertainty regarding women's susceptibility to lung cancer, female gender has long been observed to be a positive prognostic factor regardless of lung cancer type, stage and therapy [55,59,61]. Not only do women respond better to surgical and chemotherapeutic therapy, their risk of operative mortality is substantially lower than males [68] Whether these differences are of a biological, social, behavioral, or environmental nature remains unclear, and these issues are difficult to tease out epidemiologically in the human population because

of the continued confounding presence of cigarette smoking. As such, populations not exposed to cigarette smoke should be important focus of recent lung cancer research.

Recent studies highlighting links between hormone signaling and lung cancer may provide some insight into why women have a better prognosis for lung cancer than men. Kawai *et al* found that increased tumor expression of ER α was a negative prognostic factor in non-small cell lung cancer while the absence of ER β tumor expression was also a negative prognostic factor [69]. Meanwhile, other researchers found that tumor expression of the progesterone receptor was a potent positive prognostic factor [70], demonstrating that progesterone significantly suppressed cell proliferation in progesterone receptor-positive tumor cells. While at this point there is no clear consensus on the role of the hormone receptors in predicting lung cancer prognosis, the cited publications suggest that circulating female hormones may function to slow the growth of receptor positive tumors. Research is actively being pursued to more clearly define the role of the hormone receptors in lung physiology as well as pathology.

Summary

Gender plays a major role in both the healthy and diseased lung from very early life onwards. As summarized in Figure 2, sex hormones exert regulatory effects on lung development, physiology and pathology. Gender also impacts airway inflammation and the prevalence and severity of many major lung diseases including pulmonary fibrosis, asthma and lung cancer (Figure 2). The gender differences discussed in this review highlight the importance of considering sex hormones in the prevention, diagnosis and treatment of pulmonary diseases. In addition, gender should be considered as a factor when designing both human and animal pulmonary research studies. Whether hormonal manipulation may be therapeutic in defined patient populations remains an important issue to be defined.

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Glossary

Airway hyperresponsiveness

an increased sensitivity of the airways to an inhaled constrictor agonist and a characteristic feature of asthma

Bleomycin

an antibiotic produced by the bacterium *Streptomyces verticillus* used as an anti-cancer agent. The most serious complication of bleomycin is pulmonary fibrosis. It is used to induce experimental fibrosis in laboratory animals.

COPD

chronic obstructive pulmonary disease is a group of diseases characterized by limitation of airflow that is not fully reversible. It includes chronic bronchitis and emphysema.

Methacholine

a synthetic choline ester that acts as a non-selective muscarinic receptor agonist in the parasympathetic nervous system. The primary clinical use of methacholine is to diagnose bronchial hyperresponsiveness.

Pulmonary Fibrosis

a chronic, progressive interstitial lung disease that causes inflammation (swelling and irritation) and fibrosis (scarring) of the lungs

Pulmonary Surfactant

a complex substance containing phospholipids and a number of apoproteins. Surfactant is produced by the Type II alveolar cells, and lines the alveoli and smallest bronchioles. This fluid reduces surface tension throughout the lung and stabilizes the alveoli.

Figure 1.

A The interaction between sex and age in the prevalence of current asthma. The smoothed curves suggest that the increased relative risk of asthma among females during the adult years is due to a loss of asthma among males and an increased incidence among females. Source: the third National Health and Nutrition Examination Survey (NHANES III) [28]. **B** Gender differences in mortality rates from pulmonary fibrosis in the US in 2003. Source [15]. **C** Gender differences in US Lung Cancer Diagnoses and Deaths in 2003. **Source:** U.S. Cancer Statistics Working Group. United States Cancer Statistics: 2003 Incidence and Mortality. Atlanta (GA): Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute; 2007.

Figure 2.

Summary of the known effects of testosterone and estrogen in the lung. (+) indicates positive effect, (-) indicates negative effect, (+/-) indicates conflicting data, (?) indicates unknown effects.