

Hormones, sex, and asthma



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Key Messages

Clinical, epidemiological, and animal studies suggest that sex hormones are important in regulating asthma pathogenesis.

- A gender disparity exists in asthma and switches at puberty from boys having the highest prevalence as children to women having the highest prevalence as adults.
- Many women with asthma report changes in their symptoms throughout the menstrual cycle, during pregnancy, and in menopause.
- Estrogen signaling promotes and androgen signaling attenuates type 2-mediated allergic airway inflammation in mice.
- Ovarian hormones are important for interleukin-17A-mediated, neutrophilic airway inflammation in mice.

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ABSTRACT

Objective: To summarize the current literature on the sex disparity in asthma and the role of sex hormone signaling in allergic and neutrophilic airway inflammation.

Data Sources: PubMed and Centers for Disease Control and Prevention health surveys were searched.

Study Selections: Clinical and epidemiologic studies in children and adults as well as animal models of asthma were included in this review.

Results: Compared with males, females have an increase in asthma prevalence starting around puberty, and fluctuations in hormones during menstruation, pregnancy, and menopause are associated with changes in asthma symptoms. Animal studies using genetic deletions of estrogen receptors or androgen receptors have shown that estrogen signaling promotes and androgen signaling attenuates allergen-mediated type 2 airway inflammation. Furthermore, animal studies have found that ovarian hormones are important for interleukin 17A-mediated airway inflammation.

Conclusion: Sex hormones are important in regulating asthma pathogenesis. However, additional studies need to be conducted to further elucidate how sex hormones are initiating and driving the inflammatory response(s) in asthma. Determining these pathways will provide the foundation necessary for the development of treatment strategies and potentially new therapeutics for patients, in particular females, with asthma.

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Introduction

Asthma is a chronic, heterogeneous disease that ranges from mild, intermittent asthma to severe asthma. In 2015, asthma affected approximately 18 million adults and 6 million children in the United States.¹ Asthma is characterized by coughing, wheezing, shortness of breath, and/or chest tightness driven by increased airway

reactivity, inflammation, and/or mucous production. Most patients with asthma have allergic airway inflammation characterized by allergen-mediated type 2 mediated airway inflammation.² However, some patients with asthma have low (or no) allergen-mediated type 2 mediated airway inflammation but have increased neutrophils driven by type 1- or interleukin (IL) 17-mediated airway inflammation.^{2,3}

As depicted in **Figure 1**, increased airway inflammation, mucous production, and airway hyperresponsiveness (AHR) are caused by multiple pathways. Initiation of type 2 allergic airway inflammation occurs with exposures to allergens, including house dust mite, pollen, mammalian antigens, cockroach antigens, and/or fungal antigens, and results in increased production of inflammatory cytokines, including thymic stromal-derived lymphopoietin (TSLP),

