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Review

Asthma and gender: The female lung

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ABSTRACT

Asthma is a common chronic disease that affects over 300 million people worldwide, resulting in a considerable socio-economic burden.

Literature data suggest that asthma has a higher incidence in females, particularly at certain stages of pubertal development. Moreover, women seem to experience more asthma symptoms than men and to use more rescue medications, resulting in a reduced quality of life.

Although several mechanisms have been proposed to explain these differences, there are not yet final data available in the literature on the role of gender in the pathogenesis of asthma and different behavior in females.

Some study suggested a more prevalent hyper-responsiveness in women than in men. Nevertheless, in the literature definitive data on a possible different response to drugs used for asthma between males and females are not described.

Understanding the mechanisms that underlie these gender differences in clinical history of asthma patients could give inspiration to new areas of research to obtain a more specific diagnostic and therapeutic approach gender-oriented.

Contents

Abbreviations: FEV1, forced expiratory volume in the 1st second; FVC, forced expiratory volume; PD20, provocative dose of methacholine.

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1. Introduction

Asthma is a common chronic disease that affects over 300 million people worldwide, resulting in a considerable socio-economic burden. The incidence of asthma is increasing with a rise from 3.6% in 1980 to 8.2% in 2009 [1].

In 2010, asthma resulted in 1.8 million emergency department visits and 439.000 asthma-related hospitalizations determining high healthcare costs [2].

Under the Severe Asthma Research Program (SARP) the gender difference in asthma incidence, prevalence and severity was assessed [3]. Between the age of 4 and 14 years, asthma is more prevalent in boys compared to girls (11.5 vs. 9.9%). However, after puberty, asthma becomes more prevalent and severe in women [4]. Interestingly, after the menopause asthma becomes once again more severe in males [5]. Moreover, female patients have reported to experience more symptoms and more asthma episodes when compared to males with the same baseline pulmonary function tests, resulting in a poorer quality of life and increased utilization of healthcare systems [4].

Even though gender-related differences in asthma prevalence, pathophysiology, clinical features and response to treatment have been described, mechanisms underlying this phenomenon have not yet been elucidated.

Several factors have been described to be associated with increased bronchial reactivity in asthmatic people, such as atopy, smoking, and reduced pulmonary function at rest. Hormones might play a crucial role in this phenomenon. However, no definitive data is at present available in literature.

It is known that hereditary factors are associated with an increased risk of allergic asthma in childhood. To better understand the potential hereditary mechanisms, the scientific community is opening up to a new field of research that aims to analyze the influence of the prenatal period on the risk of developing asthma.

Prenatal stress is a determinant in impairing maternal endocrine adaptation to pregnancy [6] with a decrease of maternal progesterone levels in response to stress. Progesterone among other endocrine factors, such as estradiol, is important in promoting and sustaining pregnancy and therefore fetal development [7]. Lower levels of maternal progesterone during pregnancy seem to be associated with an increased risk of allergic airway diseases in females only. In this context, Vargas et al. [8] tried to evaluate the effects of prenatal stress in mice exposed to an asthma model during pregnancy. Pulmonary function and inflammatory profile were analyzed. The development of asthma was reduced in adult female mice during prenatal stress, showing an improved pulmonary function and a lower inflammatory response in the lungs. This phenomenon further supports the role of hormones in the pathogenesis of asthma.

Considering this background and given the lack of definitive data, the aim of this article is to provide a state-of-the-art review to fully clarify the role of gender in asthma, also in order to identify possible areas for future research.

2. Differences in asthma epidemiology and severity

Several epidemiological studies have addressed gender differences in asthma prevalence (Table 1).

Female patients have been reported to have a higher asthma prevalence than males (9.2% compared to 7.0%). Differences in health care encounters between men and women have not been reported [9,10].

Patients hospitalized for asthma are up to three times more likely to be female for age >15 years old and up to two times more likely to be male for age <15 years old [11].

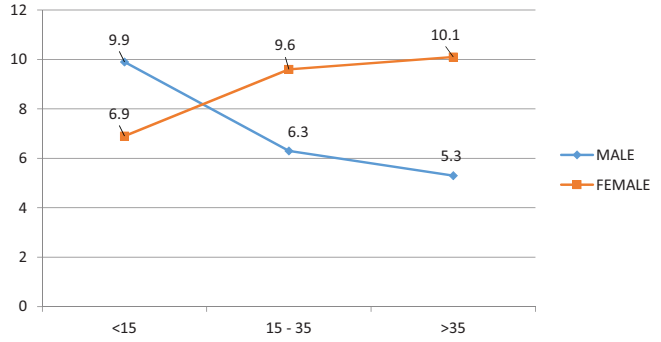

Fig. 1. Asthma prevalence per age and gender in the National Health Interview Survey, United States [15].

