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Sex hormones, gender and 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 mucus production. The majority of patients with asthma have allergic airway inflammation characterized by type 2-mediated airway inflammation.[2] However, some patients with asthma have low (or no) type 2-mediated airway inflammation but have increased neutrophils driven by type 1 or IL17-mediated airway inflammation.[2, 3]

As depicted in Figure 1, increased airway inflammation, mucus 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), 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 cell helper (Th)2 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 (immunoglobulin E)-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 IL17-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-

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related health care costs when compared to patients with milder phenotypes of asthma.[4] Increased neutrophils in the airway are driven by increased IL-17A-secreting and/or IFN (interferon)-γ-secreting cells, including Th17, γδ T cells, Th1, and NK (natural killer) cells.[5,6] In this review, we will summarize the clinical, epidemiological, and animal studies that show a gender disparity in asthma and the mechanisms by which sex hormones regulate asthma pathogenesis.

Gender disparity in asthma

A gender disparity exists in asthma and changes with age. As children, boys have an increased prevalence of asthma compared to 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 shown this gender disparity in asthma. PIAMA was unique because it recruited 4,146 pregnant women and assessed 3,308 of their children yearly for wheeze (ages 1-7) and asthma (age 8) by questionnaires. Starting at age 1 and maintained until age 8, boys had an increased cumulative incidence of parent-reported wheeze compared to girls. At age 8, 15.1% of the boys and 10.8% of the girls had asthma,[7] suggesting the gender disparity in asthma begins early in childhood. Boys also had increased atopy, measured by specific IgE or skin prick testing to common allergens, compared to girls prior to adolescence.[7–12] These findings suggest that atopy and allergen sensitization is greater in boys compared to girls as children, and may provide some rationale for increased the gender disparity in asthma prevalence in children.

Other differences in immune responses and anatomical differences may also play a role in explaining this observed gender difference in wheeze and/or asthma in boys and girls, when sex hormones are low. PHA (phytohemagglutinin)-induced mononuclear cells from boys, compared to girls, had significantly increased IFN-γ at 1 year of life and increased IFN-γ, IL-5, and IL-13 in children that wheezed at 3 years of life.[13] Further, boys had increased rates of sensitization, total IgE levels, and blood eosinophil counts compared to girls.[13] Dysanapsis, smaller airway diameters relative to lung volumes, is also detected more often in boys compared to girls.[10] Therefore, a more robust immune response and decreased airway size likely contribute to increased wheezing in young boys compared to girls.

In contrast, as adults, women have an increased prevalence of asthma compared to 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 gender switch at puberty by longitudinally tracking the average asthma symptom scores and the progression of puberty, using Tanner puberty stages, in children from ages 4 to 17.[16] Tanner stage puberty scores characterize predictable changes in puberty using a 1-5 scale, with 1 being pre-pubertal 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 around age 10, but the average asthma symptom scores began to decrease at approximately age 14.[16] Additional

studies have also shown that early aged menarche (≤11 years old) in girls increased the incidence of asthma.[17]

After puberty, the gender 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, ages 10-20, with asthma (n=274) as well as healthy controls (n=1000) determined that at age 20, the prevalence of asthma persisted in 24.5% of asthmatic participants and remained male dominated in ratio.[18] In the healthy controls, 4.8% of participants had developed asthma by age 20, and most of these patients were female. Atopy, measured by skin prick testing to inhaled allergens at age 10, was not associated with wheeze in the healthy individuals diagnosed with asthma at age 20. Therefore, these findings suggest that the gender 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 gender 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 utilization and medication use was increased in boys compared to girls from ages 2-13, was not statistically different by gender from ages 14-22, and was increased in women compared to men after age 23.[19] This large, health-care utilization cohort study highlights the gender differences in asthma health utilization throughout life.

All of these studies have provided insight on 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.