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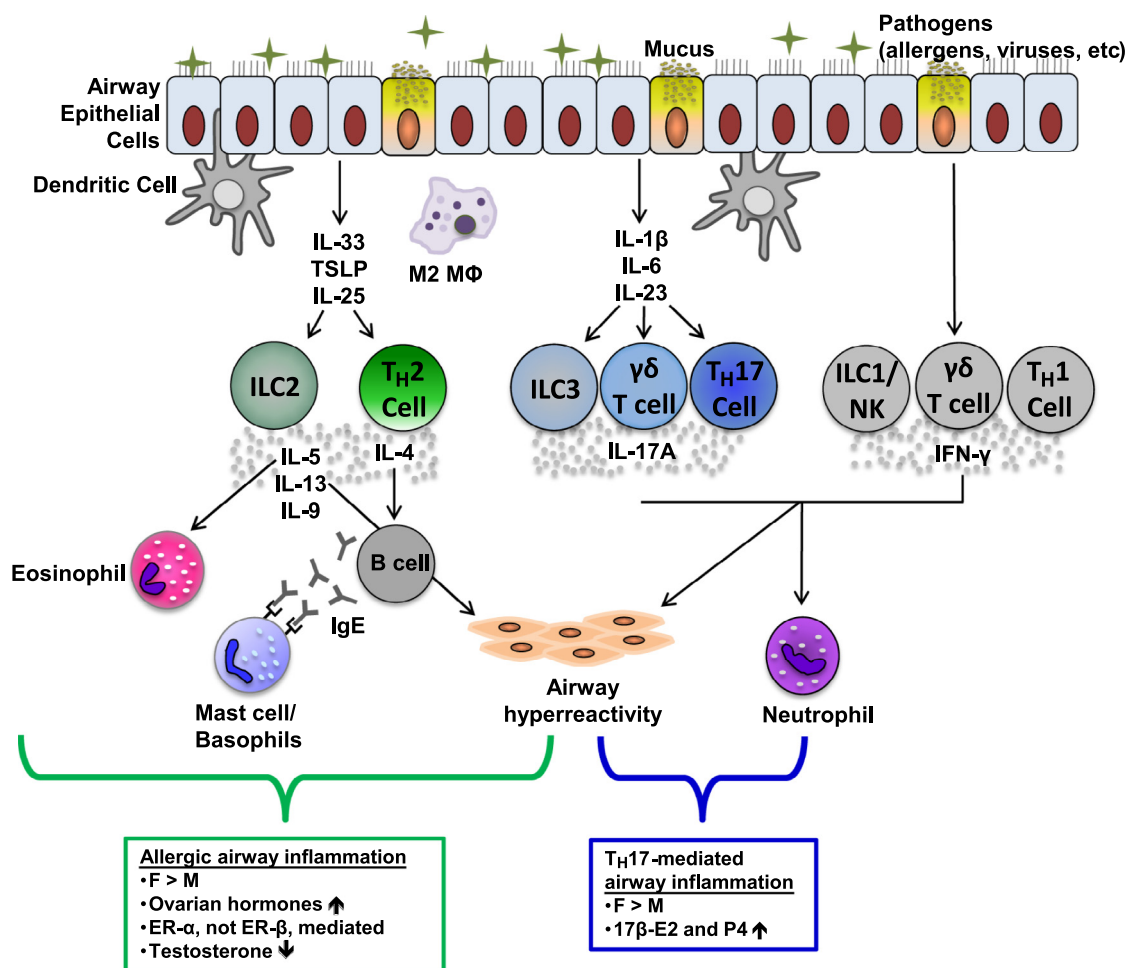


Figure 1. Schematic of allergen-mediated type 2, interleukin (IL)-17A-mediated, and interferon- γ (IFN- γ)-mediated pathways associated with different phenotypes of asthma. Summary of sex differences and the role of sex hormone signaling in allergen-mediated type 2 and IL-17A-mediated airway inflammation are shown in boxes below pathways. E2 indicates estradiol; ER, estrogen receptor; F, female; ILC, innate lymphoid cell; M ϕ , macrophage; M, male; P4, progesterone; TSLP, thymic stromal-derived lymphopoietin.

IL-33, IL-25, and/or IL-4. Increased production of these stimulatory cytokines resulted in increased expression of type 2 cytokines, IL-4, IL-5, IL-13, and IL-9 produced from CD4⁺ T_H2 cells, group 2 innate lymphoid cells (ILCs), eosinophils, basophils, mast cells, macrophages, and other cells. The release of type 2 cytokines results in increased IgE-triggered hypersensitivity to allergens, activation of airway epithelial cells, increased infiltration and activation of eosinophils, and increased airway remodeling.²

In patients with more severe type 1- or IL-17-mediated phenotypes of asthma, neutrophils are increased in the sputum and bronchoalveolar lavage (BAL) fluid. Typically, these patients do not respond well to corticosteroid treatments and have increased morbidity and asthma-related health care costs when compared with patients with milder phenotypes of asthma.⁴ Increased neutrophils in the airway are driven by increased IL-17A-secreting and/or interferon γ (IFN- γ)-secreting cells, including T_H17, $\gamma\delta$ T cells, T_H1, and natural killer cells.^{5,6} In this review, we summarize the clinical, epidemiologic, and animal studies that have a sex disparity in asthma and the mechanisms by which sex hormones regulate asthma pathogenesis.