Moreover, women admitted to the emergency room with a severe asthma attack are hospitalized more frequently than men, despite better pulmonary function and better oxygen levels. The difference in hospitalization rate doesn't seem to be related to the poorer use of medication by women [11,12].

Data from the American Lung Association showed that among adults >18 years, females were 62% more likely to develop asthma than males. The overall prevalence rate in women (97.3 per 1000 persons) was 35% higher than the rate in men (71.9 per 1000 persons); moreover, female patients were more likely burdened with mortality. In 2009, 3388 people died of asthma, and 64% of these deaths occurred in women. The female mortality rate was even higher when adjusted for age [13].

Thus, according to Center for Disease, control, and prevention, the prevalence of asthma is confirmed to be higher in adult women than in men [10].

However, this pattern is reversed among children. Childhood asthma tends to be predominantly a disease in males, with the relative male prevalence being maximal at puberty.

Specifically, asthma seems to be more prevalent in boys <18 years old, while its prevalence and severity increases in women after puberty, becoming more frequent in women older than 20. After age 20, asthma prevalence remains approximately equal until age 40, when the disease becomes more common in females [14].

The current asthma prevalence rate for boys ≤18 years old reported from the American Lung Association is 16% higher than the rate among girls [13].

In 2009, estimates from the National Health Interview Survey in the United States demonstrated that asthma prevalence was lower in 15 years old girls than in boys, while the pattern shifts in the young adult of 15–35 years old with a higher prevalence in women (6.3% in men and 9.6% in women). This difference persists in adults older than 35 years (5.6% versus 10.1% in men and women, respectively) [15] (Fig. 1).

Similar results have been shown in European studies evaluating the prevalence of asthma by age [16].

Asthma is characterized by 'airway hyper-responsiveness' to inhaled allergens [17] and other chemical stimuli including histamine, bradykinin, serotonin, prostaglandins, methacholine and acetylcholine as well as other triggers such as exercise, deep inhalation and inhalation of cold air [18]. Bronchial hyper-responsiveness is most often established with inhaled methacholine, but histamine, exercise, voluntary hyperventilation or inhaled mannitol may also be used as bronchoprovocative agents.

To test this hypothesis Leynaert et al. compared the frequency of bronchial hyper-responsiveness in men and women of 20–44 years of age and investigated the possible reasons for any differences observed. In the first part of the study, 9.918 people were randomly selected from the electoral rolls of Paris and Montpellier and were sent a self-administered questionnaire on asthma and

Table 1
Gender- and age-related prevalence of asthmatic patients.

	Female prevalence	Male prevalence	Prevalence during childhood	Prevalence after puberty
National Center for Health Statistics data brief [8]	9.2%	7%	Male > Female	Female > Male
American Lung Association [12]	9.73%	7.19%	Male > Female	Female > Male
Center for Disease, control, and prevention (CDC) [9]	10.4%	6.5%	Male > Female	Female > Male

asthma-like symptoms. In the second step, 799 lung function tests, including methacholine challenge and allergen skin tests were performed. Patients were categorized as reactors with a decline in FEV1 of 20% at the provocative dose of methacholine (PD20) <4 mg. They didn't notice significant differences in the prevalence of asthma symptoms between women and men. Men showed a higher baseline FEV1 than women, but they didn't have differences in the FEV1%FVC ratio. The prevalence of PD20 4 mg was higher in women than in men (odds ratio [OR] 3.77, 95% confidence interval [95% CI] 2.37–6.00 in Paris; OR 1.82, 95% CI 1.14–2.93 in Montpellier). This sex difference was not abolished after adjusting for asthma symptoms, height, body mass index, and lung function variables [19].

A Canadian study was performed to better understand the gender and geographical differences in asthmatic patients. In all Canadian sites, bronchial hyper-responsiveness was more prevalent in women than in men. They observed that variability in bronchial responsiveness was described in the different sites participating in the ECRHS study, but neither the geographical nor gender differences were related to any differences in age, smoking habit, skin test reactivity or baseline FEV1. They hypothesized that while sex differences could be explained by hormonal factors, geographical differences could be related to the environment [20].

Reasons for gender differences are still unclear. Possible explanations could include multiple factors, such as the well known anatomical, hormonal or smoking-related differences on the airway system, which are discussed in the following paragraphs.

