Clinical Commentary Review

Hormonal Effects on Asthma, Rhinitis, and Eczema

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Hormones significantly influence the pathogenesis of asthma, rhinitis, and eczema. This review aims to summarize relevant clinical considerations for practicing allergists and immunologists. The first section reviews the effects of sex hormones: estrogen, progesterone, and testosterone. The second concerns insulin production in the context of type 1 and type 2 diabetes. The third concludes with a discussion of thyroid and adrenal pathology in relationship to asthma, rhinitis, and eczema. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:2066-73)

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INTRODUCTION

Variations of hormones, whether physiologic or pathologic, have effects on atopic diseases. It is valuable to the practicing allergist or immunologist to appreciate these associations to provide tailored therapies and educate patients. The effects of estrogen, progesterone, testosterone, insulin, thyroxine, and cortisol on asthma, rhinitis, and eczema are reviewed (Figure 1).

ESTROGEN, PROGESTERONE, AND TESTOSTERONE

Asthma

Fluctuations in sex hormones across the reproductive stages of life can affect asthma prevalence and severity. For example, asthma prevalence and asthma-related hospitalizations are higher in prepubertal males compared with females.[1,2] Similarly, fluctuations in asthma exacerbations occur during the menstrual cycle, with higher rates in the perimenstrual phase.[3,4] Pregnancy can also affect asthma severity. A subset of pregnant asthmatic subjects experience a decline in symptom control and an increase in the rate of hospitalizations and oral corticosteroid use.[5,6] In addition, both early menarche and multiparity increase the risk for asthma.[7,8] The effects of hormonal contraceptives on asthma are less clear. Some research shows that oral contraceptive use is associated with an increased risk for asthma and asthma symptoms among normal weight and overweight women (body mass index of 20 to 30 kg/m^2), but not in lean women (body mass index of less than 20 mg/kg^2).[9] In contrast, other authors reported that hormonal contraceptives reduce the risk for physician-diagnosed asthma.[10] Finally, researchers also demonstrated that postmenopausal women who have never used hormone replacement therapy have a lower risk for asthma compared with premenopausal women. Likewise, the use of conjugated estrogen after menopause increases the risk for asthma in a dose-dependent manner.[11] Collectively, these studies suggest a strong influence of sex hormones on asthma pathogenesis.

Sex hormones can regulate key aspects of asthma pathogenesis, including airway inflammation, mucus production, and airway hyperresponsiveness. Ovarian hormones tend to exacerbate several of these cardinal features. In contrast, androgens have marked anti-inflammatory effects on asthma.

Various cell types, including airway epithelial cells, airway smooth muscle (ASM) cells, lymphocytes, eosinophils, and mast cells express estrogen receptors and have a pivotal role in the pathogenesis of asthma.[12-19] Estrogen causes various cell-specific genomic and nongenomic actions. For example, estrogen promotes the production of nitric oxide[20] and mucus[21] from bronchial epithelial cells. In addition, it prevents the store-operated calcium entry into airway epithelial cells by inhibiting the phosphorylation of stromal interaction molecule 1.[22] These alterations in calcium homeostasis can affect ion transport and goblet cell biology, which are highly relevant to asthma pathogenesis. Estrogen also can regulate ASM function. For example, estrogen treatment inhibits histamine-induced intracellular

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Abbreviations used
AD- Atopic dermatitis
AR- Androgen receptor
ASM- Airway smooth muscle
CRS- Chronic rhinosinusitis
DM- Diabetes mellitus
DM1- Type 1 diabetes mellitus
DM2- Type 2 diabetes mellitus
HPA- Hypothalamic–pituitary–adrenal axis
ILC2- Innate lymphoid cells group 2

calcium increases in ASM[19] and decreases airway responsiveness via an epithelium-dependent increase in acetylcholinesterase activity.[23]

Estrogen also affects the biology of several immune cells relevant to the pathogenesis of asthma. For example, it regulates dendritic cell differentiation and cytokine production,[24,25] stimulates IL-4 production from $CD4^+$ T cells[26], and promotes cell survival.[13,27] It favors the adhesion of eosinophils to endothelial cells,[28] their recruitment into airways,[12,29] and degranulation.[30] Likewise, it promotes mast cell degranulation.[18,31-34]

Progesterone also can significantly affect asthma pathogenesis. It inhibits ciliary beat frequency in airway epithelial cells, which can affect mucus clearance.[35] Likewise, it attenuates airway remodeling, especially combined with budesonide.[36] The effect of progesterone on mast cell degranulation is contradictory: one study indicated that it promotes activation[15] and another showed that it inhibits activation.[37]

Several clinical studies highlighted the effects of testosterone on asthma prevalence and severity. A 2020 study demonstrated that serum testosterone levels inversely correlated with asthma prevalence.[38] In addition, this study and others showed that testosterone levels were positively associated with better FEV_1 and FVC across different races and ethnic groups.[38-40] Higher expression of the androgen receptor (AR) in human asthmatic airways was also associated with better lung function and lower FeNO levels.[41] Finally, nebulized dehydroepiandrosterone-3-sulfate improved asthma control scores in subjects with moderate to severe asthma.[42]

Mechanistically, the beneficial effects of androgens in asthma occurs at multiple levels. For example, dehydroepiandrosterone induces the relaxation of ASM via an epithelial and nitric oxide–dependent pathway.[43] Androgens also inhibit the function of group 2 innate lymphoid cells (ILC2), which are an important source of IL-5 and IL-13. Specifically, androgens attenuate the differentiation of ILC2 and decrease ILC2 numbers in the lung.[44,45] In addition, testosterone decreases the adhesion of eosinophils to endothelial cells and their viability.[28] Finally, androgens also can suppress B cell development and IgE production.[46,47]

Rhinitis

Several observational studies suggested that sex hormones affect the incidence of rhinitis. For example, late-onset menarche protects against the onset of allergic rhinitis.[48] In addition, as the levels of estrogen increase during the periovulatory stage of the normal menstrual cycle, there is an associated increase in nasal congestion.[49] Other studies showed that the nasal mucosa becomes more reactive to histamine during ovulation.[50] Although higher estrogen levels are associated with more pronounced symptoms of rhinitis, lower estrogen levels are associated with an increased risk for nasal polyposis.[51] Perhaps the most compelling evidence for the effects of sex hormones on rhinitis comes from studies on pregnancy. New-onset rhinitis occurs in approximately 20% of pregnant women,[52] and changes in sex hormones are considered the primary reason for the rhinitis. However, other studies indicated that higher levels of placental growth hormones could also be implicated. The exact mechanism remains unknown.[53,54]