Sex Disparity in Asthma

A sex disparity exists in asthma and changes with age. As children, boys have an increased prevalence of asthma compared with girls, with increased atopy, wheeze, serum IgE levels, and use of

asthma medications.^{7,8} Several longitudinal studies, including the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, have reported this sex disparity in asthma. PIAMA was unique because it recruited 4,146 pregnant women and assessed 3,308 of their children yearly for wheeze (at 1–7 years of age) and asthma (at 8 years of age) by questionnaires. Starting at 1 year of age and maintained until 8 years of age, boys had an increased cumulative incidence of parent-reported wheeze compared with girls. At 8 years of age, 15.1% of the boys and 10.8% of the girls had asthma,⁷ suggesting that the sex disparity in asthma begins early in childhood. Boys also had increased atopy, measured by specific IgE or skin prick testing to common allergens, compared with girls before adolescence.^{7–12} These findings suggest that atopy and allergen sensitization is greater in boys compared with girls in childhood and may provide some rationale for the increased sex disparity in asthma prevalence in children.

Other differences in immune responses and anatomical differences may also play a role in explaining this observed sex difference in wheeze and/or asthma in boys and girls, when sex hormones are low. Phytohemagglutinin-induced mononuclear cells from boys, compared with girls, had significantly increased IFN- γ at 1 year of life and increased IFN- γ , IL-5, and IL-13 in children who wheezed at 3 years of life.¹³ Furthermore, boys had increased rates of sensitization, total IgE levels, and blood eosinophil counts compared with girls.¹³ Dysanapsis, smaller airway diameters relative to lung volumes, is also detected more often in boys compared with girls.¹⁰

Therefore, a more robust immune response and decreased airway size likely contribute to increased wheezing in young boys compared with girls.

In contrast, as adults, women have an increased prevalence of asthma compared with men. This switch in asthma prevalence coincides with puberty, suggesting that sex hormones are important in asthma pathogenesis.^{14,15} The Childhood Asthma Management Program (CAMP) study determined this sex switch at puberty by longitudinally tracking the mean asthma symptom scores and the progression of puberty, using Tanner puberty stages, in children 4 to 17 years of age.¹⁶ Tanner stage puberty scores characterize predictable changes in puberty using a 1- to 5-point scale, with 1 being prepubertal and 5 being puberty completed, fully mature. Tanner stage puberty scores started to increase in girls at approximately 10 years old, and this coincided with increases in the asthma symptom scores in girls. For boys, Tanner stage puberty scores started to increase at approximately 10 years of age, but the mean asthma symptom scores began to decrease at approximately 14 years of age.¹⁶ Additional studies have also found that early aged menarche (≤ 11 years old) in girls increased the incidence of asthma.¹⁷

After puberty, the sex difference in asthma in men and women may be explained by increased incidence in women. A longitudinal, questionnaire-based study that tracked children into adulthood (10–20 years of age) with asthma ($n = 274$) and healthy controls ($n = 1,000$) determined that at 20 years of age the prevalence of asthma persisted in 24.5% of participants with asthma and remained male dominated in ratio.¹⁸ In the healthy controls, 4.8% of participants had developed asthma by 20 years of age, and most of these patients were female. Atopy, measured by skin prick testing to inhaled allergens at 10 years of age, was not associated with wheeze in the healthy individuals diagnosed with asthma at 20 years of age. Therefore, these findings suggest that the sex switch in asthma prevalence that occurs during adolescence and early adulthood is driven by increased incidence in females over resolution in males with asthma.