2.1. Anatomical differences

Data emerging from post-mortem studies report that female lungs are smaller and lighter than male lungs. The structure of the lungs is a determinant of their ventilatory function. This data is confirmed even when matched for height. Particularly, female lung volumes seem likely to be related to a smaller total number of alveoli, as demonstrated by post-mortem examination of lungs obtained from boys and girls [21].

Despite the lungs of women and girls being smaller than men and boy's, they exhibit higher forced expiratory flow rates (standardizing for differences in body size).

The ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) is lower in boys and men than in girls and women [22].

The principle that people with larger lungs do not necessarily have larger-diameter airways if compared with individuals with smaller lungs was described for the first time in 1974 and is known as 'dysanapsis' [23].

Munakata et al. suggested that although pulmonary dysanapsis does not have a significant relation to airway responsiveness to inhaled methacholine, it could be associated with sensitization to airborne antigens [24].

2.2. Genetic differences on asthma

Asthma is a multifactorial disease and runs strongly in families [25]. Genetic studies are essential to figure out the causes of the disease and to allow the application of specific therapies. With the development of molecular genetic technologies, candidate gene studies are giving insight into different types of studies from the genomic point of view.

In a Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community, multiple markers on chromosome 17q21 were strongly and reproducibly associated with childhood-onset asthma [26,27].

Subsequently, in addition to the previous analyses of childhood-onset asthma, Moffatt et al. conducted an analysis on late-onset and occupational asthma in 10,365 subjects and 16,110 controls recruited from 23 studies. They reported an association between asthma and the single-nucleotide polymorphisms on chromosome 2, 6, 9, 15 and 22, suggesting a communicative role of epithelial damage to the adaptive immune system and activation of airway inflammation. However, the associations highlighted in the study were not significant [28]. Further studies are needed to identify the specific genetic variants that contribute to the disease.

This data helps us understand the remarkable gap between the different response to pharmacological treatments for men and women existent in all fields of medicine. Therefore there is a need for specific gender-oriented pharmacological research to better understand an improved therapeutic approach that is gender-oriented.

2.3. Hormone-related differences

As previously mentioned, the prevalence and severity of asthma are frequently associated with key moments in the reproductive life of women. Accordingly, it has been hypothesized that hormonal fluctuations during the menstrual cycle could play a crucial role in the pathophysiology of asthma, resulting in cyclic worsening of disease severity. Women seem to experience an aggravation of asthma symptoms during the premenstrual or menstrual phases of their cycle. Terms such as perimenstrual asthma (PMA) have been used to describe this phenomenon [29,30].

Matteis et al. showed that FEV1 decreased during the follicular phase of the menstrual cycle in about 30% of women and, precisely, that it was associated with lower cAMP levels in sputum. This mechanistically explains a major bronchoconstriction in this reproductive phase. They also suggested a link between PMA and testosterone levels [31].

Brenner et al. suggested that pre-ovulatory and perimenstrual phases could trigger asthma exacerbations in some women acting as "co-factors" in association to other recognized triggers of acute asthma [32].

However, there is discordant data in literature. Previous studies have shown that changes in pulmonary function and asthma-related symptoms were not related to hormonal changes [33,29], while other data supports the presence of worsening symptoms during the perimenstrual phase, resulting in an increased health care utilization [33].

To explain the mechanisms behind this phenomenon, some studies have been conducted to investigate the inflammatory changes during the menstrual cycle. Markers of inflammation, such as exhaled nitric oxide, sputum eosinophils, and serum leukotriene

C4 concentrations are higher in women who have severe asthma symptoms, emphasizing the possibility that increased inflammatory response is responsible for the worsening of asthma, coinciding with the physiological hormonal fluctuations [34,35].

Data from the Nurses' health study showed that women using postmenopausal hormone replacement therapy had a higher risk of newly diagnosed asthma and worsening of their pre-existent asthma than women without exogenous hormone exposure [36].

Supporting the notion that higher bronchial reactivity in females could be justified by hormones, Matteis et al. analyzed the airway responsiveness to methacholine during the follicular and luteal phases of the menstrual cycle and observed that 30% of asthmatic women had prominent responsiveness to methacholine during the follicular phase. However, these results were not statistically significant. They also noted that in luteal phase of menstrual cycle the levels of serum and sputum testosterone were higher than in the follicular phase, and this correlated with bronchial hyper-reactivity [37].

2.4. Effect of smoking habit

Another factor possibly implicated in the genesis of these sex differences could be tobacco exposure. Smoking is increasing in the general population and particularly in females. Some studies document increased bronchial responsiveness in women smokers compared to men.