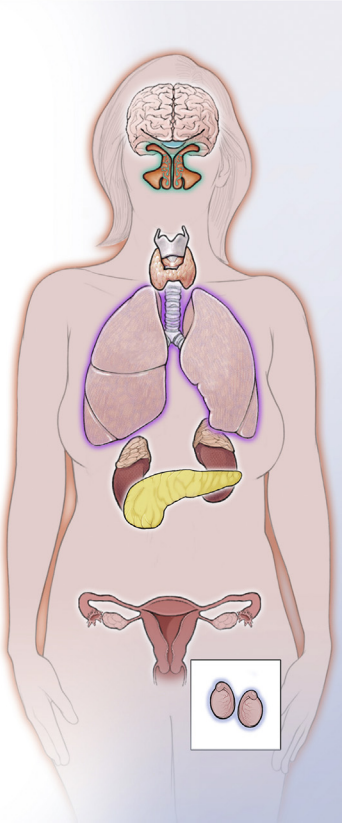
The mechanisms by which sex hormones influence rhinitis are varied. Estrogen, progesterone, and ARs are all expressed in the human nasal mucosa.[55] Estrogen exposure can lead to significant nasal histopathologic changes, including squamous metaplasia, interepithelial edema, glandular hyperplasia, fibrous tissue deposition, and increased vascularity with endothelial proliferation.[56,57] In addition, both estrogen and progesterone can significantly increase the H1 histamine receptor messenger RNA expression in nasal epithelial cells.[58] Nasal mucosa exposure to estrogen or progesterone can trigger immediate hypersensitivity reactions, which suggests that these hormones can induce mast cell degranulation.[59] Estrogen can also regulate eosinophilic adhesion to human mucosal endothelial cells; both estrogen and progesterone increase their degranulation.[28] Finally, sex hormones can regulate antibody production. In a mouse model of allergic rhinitis, antigen-specific IgE levels were higher in castrated male versus sham-operated control mice. Importantly, the levels of antigen-specific IgE decreased when the castrated mice were treated with androgens.[47]

Eczema

Sex hormones can also regulate several skin processes highly relevant to eczema. Overall, estrogen has a positive impact on skin barrier formation and recovery, whereas progesterone and testosterone have detrimental effects. The prevalence of atopic dermatitis (AD) varies, as does asthma, with the onset of puberty.[60] Furthermore, research showed that sex hormones cause fluctuations in transepidermal water loss, alter cutaneous blood flow during the menstrual cycle,[61,62] and affect skin barrier integrity and perhaps the development of AD.[63,64]

Several studies addressed the mechanisms by which sex hormones influence AD. They indicated that estrogen promoted skin barrier integrity, whereas androgen impairs it.[65] For example, bilateral oophorectomy decreases skin hydration and the integrity of the stratum corneum, which are reversed by estrogen treatment.[66] Other studies indicated that bilateral oophorectomy results in the downregulation of filaggrin, a filament-associated protein critical to epidermal homeostasis.[67] Finally, estrogen promotes the production of ceramides, important epidermal lipids, by increasing the activity of β-glucocerebrosidase.[68]

In contrast, androgen impairs skin barrier formation.[69] Castrated and flutamide (an AR antagonist)-treated mice have improved skin barrier recovery compared with controls. Furthermore, these effects are reversed with testosterone replacement.[70] The authors suggested that testosterone alters skin barrier formation by decreasing the formation and secretion of epidermal lamellar bodies, which are critical regulators of skin permeability. Moreover, studies with topical dehydroepiandrosterone indicated that androgens modulate collagen synthesis and the differentiation and cornification of keratinocytes.[71] Although



	ASTHMA	RHINITIS	ECZEMA
THYROID			
Hyperthyroidism	Can cause asthma exacerbations	Allergic rhinitis linked to exacerbation of existing Grave's disease	Associated with Pretibial myxedema
Hypothyroidism	Associated with milder asthma symptoms	Higher incidence of allergic rhinitis in patients with hypothyroidism	Associated with increased nummular eczema or eczema craquelé
DIABETES			
Type 1 (autoimmune)	May decrease asthma incidence.	No association with allergic rhinitis.	Contradictory evidence between Type 1 Diabetes and atopic dermatitis, no definite association established
Type 2	Associated with a more severe asthma outcome in adults	Chronis rhinosinusitis associated with worse glycemic control	Complex association may reduce, or increase based on specific population
ADRENAL			
Adrenal Insufficiency	Asthma exacerbations can trigger adrenal crisis		Primary adrenal insufficiency can present with hyperpigmentation
	Associated with eosinophilia.		
Hypercortisolism	Surgical cure can trigger recurrence of past inflammatory disease		
Neuroendocrine	Early life stress is linked to an increased incidence of asthma	Depression and anxiety are associated with allergic rhinitis	Circadian rhythm is associated with nocturnal pruritus in atopic dermatitis
SEX HORMONES			
Estrogen	Increased asthma prevalence and severity after puberty; during pregnancy, perimenopause and with hormone replacement therapy	Increased levels lead to more pronounced rhinitis symptoms	Improves skin barrier
Progesterone	Cell-specific and contradictory effects	Similar effects as estrogen	Impairs skin barrier recovery
Testosterone (androgens)	Decreased asthma prevalence and severity in males after puberty	Likely ameliorates rhinitis symptoms	Impairs skin barrier integrity

FIGURE 1. Visual representation of endocrine glands, with table outlining the hormonal effects on allergy, rhinitis, and eczema.

these studies suggested that androgens are implicated in the pathogenesis of AD, other studies did not suggest this.[72]

Progesterone can also affect AD. Progesterone impairs skin barrier recovery, an effect potentiated by estrogen.[69] Investigators proposed that progesterone influences skin barrier homeostasis via an interaction with the keratocyte cell membrane, but further studies are needed. Finally, maternal sex hormones also affect AD, as illustrated by an inverse association between maternal progesterone levels and the risk for AD in girls.[73]

INSULIN

Diabetes mellitus (DM), a disorder of glucose regulation,[74] is categorized as type 1 (DM1) and 2 (DM2), the former by autoimmune destruction of pancreatic islet cells leading to deficient insulin production, and the latter because of insulin resistance, followed by pancreatic islet β cell failure and loss of compensatory hyperinsulinemia. The relationship between these two DM types and atopic conditions is discussed subsequently.

