

Sex hormones and asthma: The role of estrogen in asthma development and severity

Asthma affects people of all ages and frequently persists throughout the whole life span. However, the frequency and exacerbation of asthma symptoms depend on multiple external and internal variables, fluctuating during a lifetime. Age and gender are important factors influencing asthma development and severity. In children, asthma is predominant in boys.¹ After the adolescent switch, this proportion reverse, as in adulthood, more women than men are diagnosed with the disease.² Hereford, the link between asthma development and female and male sex hormones has been proposed. The levels of estrogen and testosterone increase during maturation, with the maximum levels observed in the second decade of life, followed by a gradual decrease with age, reaching low levels during menopause. Fluctuations of estradiol and progesterone levels during the menstrual cycle were linked with the worsening of asthma symptoms in females. Serum testosterone is inversely correlated with the odds of current asthma in both women and men.³ In agreement, the prevalence of asthma rises again in males after the 50s when a decrease in testosterone levels is observed (Figure 1). The female gender is also associated with more frequent diagnoses of severe asthma,⁴ and decreased expression of glucocorticoid (GCs) receptors on circulating leukocytes. Severe asthma treatment strategy includes high doses of GCs, often proving inefficient. Gender-associated expression patterns of GCs receptors might be responsible for differences observed in GCs responsiveness.⁵

Sex hormones regulate many autoimmune and inflammatory diseases, including asthma, by modulation of various aspects of innate and adaptive immune responses. Multiple cells and tissues express estrogen and androgen (testosterone) receptors on their surface, including cells closely related to pathomechanisms of asthma, such as eosinophils, mast cells, and T cells. Estrogens are mainly considered immunoenhancers (promoting immune responses), whereas testosterone is described as immunosuppressors (suppressing immune responses). The sexual dimorphism observed in asthma prevalence is associated with the physiological production of estrogen (positive association) and testosterone (negative association) (Figure 1). Androgens (testosterone) decrease innate immune responses, whereas estrogen and progesterone enhance type 2 (T2) inflammation, the main pathophysiologic mechanism underlying the T2 high asthma phenotype.⁶ T2 high asthma is characterized by the disproportionate involvement of type 2 T helper (Th2) cells, type 2 innate lymphoid cells (ILC2s), eosinophils, basophils, and mast cells,

accompanied by secreted by those populations T2 cytokines, such as IL-4, -5, and -13. Testosterone decreased lung ILC2 numbers and ILC2-derived IL-5 and IL-13,⁷ and androgens via androgen receptors signaling stabilized suppressive function of T regulatory lymphocytes.⁸ External suppression of sex steroid production by contraceptives in young women may improve asthma symptoms.⁹ In contrast, hormone-replacement therapy (HRT) used in post-menopausal women might worsen or even induce asthma. Interestingly, a distinct pheno-endotype of asthma associated with decreased estrogen levels developed after menopause, called menopausal or post-menopausal asthma, was proposed. It can be hypothesized that HRT and subsequent increase in estrogen enhance T2 responses leading to the development/exacerbation of T2 high asthma. HRT increases (HR 1.63) the risk of new asthma development. Women terminating HRT often were able to subsequently stop asthma treatment.¹⁰ 17 β -estradiol was higher in post-menopausal women with severe asthma when compared to mild-to-moderate asthma, assessed both in serum and in induced sputum.¹¹ On the contrary, it has been demonstrated that premenopausal asthma in women is