Gender disparity across phenotypes of asthma

The heterogeneity in patients' asthma severity and the mechanisms that drive airway inflammation, mucus 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 utilizing the CAMP, the Inner City Asthma Consortium, or The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) studies showed that boys had an increased percentage in clusters with more exacerbations and/or lower baseline pulmonary function compared to 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 to clusters with milder phenotypes of asthma (clusters 1 and 2).[20] The Inner-City Asthma Consortium Asthma

Phenotypes in the Inner City (APIC) identified 5 clusters from 616 pediatric patients and found an increased percentage of boys compared to girls in all participants. Further, the more 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 gender, atopic status, smoke exposure, and race. Boys were the majority of children in all asthma clusters except one cluster that was defined by female gender.[21]

Clustering analysis in adults with asthma determined that women are more likely have more severe, less corticosteroid responsive phenotypes of asthma compared to 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 asthmatics in one study.[23] The U-BIOPRED cohort, which enrolled patients with asthma ranging from mild to severe, showed 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] Further, the European Network For Understanding Mechanisms Of Severe Asthma (UNFUMOSA) study reported that females were 4.4X more likely to be classified with severe asthma than males.[26] Cluster analysis of asthma phenotypes in 611 adult patients utilizing primary care providers in the ACCURATE trial also showed a female predominance in clusters with patients that have later onset of asthma or more asthma exacerbations.[27] Combined, cluster analyses in pediatric and adult asthma populations show that asthma is a heterogeneous disease and that the gender 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 as well as through the reproductive years of a women's life have provided valuable insight on 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 30-40% of women with asthma during the pre or perimenstrual phase of the cycle.[28, 2930–32] Sputum eosinophils and fractional exhaled nitric oxide (FeNO) were also increased during this pre-menstrual phase when compared to just after menses (7th day of cycle).[33, 34] Further, increased oral corticosteroid bursts and increased emergency department visits were reported in the SARP study in women that had peri-menstrual worsening of asthma compared to women without peri-menstrual worsening of asthma.[35] These studies suggest that pre-menstrual asthma impacts many women with asthma, but additional studies with mild to severe asthma patients reported no differences in the asthma-related emergency department visits in any phase of the menstrual cycle.[36, 37] Further, Juniper et al. determined that asthma symptoms were increased during menstruation but that medication use and FEV1 in response to methacholine were similar in patients 1 week prior and 1 week after menstruation and that changes in serum progesterone had no effect.[38] Therefore, the mechanisms driving these cyclic changes in some women are unclear.

Based on the cyclic changes in asthma symptoms in some women, asthma investigators became interested in determining if use of hormonal birth control medications affected

asthma symptoms in women. A cross-sectional postal survey study reported that contraceptive pill use in pre-menopausal women was associated with self-reported increased risk for 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 (SAPALDIA) reported that women taking oral contraceptives had a decrease in methacholine-induced AHR compared to women not taking oral contraceptives. Additionally, the Scottish Health Surveys determined that women on 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.

Utilizing 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 as well as decreased serum IL-4 and IL-5 levels.[41] Further, DHEA suppressed methacholine-induced AHR and airway eosinophils in OVA sensitized and challenged mice as well as decreased Ca^{2+}-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 moderate to severe asthmatics 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 showed that 73% of women who experienced worsening of asthma symptoms had a decline in asthma symptoms (back to pre-pregnancy levels) by 3 months post-partum.[45] Additional studies showed that women with severe asthma were at increased risk for asthma exacerbations during pregnancy compared to mild and moderate asthma patients,[46] and that the main triggers for these asthma exacerbations during pregnancy were viral infections and non-adherence to inhaled corticosteroid therapies.[47] In contrast, airway responsiveness and asthma severity, measured as a percentage of FEV1 to vital capacity as well as asthma medication use, was decreased in sixteen asthmatic women during pregnancy but returned toward pre-conception levels 1 month after delivery.[48] In addition, Belanger *et al.* 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.[49] 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 decline 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 peri and post-menopausal 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] Further, use of hormonal replacement therapy for perimenopausal women, particularly women with body mass indexes less than 25, in the RHINE study increased asthma prevalence and asthma symptoms as assessed by a questionnaire.[52] Additional studies also showed that use of hormonal replacement therapy in perimenopausal women increased the rate of new, physician diagnosed asthma[53] 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 investigated 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 epidemiological studies in pediatric and adult patients with asthma have provided valuable insight into the gender 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. Since most patents with asthma have allergic asthma, many of these studies have been focused on type 2-mediated airway inflammation, including the role of sex hormones on mediating CD4+ Th2 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