Type 1 diabetes mellitus

T_H1 cells are implicated in pancreatic islet cell destruction characteristic of DM1. Children with DM1 and their siblings versus controls have less asthma,[75] which raises the possibility that a predisposition toward T_H1- over T_H2-mediated immunity protects against the development of childhood asthma, predominantly a T_H2-mediated disease.[76] Conflicting evidence also is reported in which prior DM1 may reduce[77] or increase[78] the risk for subsequent asthma. A 2020 prospective study of children aged 9 to 11 years, who were at high risk for DM1, indicated that the presence of DM1-related autoantibodies protects against subsequent asthma.[79] However, in a longitudinal Dutch cohort study, similar rates of asthma exacerbations and asthma medication use over a 5-year follow-up were found in children both with and without DM1.[80] Children with DM1 had similar lung function independent of atopic status, with predicted values comparable to the general population.[81] These data suggest that the association between DM1 and asthma is complex and may be limited to specific populations.

In contrast to asthma, DM1-related autoantibodies do not protect against the subsequent development of allergic rhinitis.[79] A meta-analysis did not detect an association between DM1 and this disease.[82]

Atopic dermatitis is typically a T_H2-mediated disease compared with DM1, which is a T_H1-mediated disease. However, T_H1 cytokines are implicated in certain AD subsets.[60] There is conflicting evidence of an association between DM1 and AD. An international epidemiologic study found that DM1 correlates with the prevalence of AD among adolescents after adjusting for latitude.[83] Similarly, an analysis of a Taiwanese health care claims database showed that children with DM1 were at higher risk for developing AD.[84] In contrast, a large study of Danish twins, after appropriate consideration of sex and age, indicated that subjects with DM1 compared with those without it had a lower risk for self-reported AD. Furthermore, among discordant twins, twins with DM1 versus those without it had a lower risk for AD.[85] Differences in geographic location and study

design could account for these discrepant results. An association between DM1 and AD is not reliably established.

The mechanisms linking DM1 with atopic conditions may be unrelated to T_H1-T_H2 polarization and may instead relate to the effects of insulin or its deficiency on allergic inflammation or airway structural cells, which are not yet well understood.[86-89]

Type 2 diabetes mellitus

Rats and mice administered exogenous insulin exhibit enhanced bronchoconstriction,[90] possibly owing to increased laminin expression in ASM extracellular matrices.[91] Type 2 DM is associated with more severe asthma outcomes in adults. Insulin resistance characterizes DM2 and correlates with worse lung function.[92] Obesity is associated with both DM2 and asthma, and insulin resistance potentiates the association between obesity and asthma.[93] Individuals with high glycated hemoglobin (HbA1C) in the diabetic range (6.5% or greater) versus those with normal levels exhibit 33% higher rates of asthma exacerbations.[94] Glycated hemoglobin levels are directly associated with greater odds of asthma hospitalizations,[95] and individuals with asthma and DM compared with controls experience longer hospitalization rates and greater costs and risk for readmission.[96] These findings indicate that DM2 has adverse effects on asthma severity outcomes. Epidemiologic studies also indicate that antidiabetic drugs, such as metformin[97] and glucagon-like peptide-1 receptor agonists[98] may ameliorate asthma exacerbations. Clinical trials are needed to confirm this hypothesis.

Similar to asthma, many subjects with chronic rhinosinusitis (CRS) exhibit a T_H2-dominant, allergic phenotype.[99] Therefore, a potential relationship between DM2 and CRS was investigated. A 2020 study using the Korean National Health and Nutrition Examination Survey found that both DM and HbA1C levels were associated with lower odds of allergic rhinitis.[100] Elevated fasting blood glucose levels were associated with higher odds of allergic rhinitis in Japanese adults.[101] In contrast, elevated HbA1C levels were associated with greater odds of magnetic resonance imaging–ascertained paranasal sinus disease. This suggests that the relationship between DM2 and CRS may vary by phenotype. The impact of DM2 on the surgical management of complicated CRS is unclear. One retrospective study indicated a higher incidence of postoperative infections and less substantial improvements in sinonasal outcomes for individuals with DM2 versus those without it.[102] In contrast, a case-control study described similar symptomatic improvement after surgery between individuals with and without DM2.[103] Prospective studies are needed on the impact of DM2 on the surgical management of CRS.

The relationship between DM2 and AD remains controversial. A 2015 US survey-based study found that adults with AD had a higher incidence of DM.[104] Similar results were reported in a large Israeli cross-sectional study of adults with moderate to severe AD. The study was adjusted for age, sex, socioeconomic status, comorbidities, and smoking.[105] In contrast, a 2018 meta-analysis did not detect an association between hyperglycemia and AD.[106] Furthermore, a 2017 longitudinal Danish study found no relationship between DM2 and AD, and instead proposed that associations between these diseases was mediated by factors such as age, alcohol use, smoking, and the use of topical and systemic corticosteroids.[107] However, it is hypothesized that gestational DM could be a risk factor for childhood AD.[108]

THYROID HORMONE

Asthma

Hyperthyroidism is associated with asthma exacerbations.[109] The etiology is speculated to be related to alterations in the formation of reactive oxygen species.[110,111] Symptoms improve once a euthyroid state is achieved. Screening thyroid laboratory values in asthmatic patients with exacerbations should be obtained if there are clinical signs and symptoms of hyperthyroidism.[112] It is important not to confuse the clinical signs of hyperthyroidism, such as palpitations, anxiety, and tremors, with side effects from bronchodilators.[111,113,114]

Conversely, hypothyroidism is linked to milder asthma symptoms, possibly from reduced metabolic processes from the lower T4 and T3 hormones leading to decreased oxygen consumption.[115-117] During an asthma exacerbation, as with any acute illness, subjects with normal thyroid function can experience a similar protective reduction of metabolism from a decreased conversion of the inactive T4 to the biologically active T3 hormone while maintaining normal thyroid stimulating hormone (TSH) levels, a condition known as sick euthyroid syndrome.[118] Hypothyroidism is identified more frequently in women and those aged greater than 65 years.[119] Women, particularly those with nonallergic asthma, have a higher prevalence of positive thyroid peroxidase antibody levels diagnostic of Hashimoto's thyroiditis.[120,121] The higher prevalence of hypothyroidism in adult females does not imply a causation of asthma, because the latter is also independently more prevalent in this sex.[122] A population-based cohort study of Danish national registers showed an increased incidence of asthma in children born to mothers with hypothyroidism. The highest risk occurs among mothers not receiving treatment for hypothyroidism during pregnancy.[123]

A history of excessive iodine intake or thyroid gland pathology raises additional considerations in asthmatic patients. Large iodine doses, such as from amiodarone or after computed tomography scans, are associated with thyroid dysfunction.[124] Supersaturated potassium iodide, historically used as an expectorant by subjects with asthma, can still be obtained from compounding pharmacies. Several case reports linked asthma exacerbations with supersaturated potassium iodide–induced hyperthyroidism.[125,126] Tracheobronchomalacia (weakening of the airway) or excessive dynamic airway collapse (bulging of the posterior wall of the trachea that moves forward to touch the anterior wall during breathing) were associated with a history of thyroidectomy, thyroiditis, goiter, or thyroid malignancies in bronchoscopies of 34 of 264 subjects. Although these results are limited by sample size and selection bias, they remain an important consideration because subjects with tracheobronchomalacia or excessive dynamic airway collapse can present with poorly controlled asthma despite optimal therapeutic escalation.[127]

Rhinitis

Subjects with allergic rhinitis have a higher incidence of hypothyroidism versus normal patients.[128] Hypothyroidism leads to prolonged mucociliary clearance that increases the risk for upper respiratory and sinonasal infections,[129] sometimes referred to as hormonal rhinopathy. Clinically significant improvement in

FIGURE 2. Nummular eczema. Image used with permission of the American Academy of Dermatology National Library of Dermatologic Teaching Slides.