Particularly, in a study enrolling 4348 patients from 23 centers in Western Europe and the United States, bronchial reactivity (BHR) was related to smoking habit. Mean BHR was greater in women than in men. A significant difference of BHR was shown between smoking and non-smoking groups ($p < 0.0001$). Data on gender-related differences in smoking subgroups was not available [38].

Female smokers appear to be more susceptible to the effects of tobacco smoke than men. In a study from Dransfield and colleagues, 585 Caucasian and African-Americans patients were enrolled, and it was observed that Caucasian patients had a higher number of pack-years of smoking (57 vs. 43, $p = 0.0003$) than African-Americans. The racial subgroups did not show differences in lung function and BHR. However, the results of this study showed that Caucasians have less decrease in lung function percentage per pack-year smoked than African-Americans (SI = −1.02% vs. −1.34%, P = 0.007) and men less than women (SI = −0.98% vs. −1.21%, P = 0.001).

Caucasian males were quite protected from tobacco smoke, while African-American women appeared more susceptible [39].

Another important aspect to be considered is the effect of tobacco smoke during childhood. In a cohort of 5158 boys and 4902 girls aged 10–18 years, Gold et al. showed that each pack per day of smoking was associated with a reduction in FEF 25–75 of 3.2% in girls (P = 0.01) and 3.5% in boys (P = 0.007). Gold et al. showed how smoking habit in adolescents of the same sex was associated with 1.09% slower growth of FEV1 per year in girls (95% confidence interval 0.70–1.47) and 0.20% slower growth in boys (95% confidence interval, −0.16 to 0.56) if compared with non-smoking adolescents.

They also noted that FEF 25–75 had a 1.25% slower growth per year in girls (95% confidence interval 0.38–2.13) and 0.93% slower growth in boys (95% confidence interval, 0.21–1.65) in the same cohort [40].

3. Differences in asthma symptomatic status

An interesting aspect is that women have a different perception of their symptoms that tends to be more severe, resulting in poorer control of their disease and an increase of treatment and heath care use.

Some studies show that women report more asthma symptoms, analyzed using standardized questionnaires, than men having the same pulmonary function test at baseline, with a consequent poorer quality of life [41]. In an analysis of 1291 patients with moderate to severe disease exacerbations, it was noted that the majority of these patients (62%) were women. Women were more likely to report "severe" complaints regarding symptom frequency, symptom intensity, and following limitation of activity than men (all $p < 0.05$) [42].

Indeed, a longitudinal study showed that in about 914 people aged 3–55 years, half of the younger participants (3–14 yr) reported 0–1 days with symptoms per week. Two-thirds of women aged 15–55 year and men aged 35–55 reported 2 or more days with symptoms per week. Women aged 15–34 year reported more symptoms than men ($p < 0.001$) and, a similar trend was seen in the 35–55 year old group, although this did not reach the statistical significance ($p < 0.083$) [43].

However, differences in duration of symptoms and need of treatments are not reported. Women tend to report their symptoms as more severe than men and, after hospitalization, more than 50% of women refer to persistent dyspnea [44].

Data from the American Lung Association showed that females tend to have a consistently higher attack prevalence rate than males. Specifically, in 2011, 51.6% of women had an asthma attack compared to 34.3% of male. Moreover, the difference in attack prevalence rates between sexes has been significant each year since 1999 [13].

The Center for Disease Control and Prevention reported data regarding asthma attacks in children (age <18 years old) and adults (age >18 years old), where children experienced more asthma attacks than adults (48% vs. 43.6%). But no data on gender-related differences is available [10].

As previously highlighted, the presence of one or more asthma attacks per year is associated with a higher health care use, determining a remarkable socio-economic burden of this disease.

4. Differences in therapy response

Over the last two decades, awareness on asthma heterogeneity has increased. Cluster analysis and observational data have suggested that factors such as environment, genetics, race, obesity, sex, and specific phenotypes may have important implications in asthma symptoms and management. It is still unknown if gender influences the response to therapy.

Many drugs are currently available in asthma therapy, as shown in Table 2, but no different doses between male and female have not been reported, according to current guidelines [45].

Regarding the use of medication, as part of a longitudinal study it was shown that in about 914 people aged 3–55 years, the older participants reported a higher use of medication per day. Accordingly, older patients, in particular females, were more likely to use inhaled corticosteroids ($p < 0.001$), while younger participants were significantly more likely to use cromolyn ($p < 0.001$) [43].

An American cohort analysis focused on gender differences in response to asthma therapy. Data from the National Heart, Lung and Blood Institute's Asthma Clinical Research Network (ACRN) was collected and analyzed [46].