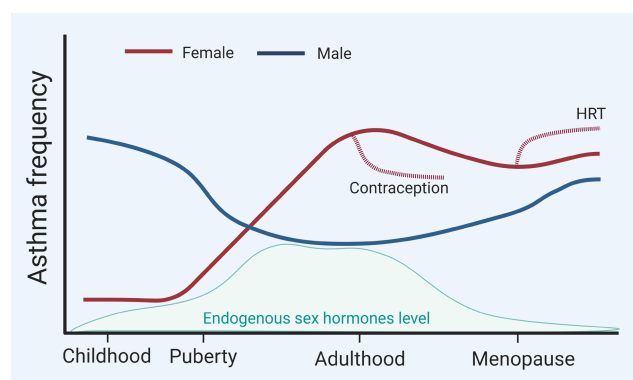
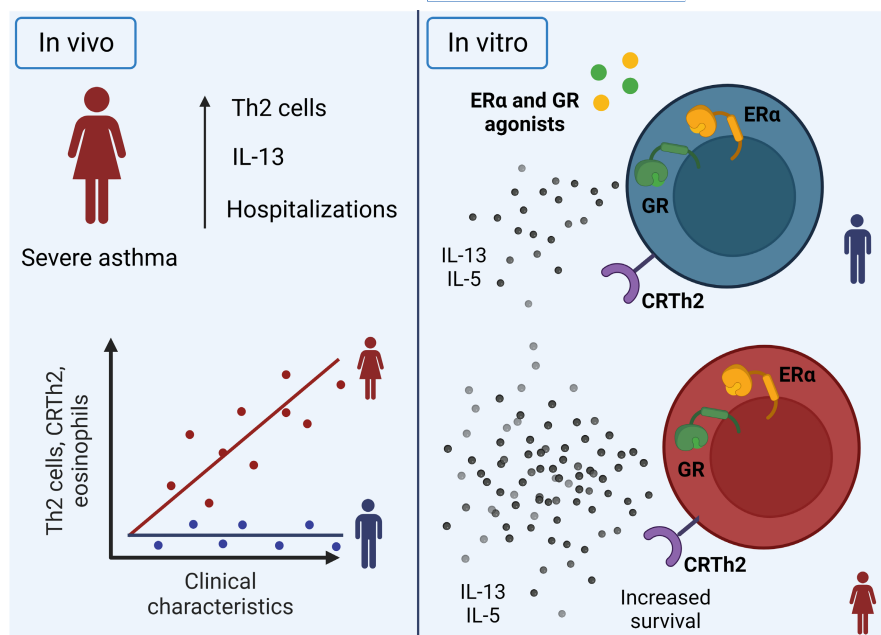


FIGURE 1 Relation between the fluctuation of sex hormones levels and asthma diagnosis. During childhood, boys have a higher prevalence of asthma than girls. This ratio changes during puberty when adult women are more frequently diagnosed with asthma than men. After menopause, increased asthma frequency is observed in men and might be related to a decreased production of endogenous testosterone. Females undergoing contraceptive or hormone-replacement therapy (HRT) present decreased and increased asthma prevalence, accordingly. Figure created with [Biorender.com](https://biorender.com)

FIGURE 2 Upregulation of CRTh2-mediated type 2 responses in Th2 cells is mediated by estrogen receptor α and glucocorticoid receptor activation. Women with severe asthma present increased frequencies of Th2 cells, secreted IL-13, and hospitalization. Clinical characteristics of asthma correlate with Th2 cells, CRTh2, and eosinophils in female but not male patients. Dual activation of estrogen receptor α (ER α) and glucocorticoid receptor (GR) enhances the CRTh2-dependent section of IL-13, IL-5, and Th2 cells survival in women. Figure created with [Biorender.com](https://www.biorender.com)



characterized by low estradiol concentrations and persistent neutrophilic airway inflammation, characteristic of the non-T2 asthma phenotype. The concept of premenopausal asthma requires further investigation in properly designed big cohorts to fully understand its biology and the involvement of endogenous and exogenous estrogens in eosinophilic- and neutrophilic-predominant phenotypes.

In a recent study, Vijeyakumaran et al. investigated the association between T2 inflammation and estrogen receptor signaling on Th2 cells in severe asthma (Figure 2).¹² In vivo, women diagnosed with severe asthma presented elevated levels of Th2 circulating cells. Increased T2 responses and IL-13 levels in the serum were related to more frequent hospitalizations, when compared to females diagnosed with mild/moderate asthma. Interestingly, the correlation between clinical asthma characteristics and Th2 cells, eosinophils, and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) mRNA levels were observed in women but not male patients. As subsequently observed in vitro, GCs and ER α agonists prevented Th2 cell apoptosis and at the same time upregulated CRTH2, IL5, and IL13 gene expression following CRTh2 activation compared with Th2 cells treated with GCs alone. This elegant study by Vijeyakumaran et al. showed that women with severe asthma had higher levels of circulating Th2 cells, which might be partially explained by estrogen-mediated enhancement of Th2 survival and T2 cytokines production.