FIGURE 3. Pretibial myxedema in patient with Graves' disease.

turbinate hypertrophy, mucosal pallor, clearance time, and nasal peak flow were noted in 25 hypothyroid subjects with allergic rhinitis when levothyroxine was initiated and a thyroid stimulating hormone less than 4.0 mIU/L was achieved.[130] Concomitant treatment of allergic rhinitis and hypothyroidism is more effective for rhinitis than just hypothyroid treatment alone.[131] The inflammatory effect of seasonal allergic rhinitis led to exacerbations of existing and new-onset Graves' disease in case reports from Japan.[132,133]

Eczema

The literature does not support a causal relationship between atopic eczema and hypothyroidism, but hypothyroidism could exacerbate atopic eczema. Nummular eczema (or asteatotic eczema, a much more severe form) is characteristic of hypothyroidism. It is associated with dry skin and pruritus, subject to scratching. It presents with round, pruritic lesions (Figure 2).[134,135] The more severe asteatotic eczema, also known as eczema craquelé, presents with dry, cracked, and scaling skin with irregular fissuring.[136] Management of both includes treatment of hypothyroidism. With autoimmune hyperthyroidism (Graves' disease), pretibial myxedema or thyroid dermopathy presents as nonpitting nodules caused by the accumulation of glycosaminoglycans (Figure 3). Treatment of Graves' disease does not resolve the problem; management is supportive.[137]

CORTISOL

Cortisol release is dictated by the hypothalamic–pituitary–adrenal (HPA) axis. The hypothalamus responds to complex environmental and hormonal stimuli through the neuroendocrine system. Some of these complex associations are reviewed followed by specifics on the effects of hypocortisolism and hypercortisolism.

Multiple studies show a connection between psychological stress and asthma exacerbations. Activation of the anterior cingulate cortex, insula, and limbic structures in the hypothalamus initiate signal transduction directly affecting the lungs and indirectly affecting the HPA and the sympathetic–adrenal–medullary axis.[138,139] This results in amplification of T_H2-type inflammation in the lungs and can lead to immune dysregulation and suppression.[140] Early life, including prenatal stress, is linked to an increased incidence of asthma.[141,142]

Seasonal allergic rhinitis, a concept termed "allergic mood," is linked to depression and anxiety.[143] High levels of vasoactive intestinal peptide and substance P in the mucosal tissue of subjects with allergic rhinitis likely have a role in its pathogenesis.[144] Alterations in the response of the HPA in cases of atopic eczema in subjects with depression and attention-deficit hyperactivity disorder are documented.[145-147] Finally, circadian rhythm–related neuroendocrine factors are associated with nocturnal pruritus in subjects with atopic eczema.[148]

Adrenal insufficiency (AI) can be primary, from adrenal destruction, or secondary, from hypothalamic–pituitary pathology or suppression from prolonged glucocorticoid use. Although AI does not cause asthma, severe exacerbations of asthma are associated with it and can potentially trigger an adrenal crisis manifested as hypoglycemia, decreased consciousness or coma, convulsions, hypotension, abdominal pain, syncope, and death.[149-151] Chronic AI can present with vague symptoms: fatigue, decreased appetite, nausea, weakness, anhedonia, and weight loss. Hyperpigmentation and salt wasting are exclusive to primary adrenal destruction. Eosinophilia can be present and resolves with corticosteroids.[152] If AI is suspected a random 8 to 9 AM cortisol level should be performed. A cortisol of 5 μmg/dL or less is highly suspicious for the disease.[153] A cosyntropin stimulation test is used to confirm the diagnosis.[154]

Endogenous hypercortisolism, known as Cushing syndrome, causes extreme catabolic and anti-inflammatory effects. The latter can result in the resolution of asthma.[155] Surgical treatment of Cushing syndrome can lead to the reoccurrence of asthma and asthma exacerbations.[156]

CONCLUSIONS

Physiologic and pathologic hormonal fluctuations can affect asthma, rhinitis, and eczema (Figure 1). Guidelines to screen for these endocrine disorders are lacking. Recognizing these hormonal associations and, when necessary, appropriately treating them will improve asthma, rhinitis, and eczema outcomes as well as the underlying endocrinopathy. When necessary, an endocrinologist should be consulted.

REFERENCES

1. Chen Y, Stewart P, Johansen H, McRae L, Taylor G. Sex difference in hospitalization due to asthma in relation to age. J Clin Epidemiol 2003;56:180-7.