Since 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 OVA-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 to male mice.[56–58] Ovarian hormones are important in inducing allergic airway inflammation because gonadectomized female mice have decreased OVA-induced eosinophils in the BAL fluid, IL-5 production, AHR, and total serum IgE compared to 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 ER-α and ER-β as well as the membrane bound G protein-couple estrogen receptor 1 (GPER1). Upon 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 while 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 OVA-induced allergic airway inflammation and AHR compared to 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 OVA-induced AHR, but no effect on airway inflammation was seen.[63]

Studies also suggest that estrogen signaling is important for increasing DC function in 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 OVA sensitized and challenged female mice are increased in the mediastinal lymph nodes compared to male OVA sensitized and challenged mice.[64] Additionally, DCs treated with 17β-E2 (20 μg/ml) had increased cytokine expressions of IL-6, IL-8, and MCP-1 compared to baseline control, and pre-treatment of DCs with 17β-E2 (20 μg/ml) increased lipopolysaccharide (LPS)-induced T cell proliferation compared to vehicle.[65] CD11c+ CD11b^{int} DC differentiation was also inhibited by ER antagonists and in esr1$^{-/-}$ mice.[66] Combined, these data show that estrogen signaling is important for increasing DC function in 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 to healthy controls,[67] and in mice, intratracheal administration of alveolar macrophages from OVA-sensitized and challenged mice increased eosiniophilic airway inflammation.[64] Further, M2, but not M1, alveolar macrophages are increased in female mice compared to male mice after OVA sensitization and challenge.[60] Recent findings suggest that female mice may skew more readily to this M2 macrophage phenotype upon allergen exposure because of increased IL-4R-α expression as well as increased ER-α expression and production of YM1 and Arg1 when compared to macrophages from male mice.[60] Serum IgE is also increased in OVA sensitized and challenged female mice compared to male mice,[56–58] suggesting increased activation and degranulation of mast cells and basophils in females. Although these results show the importance of estrogen signaling in allergen-mediated type 2 airway inflammation, additional studies are needed to determine if estrogen and other ovarian hormones, including progesterone, synergistically enhance allergic airway inflammation.

Ovarian hormones regulate neutrophilic inflammation and mucus production in mice

Neutrophils and IL-17A are increased in the BAL fluid in patients with more severe asthma compared to milder phenotypes of asthma.[68, 69] Studies conducted by our laboratory showed that women with severe asthma had increased IL-17A producing memory Th17 cells compared to men with severe asthma. Further, we showed in mice that both 17β-estradiol and progesterone were required for enhancing Th17 cell differentiation and IL-17A production as well as IL-17A-mediated airway inflammation.[70] Additionally, estradiol treatment of γδ 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 γδ T cell migration from the lymph nodes to various tissues.[71] However, studies examining the role of sex hormones on IL-17A producing γδ 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 mucus 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 mucus production through various mechanisms, including an ERK1/2-dependent mechanism, an ER-β signaling dependent mechanism that increased NFATc1, and post-transcriptionally modifying fucosylation of mucin proteins.[72, 73] Progesterone alone also decreased cilia beat frequency from cultured primary human airway epithelial cells compared to vehicle. However, primary human airway epithelial cells co-administered 17β-E2 with progesterone had a cilia beat frequency that was similar to vehicle treated cells.[74] In summary, estrogen and progesterone signaling are important in regulating airway inflammation, AHR, and mucus production.