Pediatric and adult sex disparities in asthma were also shown in a large, retrospective cohort study using the Kaiser-Permanente care computerized data from 60,694 patients. This study determined that asthma-related health care use and medication use was increased in boys compared with girls from 2 to 13 years of age, was not statistically different by sex from 14 to 22 years of age, and was increased in women compared with men after 23 years of age.¹⁹ This large, health care use cohort study highlights the sex differences in asthma health use throughout life.

All these studies have provided insight into when the highest asthma prevalence begins to shift from boys to women, but additional studies need to be conducted to determine the hormones that are important for driving the observed switch in asthma prevalence. It is important to leverage information on which sex hormones are associated with asthma symptoms, control, and frequency of exacerbations as established pediatric asthma cohorts age through puberty and into adolescence and adulthood. This information will be imperative to further defining the mechanisms of asthma pathogenesis and potential hormonal-related causes to later-onset asthma in females.

Sex Disparity Across Phenotypes of Asthma

The heterogeneity in patients' asthma severity and the mechanisms that drive airway inflammation, mucous production, and/or airway reactivity led researchers to categorize asthma based on phenotypes and endotypes. Unsupervised clustering analyses to identify and categorize asthma phenotypes with similar characteristics using multiple variables have been ongoing in both pediatric and adult asthma populations. Pediatric population cluster analyses using CAMP, the Inner City Asthma Consortium, or The Epidemiology and

Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) studies found that boys had an increased percentage in clusters with more exacerbations and/or lower baseline pulmonary function compared with girls.^{20–22} The CAMP study determined 5 clusters based on atopic burden, degree of airway obstruction, and history of exacerbation. The clusters with the largest percentages of boys (clusters 3–5) also had high airway obstruction, medium to high atopy, and high exacerbation rates compared with clusters with milder phenotypes of asthma (clusters 1 and 2).²⁰ The Inner-City Asthma Consortium Asthma Phenotypes in the Inner City identified 5 clusters from 616 pediatric patients and found an increased percentage of boys compared with girls in all participants. Furthermore, the more allergen-mediated type 2 mediated allergic asthma clusters (clusters C, D, and E in the study) had more boys than girls.²² The TENOR study used hierarchical clustering algorithms and determined clusters in children based on sex, atopic status, smoke exposure, and race. Boys constituted most of the children in all asthma clusters except one cluster that was defined by female sex.²¹

Clustering analysis in adults with asthma determined that women are more likely to have more severe, less corticosteroid responsive phenotypes of asthma compared with men.^{23,24} In particular, women had a higher prevalence than men in a cluster of later onset with less atopy and worse lung function and a cluster of obese, less atopic, and older individuals with asthma in one study.²³ The U-BIOPRED (Unbiased Biomarkers in Prediction of Respiratory Disease Outcomes) cohort, which enrolled patients with asthma ranging from mild to severe, found that women have an increased prevalence in a cluster composed of obese patients with uncontrolled severe asthma and increased exacerbations but normal lung function.²⁵ Furthermore, the European Network for Understanding Mechanisms of Severe Asthma study reported that females were 4.4 times more likely to be classified as having severe asthma than males.²⁶ Cluster analysis of asthma phenotypes in 611 adult patients using primary care practitioners in the Asthma Control Cost-Utility Randomized Trial Evaluation trial also found a female predominance in clusters with patients who have later onset of asthma or more asthma exacerbations.²⁷ Combined, cluster analyses in pediatric and adult asthma populations found that asthma is a heterogeneous disease and that the sex disparity is observed in the more severe or exacerbation prone clusters in children and adults.