2. Kynyk JA, Mastronarde JG, McCallister JW. Asthma, the sex difference. Curr Opin Pulm Med 2011;17:6-11.
3. Skobeloff EM, Spivey WH, Silverman R, Eskin BA, Harchelroad F, Alessi TV. The effect of the menstrual cycle on asthma presentations in the emergency department. Arch Intern Med 1996;156:1837-40.
4. Tan KS, McFarlane LC, Lipworth BJ. Loss of normal cyclical beta 2 adrenoceptor regulation and increased premenstrual responsiveness to adenosine monophosphate in stable female asthmatic patients. Thorax 1997;52:608-11.
5. Schatz M, Harden K, Forsythe A, Chilingar L, Hoffman C, Sperling W, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. J Allergy Clin Immunol 1988;81:509-17.
6. Schatz M, Camargo CA Jr. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. Ann Allergy Asthma Immunol 2003;91:553-8.
7. Jenkins MA, Dharmage SC, Flander LB, Douglass JA, Ugoni AM, Carlin JB, et al. Parity and decreased use of oral contraceptives as predictors of asthma in young women. Clin Exp Allergy 2006;36:609-13.
8. Lieberoth S, Gade EJ, Brok J, Backer V, Thomsen SF. Age at menarche and risk of asthma: systematic review and meta-analysis. J Asthma 2014;51:559-65.
9. Macsali F, Real FG, Omenaas ER, Bjorge L, Janson C, Franklin K, et al. Oral contraception, body mass index, and asthma: a cross-sectional Nordic-Baltic population survey. J Allergy Clin Immunol 2009;123:391-7.
10. Nwaru BI, Sheikh A. Hormonal contraceptives and asthma in women of reproductive age: analysis of data from serial national Scottish Health Surveys. J R Soc Med 2015;108:358-71.
11. Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. Am J Respir Crit Care Med 1995;152:1183-8.
12. Cai Y, Zhou J, Webb DC. Estrogen stimulates Th2 cytokine production and regulates the compartmentalisation of eosinophils during allergen challenge in a mouse model of asthma. Int Arch Allergy Immunol 2012;158:252-60.
13. Grimaldi CM, Cleary J, Dagtas AS, Moussai D, Diamond B. Estrogen alters thresholds for B cell apoptosis and activation. J Clin Invest 2002;109:1625-33.
14. Ivanova MM, Mazhawidza W, Dougherty SM, Minna JD, Klinge CM. Activity and intracellular location of estrogen receptors alpha and beta in human bronchial epithelial cells. Mol Cell Endocrinol 2009;305:12-21.
15. Jensen F, Woudwyk M, Teles A, Woidacki K, Taran F, Costa S, et al. Estradiol and progesterone regulate the migration of mast cells from the periphery to the uterus and induce their maturation and degranulation. PLoS One 2010;5:e14409.
16. Lee SH. Uterine epithelial and eosinophil estrogen receptors in rats during the estrous cycle. Histochemistry 1982;74:443-52.
17. Phiel KL, Henderson RA, Adelman SJ, Elloso MM. Differential estrogen receptor gene expression in human peripheral blood mononuclear cell populations. Immunol Lett 2005;97:107-13.
18. Zaitsu M, Narita S, Lambert KC, Grady JJ, Estes DM, Curran EM, et al. Estradiol activates mast cells via a non-genomic estrogen receptor-alpha and calcium influx. Mol Immunol 2007;44:1977-85.
19. Townsend EA, Thompson MA, Pabelick CM, Prakash YS. Rapid effects of estrogen on intracellular Ca2+ regulation in human airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 2010;298:L521-30.
20. Townsend EA, Meuchel LW, Thompson MA, Pabelick CM, Prakash YS. Estrogen increases nitric-oxide production in human bronchial epithelium. J Pharmacol Exp Ther 2011;339:815-24.
21. Tam A, Wadsworth S, Dorscheid D, Man SF, Sin DD. Estradiol increases mucus synthesis in bronchial epithelial cells. PLoS One 2014;9:e100633.
22. Sheridan JT, Gilmore RC, Watson MJ, Archer CB, Tarran R. 17beta-Estradiol inhibits phosphorylation of stromal interaction molecule 1 (STIM1) protein: implication for store-operated calcium entry and chronic lung diseases. J Biol Chem 2013;288:33509-18.
23. Degano B, Prevost MC, Berger P, Molimard M, Pontier S, Rami J, et al. Estradiol decreases the acetylcholine-elicited airway reactivity in ovariectomized rats through an increase in epithelial acetylcholinesterase activity. Am J Respir Crit Care Med 2001;164:1849-54.
24. Masuda C, Miyasaka T, Kawakami K, Inokuchi J, Kawano T, Dobashi-Okuyama K, et al. Sex-based differences in CD103(+) dendritic cells promote female-predominant Th2 cytokine production during allergic asthma. Clin Exp Allergy 2018;48:379-93.
25. Paharkova-Vatchkova V, Maldonado R, Kovats S. Estrogen preferentially promotes the differentiation of CD11c+ CD11b(intermediate) dendritic cells from bone marrow precursors. J Immunol 2004;172:1426-36.
26. Lambert KC, Curran EM, Judy BM, Milligan GN, Lubahn DB, Estes DM. Estrogen receptor alpha (ERalpha) deficiency in macrophages results in increased stimulation of CD4+ T cells while 17beta-estradiol acts through ERalpha to increase IL-4 and GATA-3 expression in CD4+ T cells independent of antigen presentation. J Immunol 2005;175:5716-23.
27. Bynoe MS, Grimaldi CM, Diamond B. Estrogen up-regulates Bcl-2 and blocks tolerance induction of naive B cells. Proc Natl Acad Sci U S A 2000;97:2703-8.
28. Hamano N, Terada N, Maesako K, Numata T, Konno A. Effect of sex hormones on eosinophilic inflammation in nasal mucosa. Allergy Asthma Proc 1998;19:263-9.
29. Watanabe Y, Tajiki-Nishino R, Tajima H, Fukuyama T. Role of estrogen receptors alpha and beta in the development of allergic airway inflammation in mice: a possible involvement of interleukin 33 and eosinophils. Toxicology 2019;411:93-100.
30. Tchernitchin AN, Barrera J, Arroyo P, Mena MA, Vilches K, Grunert G. Degranulatory action of estradiol on blood eosinophil leukocytes in vivo and in vitro. Agents Actions 1985;17:60-6.
31. Kim MS, Chae HJ, Shin TY, Kim HM, Kim HR. Estrogen regulates cytokine release in human mast cells. Immunopharmacol Immunotoxicol 2001;23:495-504.
32. Munoz-Cruz S, Mendoza-Rodriguez Y, Nava-Castro KE, Yepez-Mulia L, Morales-Montor J. Gender-related effects of sex steroids on histamine release and FcεRI expression in rat peritoneal mast cells. J Immunol Res 2015;2015:351829.
33. Narita S, Goldblum RM, Watson CS, Brooks EG, Estes DM, Curran EM, et al. Environmental estrogens induce mast cell degranulation and enhance IgE-mediated release of allergic mediators. Environ Health Perspect 2007;115:48-52.
34. Vliagoftis H, Dimitriadou V, Boucher W, Rozniecki JJ, Correia I, Raam S, et al. Estradiol augments while tamoxifen inhibits rat mast cell secretion. Int Arch Allergy Immunol 1992;98:398-409.
35. Jain R, Ray JM, Pan JH, Brody SL. Sex hormone-dependent regulation of cilia beat frequency in airway epithelium. Am J Respir Cell Mol Biol 2012;46:446-53.
36. Zhang X, Bao W, Fei X, Zhang Y, Zhang G, Zhou X, et al. Progesterone attenuates airway remodeling and glucocorticoid resistance in a murine model of exposing to ozone. Mol Immunol 2018;96:69-77.
37. Vasiadi M, Kempuraj D, Boucher W, Kalogeromitros D, Theoharides TC. Progesterone inhibits mast cell secretion. Int J Immunopathol Pharmacol 2006;19:787-94.
38. 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;8:3029-35.e4.
39. Mohan SS, Knuiman MW, Divitini ML, James AL, Musk AW, Handelsman DJ, et al. Higher serum testosterone and dihydrotestosterone, but not oestradiol, are independently associated with favourable indices of lung function in community-dwelling men. Clin Endocrinol (Oxf) 2015;83:268-76.
40. Svartberg J, Schirmer H, Medbo A, Melbye H, Aasebo U. Reduced pulmonary function is associated with lower levels of endogenous total and free testosterone. The Tromso study. Eur J Epidemiol 2007;22:107-12.
41. Zein JG, McManus JM, Sharifi N, Erzurum SC, Marozkina N, Lahm T, et al. Benefits of airway androgen receptor expression in human asthma. Am J Respir Crit Care Med 2021;204:285-93.
42. Wenzel SE, Robinson CB, Leonard JM, Panettieri RA Jr. Nebulized dehydroepiandrosterone-3-sulfate improves asthma control in the moderate-to-severe asthma results of a 6-week, randomized, double-blind, placebo-controlled study. Allergy Asthma Proc 2010;31:461-71.
43. Espinoza J, Montano LM, Perusquia M. Nongenomic bronchodilating action elicited by dehydroepiandrosterone (DHEA) in a guinea pig asthma model. J Steroid Biochem Mol Biol 2013;138:174-82.
44. Cephus JY, Stier MT, Fuseini H, Yung JA, Toki S, Bloodworth MH, et al. Testosterone attenuates group 2 innate lymphoid cell-mediated airway inflammation. Cell Rep 2017;21:2487-99.
45. Laffont S, Blanquart E, Savignac M, Cenac C, Laverny G, Metzger D, et al. Androgen signaling negatively controls group 2 innate lymphoid cells. J Exp Med 2017;214:1581-92.
46. Olsen NJ, Gu X, Kovacs WJ. Bone marrow stromal cells mediate androgenic suppression of B lymphocyte development. J Clin Invest 2001;108:1697-704.
47. Yamatomo T, Okano M, Ono T, Nakayama E, Yoshino T, Satoskar AR, et al. Sex-related differences in the initiation of allergic rhinitis in mice. Allergy 2001;56:525-31.
48. Wei J, Gerlich J, Genuneit J, Nowak D, Vogelberg C, von Mutius E, et al. Hormonal factors and incident asthma and allergic rhinitis during puberty in girls. Ann Allergy Asthma Immunol 2015;115:21-7.e2.
49. Philpott CM, El-Alami M, Murty GE. The effect of the steroid sex hormones on the nasal airway during the normal menstrual cycle. Clin Otolaryngol Allied Sci 2004;29:138-42.
50. Haeggstrom A, Ostberg B, Stjerna P, Graf P, Hallen H. Nasal mucosal swelling and reactivity during a menstrual cycle. ORL J Otorhinolaryngol Relat Spec 2000;62:39-42.