Androgen signaling regulates asthma pathogenesis

The role of androgens, including testosterone, have 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 to hormonally intact, sham-operated male mice. Further, as mentioned in an above section, administration of DHEA in the chow of mice undergoing the HDM protocol decreased allergic airway inflammation compared to mice on normal chow.[41] Recent studies have also reported that androgen receptor signaling regulates ILC2-mediated airway inflammation. ILC2 production of IL-13 and IL-5 was increased in female mice compared to male mice stimulated with *Alternaria alternata* extract (Alt Ext), HDM, or OVA.[75–77] Further, male mice with a mutation in the androgen receptor (AR) that prevents AR signaling had increased Alt Ext or HDM-induced airway inflammation compared to 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 Alt Ext-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 type 2-mediated 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 as well as increased smooth muscle contractility compared to female mice.[78, 79] This baseline difference is attributed to androgens increasing vagal nerve responses, since 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/AHR and provide insight on the decline in asthma prevalence and incidence in adolescent males compared to females.

Conclusions

A gender disparity exists in asthma, which changes at puberty from males having the highest prevalence to females having the highest prevalence. Further, 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, mucus production, and airway hyperreactivity are not fully elucidated. Animal studies using genetic deletions of estrogen receptors and a mutated androgen receptor have shown that estrogen signaling promotes and androgen signaling attenuates type 2-mediated airway inflammation. Further, animal studies have shown 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 as well as 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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Abbreviations

AHR	airway hyperresponsiveness
Alt Ext	*Alternaria alternata* extract
AR	androgen receptor
BAL	bronchoalveolar lavage
DC	dendritic cell
DHEA	dehydroepiandrosterone

DHEAS	dehydroepiandrosterone-3-sulfate
GPER1	G protein-couple estrogen receptor 1
HDM	house dust mite
IFN	interferon
IgE	immunoglobulin E
ILCs	innate lymphoid cells
LPS	lipopolysaccharide
NK	natural killer
PHA	phytohemagglutinin
Th	T helper cell
TSLP	thymic stromal-derived lymphopoietin

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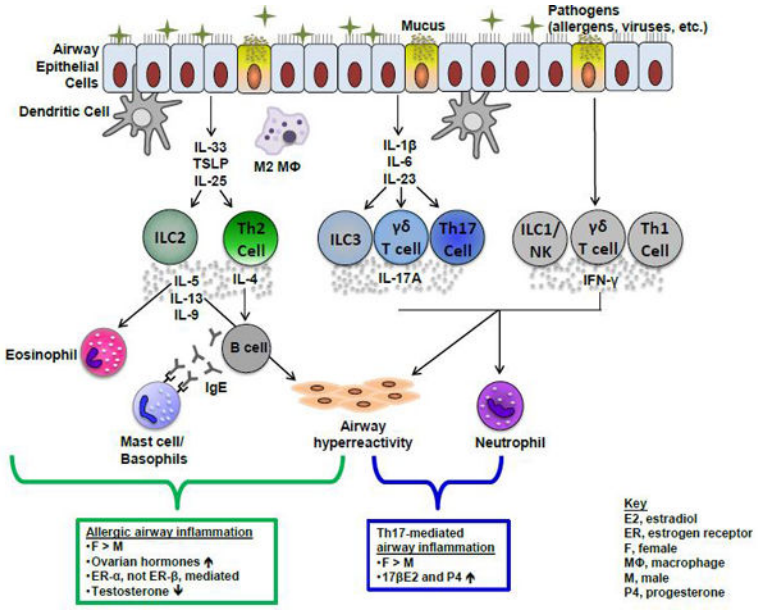

Figure 1. How sex hormones regulate different airway inflammatory pathways in asthma

Schematic of type 2, IL-17A-mediated, and IFN-γ-mediated pathways associated with different phenotypes of asthma. Summary of gender differences and the role of sex hormone signaling in type 2 and IL-17A-mediated airway inflammation are shown in boxes below pathways.