Changes in Asthma Symptoms during the Menstrual Cycle

Changes in ovarian hormone concentrations each month and through the reproductive years of a women's life have provided valuable insight into the role of sex hormones on asthma control and exacerbations. Early studies reported worsening of asthma symptoms, decreased peak flow rates, and increased use of rescue medications in 30% to 40% of women with asthma during the premenstrual or perimenstrual phase of the cycle.^{28–32} Sputum eosinophils and fractional exhaled nitric oxide were also increased during this premenstrual phase when compared with just after menses (seventh day of cycle).^{33,34} Furthermore, increased oral corticosteroid bursts and increased emergency department visits were reported in the Severe Asthma Research Program study in women who had perimenstrual worsening of asthma compared with women without perimenstrual worsening of asthma.³⁵ These studies suggest that premenstrual asthma affects many women with asthma, but additional studies of patients with mild to severe asthma reported no differences in the asthma-related emergency department visits in any phase of the menstrual cycle.^{36,37} Furthermore, Juniper et al³⁸ determined that asthma symptoms were increased during menstruation but that medication use and forced expiratory volume in 1 second (FEV₁) in response to methacholine were similar in

patients 1 week before and 1 week after menstruation and that changes in serum progesterone had no effect. Therefore, the mechanisms that drive these cyclic changes in some women are unclear.

On the basis of the cyclic changes in asthma symptoms in some women, asthma investigators became interested in determining whether the use of hormonal birth control medications affected asthma symptoms in women. A cross-sectional postal survey study reported that contraceptive pill use in premenopausal women was associated with self-reported increased risk of asthma and increased wheezing in normal and overweight women.³⁹ However, in another study, use of oral contraceptives decreased serum progesterone levels but had no effect on asthma medication use and changes in FEV₁ in response to methacholine.³⁸ Other studies, such as the Swiss Cohort Study on Air Pollution and Lung Disease in Adults, reported that women taking oral contraceptives had a decrease in methacholine-induced AHR compared with women not taking oral contraceptives. In addition, the Scottish Health Surveys determined that women taking oral contraceptives had a reduced risk of current, physician-diagnosed asthma and urgent care use of more than 3 times per year for asthma.⁴⁰ These conflicting findings suggest that additional studies are needed to determine the therapeutic value of birth control medications on asthma.

Using dehydroepiandrosterone (DHEA), a hormone secreted by the adrenal cortex that is converted into androgens and estrogen, has also been explored as a potential therapeutic for patients with asthma. Mice fed DHEA-containing chow during dust mite–induced allergic airway inflammation had decreased airway eosinophils and decreased serum IL-4 and IL-5 levels.⁴¹ Furthermore, DHEA suppressed methacholine-induced AHR and airway eosinophils in ovalbumin sensitized and challenged mice and decreased Ca²⁺-induced airway smooth muscle contraction in tracheal rings from guinea pigs.^{42,43} In humans, nebulized dehydroepiandrosterone-3-sulfate (DHEAS), but not DHEA, improved asthma control, as measured by the asthma control questionnaire, in individuals with moderate to severe asthma after a 6-week, randomized, double-blind, placebo-controlled study.⁴⁴ Use of contraceptives or DHEAS as therapeutics for patients with asthma, particularly moderate to severe asthma, is plausible, but additional studies are needed.

Pregnancy and Asthma

Changes in asthma severity and symptoms have also been reported by some women during pregnancy. Results from an initial study in which women kept daily asthma symptom diaries and had monthly spirometries conducted during pregnancy and 3 months post partum suggested that asthma symptoms increased in approximately one-third of patients with asthma.⁴⁵ This study also found that 73% of women who experienced worsening of asthma symptoms had a decrease in asthma symptoms (back to prepregnancy levels) by 3 months post partum.⁴⁵ Additional studies found that women with severe asthma were at increased risk for asthma exacerbations during pregnancy compared with patients with mild and moderate asthma⁴⁶ and that the main triggers for these asthma exacerbations during pregnancy were viral infections and nonadherence to inhaled corticosteroid therapies.⁴⁷ In contrast, airway responsiveness and asthma severity, measured as a percentage of FEV₁ to vital capacity and asthma medication use, was decreased in 16 women with asthma during pregnancy but returned to preconception levels 1 month after delivery.⁴⁸