51. Espersen J, Weber U, Romer-Franz A, Lenarz T, Stolle SRO, Warnecke A. Level of sex hormones and their association with acetylsalicylic acid intolerance and nasal polyposis. PLoS One 2020;15:e0243732.
52. Ellegard E, Hellgren M, Toren K, Karlsson G. The incidence of pregnancy rhinitis. Gynecol Obstet Invest 2000;49:98-101.
53. Ellegard E, Oscarsson J, Bougoussa M, Igout A, Hennen G, Eden S, et al. Serum level of placental growth hormone is raised in pregnancy rhinitis. Arch Otolaryngol Head Neck Surg 1998;124:439-43.
54. Ellegard EK, Karlsson NG, Ellegard LH. Rhinitis in the menstrual cycle, pregnancy, and some endocrine disorders. Clin Allergy Immunol 2007;19:305-21.
55. Shirasaki H, Watanabe K, Kanaizumi E, Konno N, Sato J, Narita S, et al. Expression and localization of steroid receptors in human nasal mucosa. Acta Otolaryngol 2004;124:958-63.
56. Helmi AM, El Ghazzawi IF, Mandour MA, Shehata MA. The effect of oestrogen on the nasal respiratory mucosa. An experimental histopathological and histochemical study. J Laryngol Otol 1975;89:1229-41.
57. Toppozada H, Toppozada M, El-Ghazzawi I, Elwany S. The human respiratory nasal mucosa in females using contraceptive pills. An ultramicroscopic and histochemical study. J Laryngol Otol 1984;98:43-51.
58. Hamano N, Terada N, Maesako K, Ikeda T, Fukuda S, Wakita J, et al. Expression of histamine receptors in nasal epithelial cells and endothelial cells—the effects of sex hormones. Int Arch Allergy Immunol 1998;115:220-7.
59. Pelikan Z. Possible immediate hypersensitivity reaction of the nasal mucosa to oral contraceptives. Ann Allergy 1978;40:211-9.
60. Tokura Y, Hayano S. Subtypes of atopic dermatitis: from phenotype to endotype. Allergol Int 2022;71:14-24.
61. Harvell J, Hussona-Saeed I, Maibach HI. Changes in transepidermal water loss and cutaneous blood flow during the menstrual cycle. Contact Dermatitis 1992;27:294-301.
62. Kiriyama K, Sugiura H, Uehara M. Premenstrual deterioration of skin symptoms in female patients with atopic dermatitis. Dermatology 2003;206:110-2.
63. Kanda N, Hoashi T, Saeki H. The roles of sex hormones in the course of atopic dermatitis. Int J Mol Sci 2019;20:4660.
64. Zouboulis CC, Chen WC, Thornton MJ, Qin K, Rosenfield R. Sexual hormones in human skin. Horm Metab Res 2007;39:85-95.
65. Hanley K, Rassner U, Jiang Y, Vansomphone D, Crumrine D, Komuves L, et al. Hormonal basis for the gender difference in epidermal barrier formation in the fetal rat. Acceleration by estrogen and delay by testosterone. J Clin Invest 1996;97:2576-84.
66. Chen Y, Yokozeki H, Katagiri K. Physiological and functional changes in the stratum corneum restored by oestrogen in an ovariectomized mice model of climacterium. Exp Dermatol 2017;26:394-401.
67. Hung CF, Chen WY, Aljuffali IA, Lin YK, Shih HC, Fang JY. Skin aging modulates percutaneous drug absorption: the impact of ultraviolet irradiation and ovariectomy. Age (Dordr) 2015;37:21.
68. Hanley K, Jiang Y, Holleran WM, Elias PM, Williams ML, Feingold KR. Glucosylceramide metabolism is regulated during normal and hormonally stimulated epidermal barrier development in the rat. J Lipid Res 1997;38:576-84.
69. Tsutsumi M, Denda M. Paradoxical effects of beta-estradiol on epidermal permeability barrier homeostasis. Br J Dermatol 2007;157:776-9.
70. Kao JS, Garg A, Mao-Qiang M, Crumrine D, Ghadially R, Feingold KR, et al. Testosterone perturbs epidermal permeability barrier homeostasis. J Invest Dermatol 2001;116:443-51.
71. Calvo E, Luu-The V, Morissette J, Martel C, Labrie C, Bernard B, et al. Pangenomic changes induced by DHEA in the skin of postmenopausal women. J Steroid Biochem Mol Biol 2008;112:186-93.
72. Kasperska-Zajac A, Brzoza Z, Rogala B. Serum concentration of dehydroepiandrosterone sulfate and testosterone in women with severe atopic eczema/dermatitis syndrome. J Investig Allergol Clin Immunol 2007;17:160-3.
73. Pincus M, Keil T, Rucke M, Bruenahl C, Magdorf K, Klapp BF, et al. Fetal origin of atopic dermatitis. J Allergy Clin Immunol 2010;125:273-5.e1-4.
74. Centers for Disease Control and Prevention. National Diabetes Statistics Report 2020. Estimates of diabetes and its burden in the United States. Acessed December 16, 2021. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf
75. Douek IF, Leech NJ, Gillmor HA, Bingley PJ, Gale EA. Children with type-1 diabetes and their unaffected siblings have fewer symptoms of asthma. Lancet 1999;353:1850.
76. Conrad LA, Cabana MD, Rastogi D. Defining pediatric asthma: phenotypes to endotypes and beyond. Pediatr Res 2021;90:45-51.
77. Metsala J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM, et al. The association between asthma and type 1 diabetes: a paediatric case-cohort study in Finland, years 1981-2009. Int J Epidemiol 2018;47:409-16.