Between 1993 and 2003 10 trials were conducted from the ACRN, a consortium of multiple asthma clinical research centers [47–56]. Data acquired during these studies allowed a thorough analysis of the impact of sex and age on the response to specific treatments in a group of subjects with mild to moderate asthma.

This study cohort consisted of 1200 subjects. Detailed demographic and baseline data was collected and included age, sex, self-reported race, peak expiratory flows, FEV1, bronchial

Table 2
Medication categories for asthma treatment [45].

Controller	Reliever	Add-on therapy
Inhaled corticosteroid (ICS)	Short-acting beta-2-agonists (SABA)	Anti-IgE therapy
ICS/LABA (long-acting beta-2-agonist)	Short-acting anticholinergics (LAMA)	Systemic/oral corticosteroids (OCS)
Combination Leukotriene receptor agonists (LTRA)		Anti-IL5 therapy
Long-acting anticholinergics (LAMA)		Special (phenotype-specific) treatments and interventions by specialized centers
Methylxanthines (theophylline)		
Chromones (practically no longer in use)		

hyper-responsiveness, asthma symptoms, use of asthma rescue medication, and asthma quality-of-life scores.

The primary outcome of the study was to demonstrate differences in gender and/or age in treatment failure rates. They observed only age-related differences, where diversity in treatment failure according to gender was not-identified.

Females showed a slightly higher FEV1 percentage than males (84.5% vs. 81.1%; $p < 0.001$). No other statistically significant differences regarding Ig-E levels, daily symptom score, exhaled nitric oxide levels, β-agonist use, or blood eosinophils were noted.

Despite treatment failures being more common in females (103 of 680 [15.2%] vs. 61 of 520 [11.7%]) than in males, this difference was not statistically significant. A trend toward increased use of asthma rescue medication in females was observed (36.2% vs. 13.1%; $p = 0.051$), but this also was not statistically significant.

In a combined model that looked at age group and gender, there was no difference in the risk of treatment failure between females aged 30 and older and their male counterparts (18.8% vs. 15.3%; $p = 0.267$) [46].

Differences in bronchodilator responsiveness were not clearly identified. Several studies are trying to understand the mechanism underlying gender differences in the prevalence, severity, and approach to treatment of chronic asthma.

A trial which focused on the influence of personality traits and beliefs about medicines in adults with asthma, noted that personality traits might affect adherence to therapy in this specific clinical setting, in particular, some gender differences were observed. In detail, a personality trait called "Neuroticism" was associated with lower adherent behavior in men but not in women. However, beliefs about the necessity of medication, measured through a specific questionnaire (Belief About Medicines Questionnaire) were positively associated with medication adherence in women, but not in men [57].

5. Discussion and future perspectives

Although gender differences have been reported in some clinical asthma characteristics, such as bronchial reactivity or degree of symptoms. So far, only the impact of both gender and age on different prevalence rates has been established [58]. Cyclic hormonal effects are often quoted to explain these differences. Women with asthma may become symptomatic during the premenstrual or menstrual phase with an unclear influence of exogenous hormone therapy on these symptoms. Clarifying this phenomenon would be necessary for the potential implications for an asthmatic patient's treatment. Particularly, considering that women with asthma seem to use rescue therapies more frequently and require regular follow-up visits more often, including those to the emergency department, a gender-related approach could lead to an improvement in clinical management of these patients and, accordingly, a reduction in health-related costs.

The International Guidelines on Asthma (GINA) do not deal with gender differences in preventive, diagnostic or therapeutic approach within the context of the chronic respiratory obstructive disease.

Given the lack of solid clinical data on treatment options for menstrual-related symptoms, the most careful approach could include early identification of potential gender-related triggers and emphasis on patient education regarding the management of these symptoms.

Knowledge of gender-related differences in asthma prevalence and expression is critical in the evaluation and management of all patients with asthma and should be the focus of ongoing research efforts.

Over the years the interest in the different responses to medical therapy between men and women have increased. Patsopoulos N A et al. collected 215 articles from Pubmed to assess whether there was a sufficient internal and external validity in gender differences related to genetic effects. Only 77 articles were eligible (i.e. studies addressing a genetic effect across gender of 1 or more gene variants for any human disease phenotype) and most claims were insufficiently documented or spurious [59]. Collectively from the evidence previously reported, it appears clear that data is needed to clearly elucidate if there are relevant gender differences in the clinical management of patients with asthma. Properly powered and designed studies should be encouraged to address specific research questions that are able to clarify these issues and provide reliable data.

Currently, no specific focus has been given by international guidelines, and no consensus has been reached about possible gender differences in asthma. Future studies are therefore needed to address and clarify this issue properly.

Declaration of interest

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