In addition, Belanger et al⁴⁹ reported that pregnancy did not affect asthma severity when patients continued to use their prescribed medications and that the trimester of pregnancy was not associated with changes in asthma severity. Controlling asthma during pregnancy is vital to reducing perinatal risks that have been associated with asthma during pregnancy, including low birth rates and

small sizes for gestational age, but the effects of pregnancy on asthma need further study.⁵⁰

Menopause and Asthma

If ovarian hormones were imperative for increasing asthma symptoms, then a decrease in asthma symptoms and asthma prevalence would be expected in women after menopause. However, as discussed below, studies have reported variations in asthma symptoms, prevalence, and phenotypes in perimenopausal and postmenopausal women. The Respiratory Health in Northern Europe (RHINE) study reported that the risk of respiratory symptoms increased in early postmenopausal and late postmenopausal women and that transitional times in reproductive aging were more prone to new-onset asthma and respiratory symptoms.⁵¹ Furthermore, use of hormonal replacement therapy for perimenopausal women, particularly women with body mass indexes less than 25 (calculated as weight in kilograms divided by the square of height in meters), in the RHINE study increased asthma prevalence and asthma symptoms as assessed by a questionnaire.⁵² Additional studies also found that use of hormonal replacement therapy in perimenopausal women increased the rate of new physician-diagnosed asthma⁵³ and asthma incidence.⁵⁴ These results suggest that fluctuations in hormone levels during menopause or use of hormonal replacement therapy during menopause may increase asthma symptoms. However, further investigation is warranted to determine the effects of menopause and hormone replacement therapy on asthma symptoms and newly described asthma phenotypes in older patients.⁵⁵

Animal Studies on Asthma

Clinical and epidemiologic studies in pediatric and adult patients with asthma have provided valuable insight into the sex disparity in asthma. However, mouse models of eosinophilic- or neutrophilic-mediated airway inflammation have been essential in providing insight on the role of testosterone and ovarian hormones in asthma pathogenesis. Because most patients with asthma have allergic asthma, many of these studies have been focused on allergen-mediated type 2 airway inflammation, including the role of sex hormones on mediating CD4⁺ T_H2 cell, M2 macrophage, dendritic cell (DC), mast cell, and basophil responses. Results from these studies are summarized in [Figure 1](#).

Estrogen Signaling Regulates Allergic Airway Inflammation in Mice

Because females have an increase in asthma prevalence and incidence starting around puberty, the role of female sex hormones have been explored in mouse models of allergic asthma. Female mice undergoing ovalbumin-induced or house dust mite (HDM)–induced allergic airway inflammation had increased eosinophils in the BAL fluid, increased IL-5 and IL-13 production in whole lung homogenates, and/or increased serum IgE production compared with male mice.^{56–58} Ovarian hormones are important in inducing allergic airway inflammation because gonadectomized female mice have decreased ovalbumin-induced eosinophils in the BAL fluid, IL-5 production, AHR, and total serum IgE compared with hormonally intact, sham-operated female mice.⁵⁹

Estrogen is the primary ovarian hormone that has been studied in airway inflammation. Estrogen signals through the nuclear receptors estrogen receptor α (ER- α) and estrogen receptor β (ER- β) and the membrane-bound G protein–coupled estrogen receptor 1. On binding estrogen, estrogen receptors homodimerize and recruit essential cofactors to activate or repress transcription of genes with estrogen response elements. ER- α and ER- β are expressed on hematopoietic cells and stromal cells, but the expression levels of ER- α

and ER- β vary in cell types. For example, CD4⁺ T cells and M2 macrophages express more ER- α , whereas B cells and airway epithelial cells express more ER- β .^{60–62}