78. Hsiao YT, Cheng WC, Liao WC, Lin CL, Shen TC, Chen WC, et al. Type 1 diabetes and increased risk of subsequent asthma: a nationwide population-based cohort study. Medicine (Baltimore) 2015;94:e1466.
79. Krischer JP, Cuthbertson D, Couluris M, Knip M, Virtanen SM. Association of diabetes-related autoantibodies with the incidence of asthma, eczema and allergic rhinitis in the TRIGR randomised clinical trial. Diabetologia 2020;63:1796-807.
80. Ahmadizar F, Souverein PC, Arets HG, de Boer A, Maitland-van der Zee AH. Asthma related medication use and exacerbations in children and adolescents with type 1 diabetes. Pediatr Pulmonol 2016;51:1113-21.
81. Tosca MA, Silvestri M, Olcese R, D'Annunzio G, Pistorio A, Lorini R, et al. Allergic sensitization and symptoms, body mass index, and respiratory function in children with type 1 diabetes mellitus. Ann Allergy Asthma Immunol 2012;108:128-9.
82. Cardwell CR, Shields MD, Carson DJ, Patterson CC. A meta-analysis of the association between childhood type 1 diabetes and atopic disease. Diabetes Care 2003;26:2568-74.
83. Fsadni P, Fsadni C, Fava S, Montefort S. Correlation of worldwide incidence of type 1 diabetes (DiaMond) with prevalence of asthma and atopic eczema (ISAAC). Clin Respir J 2012;6:18-25.
84. Lin CH, Wei CC, Lin CL, Lin WC, Kao CH. Childhood type 1 diabetes may increase the risk of atopic dermatitis. Br J Dermatol 2016;174:88-94.
85. Thomsen SF, Duffy DL, Kyvik KO, Skytthe A, Backer V. Relationship between type 1 diabetes and atopic diseases in a twin population. Allergy 2011;66:645-7.
86. Ferreira SS, Oliveira MA, Tsujita M, Nunes FPB, Casagrande FB, Gomes E, et al. Insulin modulates the immune cell phenotype in pulmonary allergic inflammation and increases pulmonary resistance in diabetic mice. Front Immunol 2020;11:84.
87. Martins JO, Campos CA, Cruz JW, Manzolli S, Alves VA, Vianna EO, et al. Insulin modulates cytokine release and selectin expression in the early phase of allergic airway inflammation in diabetic rats. BMC Pulm Med 2010;10:39.
88. Sun Q, Li J, Gao F. New insights into insulin: The anti-inflammatory effect and its clinical relevance. World J Diabetes 2014;5:89-96.
89. Cavalher-Machado SC, de Lima WT, Damazo AS, de Frias Carvalho V, Martins MA, e Silva PM, et al. Down-regulation of mast cell activation and airway reactivity in diabetic rats: role of insulin. Eur Respir J 2004;24:552-8.
90. Proskocil BJ, Calco GN, Nie Z. Insulin acutely increases agonist-induced airway smooth muscle contraction in humans and rats. Am J Physiol Lung Cell Mol Physiol 2021;320:L545-56.
91. Dekkers BG, Schaafsma D, Tran T, Zaagsma J, Meurs H. Insulin-induced laminin expression promotes a hypercontractile airway smooth muscle phenotype. Am J Respir Cell Mol Biol 2009;41:494-504.
92. Forno E, Han YY, Muzumdar RH, Celedon JC. Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma. J Allergy Clin Immunol 2015;136:304-11.e8.
93. Cardet JC, Ash S, Kusa T, Camargo CA Jr, Israel E. Insulin resistance modifies the association between obesity and current asthma in adults. Eur Respir J 2016;48:403-10.
94. Wu TD, Brigham EP, Keet CA, Brown TT, Hansel NN, McCormack MC. Association between prediabetes/diabetes and asthma exacerbations in a claims-based obese asthma cohort. J Allergy Clin Immunol Pract 2019;7:1868-73.e5.
95. Yang G, Han YY, Forno E, Yan Q, Rosser F, Chen W, et al. Glycated hemoglobin A1c, lung function, and hospitalizations among adults with asthma. J Allergy Clin Immunol Pract 2020;8:3409-15.e1.
96. Zhang P, Lopez R, Attaway AH, Georas SN, Khatri SB, Abi-Saleh S, et al. Diabetes mellitus is associated with worse outcome in patients hospitalized for asthma. J Allergy Clin Immunol Pract 2021;9:1562-9.e1.
97. Wu TD, Keet CA, Fawzy A, Segal JB, Brigham EP, McCormack MC. Association of metformin initiation and risk of asthma exacerbation. A claims-based cohort study. Ann Am Thorac Soc 2019;16:1527-33.
98. Foer D, Beeler PE, Cui J, Karlson EW, Bates DW, Cahill KN. Asthma exacerbations in patients with type 2 diabetes and asthma on glucagon-like peptide-1 receptor agonists. Am J Respir Crit Care Med 2021;203:831-40.
99. McCormick JP, Thompson HM, Cho DY, Woodworth BA, Grayson JW. Phenotypes in chronic rhinosinusitis. Curr Allergy Asthma Rep 2020;20:20.
100. Lee TK, Jeon YJ, Jung SJ. Bi-directional association between allergic rhinitis and diabetes mellitus from the national representative data of South Korea. Sci Rep 2021;11:4344.
101. Hashimoto Y, Futamura A. Prevalence of allergic rhinitis is lower in subjects with higher levels of fasting plasma glucose. Diabetes Care 2010;33:e143.
102. Zhang Z, Adappa ND, Lautenbach E, Chiu AG, Doghramji L, Howland TJ, et al. The effect of diabetes mellitus on chronic rhinosinusitis and sinus surgery outcome. Int Forum Allergy Rhinol 2014;4:315-20.