The data presented in this study contribute to a better understanding of the role of sex hormones in the pathophysiology of asthma. Further studies delineating the role of estrogens as well as contraceptives/HRT in different phenotypes of the disease and acknowledging the phase of the menstrual cycle, will shed light on the mechanisms behind the role of hormones in modulating the innate and adaptive immune responses in the pathology of asthma. Importantly, environmental exposure to estrogen-stimulating factors should not be ignored. Environmental estrogens (xenoestrogens) might enhance the development of atopic disorders, like

T2-high asthma. The levels of bisphenol S and F, analogs of bisphenol A, widely used in plastic products, were higher in urine collected from females diagnosed with asthma as compared to healthy controls. At the same time, no differences were observed in males.¹³ We are curious and ready to learn more.

KEYWORDS

asthma, estrogen, immune mechanisms, menopause, testosterone

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding this manuscript.

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REFERENCES

- Trivedi M, Denton E. Asthma in children and adults-what are the differences and what can they tell us about asthma? *Front Pediatr*. 2019;7:256.

2. Han YY, Forno E, Celedon JC. Sex steroid hormones and asthma in a Nationwide study of U.S. Adults *Am J Respir Crit Care Med*. 2020;201(2):158-166.
3. Bulkhi AA, Shepard KV, 2nd, Casale TB, Cardet JC. Elevated testosterone is associated with decreased likelihood of current asthma regardless of sex. *J Allergy Clin Immunol Pract* 2020;8(9):3029-3035. e3024
4. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European network for understanding mechanisms of severe asthma. *Eur Respir J*. 2003;22(3):470-477.
5. Lu KD, Radom-Aizik S, Haddad F, Zaldivar F, Kraft M, Cooper DM. Glucocorticoid receptor expression on circulating leukocytes differs between healthy male and female adults. *J Clin Transl Sci*. 2017;1(2):108-114.
6. Fuseini H, Newcomb DC. Mechanisms driving gender differences in asthma. *Curr Allergy Asthma Rep*. 2017;17(3):19.
7. Cephus JY, Stier MT, Fuseini H, et al. Testosterone attenuates group 2 innate lymphoid cell-mediated airway inflammation. *Cell Rep*. 2017;21(9):2487-2499.
8. Gandhi VD, Cephus JY, Norlander AE, et al. Androgen receptor signaling promotes Treg suppressive function during allergic airway inflammation. *J Clin Invest*. 2022;132(4):e153397.
9. Nwaru BI, Tibble H, Shah SA, et al. Hormonal contraception and the risk of severe asthma exacerbation: 17-year population-based cohort study. *Thorax*. 2021;76(2):109-115.
10. Hansen ESH, Aasbjerg K, Moeller AL, Gade EJ, Torp-Pedersen C, Backer V. Hormone replacement therapy and development of new asthma. *Chest*. 2021;160(1):45-52.
11. Scioscia G, Carpagnano GE, Lacedonia D, et al. The role of airways 17beta-estradiol as a biomarker of severity in postmenopausal asthma: a pilot study. *J Clin Med*. 2020;9(7):2037.
12. Vijeyakumaran M, Al Jawhri M, Fortunato J, et al. Dual Activation of estrogen receptor alpha and glucocorticoid receptor upregulate CRTh2-mediated type 2 inflammation; mechanism driving asthma severity in women? *Allergy*. 2023;78:767-779. doi:<https://doi.org/10.1111/all.15543>
13. Kiook B, Jong-Tae P, Kyeongmin K. Association of Urinary Bisphenols Concentration with asthma in Korean adolescents: data from the third Korean National Environmental Health Survey. *Toxics*. 2021;9(11):291.