Estrogen receptor knockout mice have been used to study the effects of estrogen signaling on asthma. Studies suggest that ER- α signaling increases allergic airway inflammation. For example, mice deficient in ER- α (esr1^{-/-} mice) had decreased ovalbumin-induced allergic airway inflammation and AHR compared with wild-type (WT) mice, but mice deficient in ER- β (esr2^{-/-} mice) had similar airway inflammation and AHR as WT mice.⁶³ An additional study also determined that ER- α signaling increased ovalbumin-induced AHR, but no effect on airway inflammation was seen.⁶³

Studies also suggest that estrogen signaling is important for increasing DC function in allergen-mediated type 2 mediated airway inflammation. Antigen presentation by DCs is essential for inducing allergic airway inflammation, and a sexual dimorphism is seen with DC accumulation after allergen challenge. Myeloid DCs and plasmacytoid DCs from ovalbumin sensitized and challenged female mice are increased in the mediastinal lymph nodes compared with male ovalbumin sensitized and challenged mice.⁶⁴ In addition, DCs treated with 17 β -E2 (20 μ g/mL) had increased cytokine expressions of IL-6, IL-8, and monocyte chemoattractant protein 1 compared with baseline control, and pretreatment of DCs with 17 β -E2 (20 μ g/mL) increased lipopolysaccharide-induced T-cell proliferation compared with vehicle.⁶⁵ CD11c⁺ CD11b^{int} DC differentiation was also inhibited by ER antagonists and in esr1^{-/-} mice.⁶⁶ Combined, these data indicate that estrogen signaling is important for increasing DC function in allergen-mediated type 2 mediated airway inflammation.

Estrogen signaling is also important for increasing allergen-mediated type 2 airway inflammation in M2 macrophages, mast cells, and basophils. M2-polarized macrophages are increased in the BAL fluid in patients with asthma compared with healthy controls,⁶⁷ and in mice, intratracheal administration of alveolar macrophages from ovalbumin sensitized and challenged mice increased eosinophilic airway inflammation.⁶⁴ Furthermore, M2, but not M1, alveolar macrophages are increased in female mice compared with male mice after ovalbumin sensitization and challenge.⁶⁰ Recent findings suggest that female mice may skew more readily to this M2 macrophage phenotype on allergen exposure because of increased IL-4 receptor α expression and increased ER- α expression and production of chitinase-like protein 3, YM1, and arginase 1 when compared with macrophages from male mice.⁶⁰ Serum IgE is also increased in ovalbumin sensitized and challenged female mice compared with male mice,^{56–58} suggesting increased activation and degranulation of mast cells and basophils in females. Although these results reveal the importance of estrogen signaling in allergen-mediated type 2 airway inflammation, additional studies are needed to determine whether estrogen and other ovarian hormones, including progesterone, synergistically enhance allergic airway inflammation.

Ovarian Hormones Regulate Neutrophilic Inflammation and Mucous Production in Mice

Neutrophils and IL-17A are increased in the BAL fluid in patients with more severe asthma compared with those with milder phenotypes of asthma.^{68,69} Studies conducted by our laboratory found that women with severe asthma had increased IL-17A-producing memory T_H17 cells compared with men with severe asthma. Furthermore, we found in mice that both 17 β -estradiol and progesterone were required for enhancing T_H17 cell differentiation and IL-17A production as well as IL-17A-mediated airway inflammation.⁷⁰ In addition, estradiol treatment of $\gamma\delta$ T cells, which produce IL-17A and augment the IL-17A-mediated airway response, decreased numbers of IL-17⁺ T cells in the draining lymph nodes, suggesting that estrogen mediates $\gamma\delta$ T-cell migration from the lymph nodes to various

tissues.⁷¹ However, studies examining the role of sex hormones on IL-17A-producing $\gamma\delta$ T cells and ILC3s, which also produce IL-17A and augment the IL-17A-mediated airway response, are limited and an important area for future research.

Estrogen and progesterone are also important in mucous production and mucociliary clearance as airway epithelial cells express estrogen receptors, predominantly ER- β , and progesterone receptors. Administration of estradiol to human airway or nasal epithelial cells increased mucin proteins, Muc5AC and Muc5B, and mucous production through various mechanisms, including an ERK1/2-dependent mechanism, an ER- β signaling dependent mechanism that increased NFATc1, and posttranscriptionally modifying fucosylation of mucin proteins.^{72,73} Progesterone alone also decreased cilia beat frequency from cultured primary human airway epithelial cells compared with vehicle. However, primary human airway epithelial cells administered 17 β -E2 with progesterone had a cilia beat frequency that was similar to vehicle-treated cells.⁷⁴ In summary, estrogen and progesterone signaling is important in regulating airway inflammation, AHR, and mucous production.

Regulation of Asthma Pathogenesis by Androgen Signaling

The role of androgens, including testosterone, has also been explored in mouse models of allergic asthma. Gonadectomized male mice, which lack testosterone, had increased eosinophils, lymphocytes, and IL-13 protein expression compared with hormonally intact, sham-operated male mice. Furthermore, as mentioned previously, administration of DHEA in the chow of mice undergoing the HDM protocol decreased allergic airway inflammation compared with mice fed normal chow.⁴¹ Recent studies have also reported that androgen receptor (AR) signaling attenuates ILC2-mediated airway inflammation. ILC2 production of IL-13 and IL-5 was increased in female mice compared with male mice stimulated with *Alternaria alternata* extract, HDM, or ovalbumin.^{75–77} Furthermore, male mice with a mutation in the AR that prevents AR signaling had increased *A alternata* extract or HDM-induced airway inflammation compared with WT male mice.^{75,77} Androgens were also important in the secretion of IL-33 and TSLP, cytokines that stimulate ILC2 production of IL-5 and IL-13, because gonadectomized male mice, which lack testosterone, had increased *A alternata* extract-induced IL-33 and TSLP secretion compared to hormonally intact, sham-operated male mice.⁷⁷ These data show that AR signaling is important in regulating allergen-mediated type 2 airway inflammation.

Androgens also regulate smooth muscle contractility. At baseline, male mice from both BALB/c and C57BL/6 strains of mice have increased AHR and increased smooth muscle contractility compared with female mice.^{78,79} This baseline difference is attributed to androgens increasing vagal nerve responses because gonadectomized male mice had similar levels of vagal nerve responses as intact female mice and the administration of androgens to gonadectomized male mice increased vagal nerve responses to AHR.⁷⁹ Combined, these studies suggest that androgen signaling is important in decreasing airway inflammation and AHR and provide insight on the decrease in asthma prevalence and incidence in adolescent males compared with females.

Conclusion

A sex disparity exists in asthma, which changes at puberty from males having the highest prevalence to females having the highest prevalence. Furthermore, fluctuations in hormones during menstruation, pregnancy, and menopause are associated with changes in asthma symptoms. These findings suggest that sex hormones are important in asthma pathogenesis, but the mechanisms by which estrogen and/or androgen signaling regulate airway inflammation, mucous production, and airway hyperreactivity are not fully

elucidated. Animal studies using genetic deletions of estrogen receptors and a mutated androgen receptor have found that estrogen signaling promotes and androgen signaling attenuates allergen-mediated type 2 airway inflammation. Furthermore, animal studies have found that ovarian hormones are important for IL-17A-mediated airway inflammation. However, additional studies need to be conducted to determine mechanisms by which sex hormones are regulating neutrophil infiltration into the airway and regulating alarmins that are important in initiating the inflammatory response. Elucidating these pathways will provide the foundational research necessary for the development of treatment strategies, including use of hormonal contraceptives or DHEAS, for women with asthma during the various reproductive phases of life.

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