103. Hajjij A, Mace JC, Soler ZM, Smith TL, Hwang PH. The impact of diabetes mellitus on outcomes of endoscopic sinus surgery: a nested case-control study. Int Forum Allergy Rhinol 2015;5:533-40.
104. Silverberg JI, Greenland P. Eczema and cardiovascular risk factors in 2 US adult population studies. J Allergy Clin Immunol 2015;135:721-8.e6.
105. Shalom G, Dreiher J, Kridin K, Horev A, Khoury R, Battat E, et al. Atopic dermatitis and the metabolic syndrome: a cross-sectional study of 116 816 patients. J Eur Acad Dermatol Venereol 2019;33:1762-7.
106. Ali Z, Ulrik CS, Agner T, Thomsen SF. Association between atopic dermatitis and the metabolic syndrome: a systematic review. Dermatology 2018;234:79-85.
107. Andersen YMF, Egeberg A, Gislason GH, Skov L, Knop FK, Thyssen JP. Adult atopic dermatitis and the risk of type 2 diabetes. J Allergy Clin Immunol 2017;139:1057-9.
108. Kumar R, Ouyang F, Story RE, Pongracic JA, Hong X, Wang G, et al. Gestational diabetes, atopic dermatitis, and allergen sensitization in early childhood. J Allergy Clin Immunol 2009;124:1031-8.e1-4.
109. Spector SL. Common triggers of asthma. Postgrad Med 1991;90:50-9.
110. Voraphani N, Gladwin MT, Contreras AU, Kaminski N, Tedrow JR, Milosevic J, et al. An airway epithelial iNOS-DUOX2-thyroid peroxidase metabolome drives Th1/Th2 nitrative stress in human severe asthma. Mucosal Immunol 2014;7:1175-85.
111. Luong KV, Nguyen LT. Hyperthyroidism and asthma. J Asthma 2000;37:125-30.
112. Jerez FR, Plaza V, Tarrega J, Casan P, Rodriguez J. Thyroid function and difficult to manage asthma [in Spanish]. Arch Bronconeumol 1998;34:429-32.
113. Settipane GA. Hyperthyroidism exacerbating asthma. Allergy Asthma Proc 2000;21:75-7.
114. White NW, Raine RI, Bateman ED. Asthma and hyperthyroidism. A report of 4 cases. S Afr Med J 1990;78:750-2.
115. Bingyan Z, Dong W. Impact of thyroid hormones on asthma in older adults. J Int Med Res 2019;47:4114-25.
116. Fedrick J, Baldwin JA. Thyroid disease and asthma. BMJ 1977;2:1539.
117. Harrison RN, Tattersfield AE. Airway response to inhaled salbutamol in hyperthyroid and hypothyroid patients before and after treatment. Thorax 1984;39:34-9.
118. Langouche L, Jacobs A, Van den Berghe G. Nonthyroidal illness syndrome across the ages. J Endocr Soc 2019;3:2313-25.
119. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet 2017;390:1550-62.
120. Mohammad HA, Abdelfattah MT, Ali LH, Morsi ZI. Association between anti-thyroid peroxidase and anti-cytokeratin 18 autoantibodies and bronchial asthma in women. Egypt J Chest Dis Tuberc 2016;65:7-14.
121. Samareh Fekri M, Shokoohi M, Gozashti MH, Esmailian S, Jamshidian N, Shadkam-Farokhi M, et al. Association between anti-thyroid peroxidase antibody and asthma in women. Iran J Allergy Asthma Immunol 2012;11:241-5.
122. Centers for Disease Control and Prevention. Asthma prevalence. Accessed February 28, 2022. https://www.cdc.gov/asthma/data-visualizations/prevalence.htm
123. Liu X, Andersen SL, Olsen J, Agerbo E, Schlunssen V, Dharmage SC, et al. Maternal hypothyroidism in the perinatal period and childhood asthma in the offspring. Allergy 2018;73:932-9.
124. Burgi H, Gubler R, Radvila A, Studer H. Hypothyroidism, a side effect of asthma therapy with high doses of iodine [in German]. Schweiz Med Wochenschr 1972;102:837-41.
125. Korsager S, Ostergaard Kristensen HP. Iodine-induced hypothyroidism and its effect on the severity of asthma. Acta Med Scand 1979;205:115-7.
126. Sabih DE, Inayatullah M. Managing thyroid dysfunction in selected special situations. Thyroid Res 2013;6:2.
127. Dal Negro RW, Tognella S, Guerriero M, Micheletto C. Prevalence of tracheobronchomalacia and excessive dynamic airway collapse in bronchial asthma of different severity. Multidiscip Respir Med 2013;8:32.
128. Degirmenci PB, Kirmaz C, Oz D, Bilgir F, Ozmen B, Degirmenci M, et al. Allergic rhinitis and its relationship with autoimmune thyroid diseases. Am J Rhinol Allergy 2015;29:257-61.
129. Kulekci Ozturk S, Sakci E, Kavvasoglu C. Rhinitis in patients with acquired hypothyroidism. Eur Arch Otorhinolaryngol 2021;278:87-92.
130. Gunel C, Basak HS, Guney E. The relationship between hypothyroidism and rhinitis [in Turkish]. Kulak Burun Bogaz Ihtis Derg 2010;20:163-8.
131. Gamzatova AA, Gadzhimirzaev GA, Abusuev SA, Gamzatova EG. Treatment of allergic rhinitis associated with hypothyroidism [in Russian]. Vestn Otorinolaringol 2006;6:34-7.
132. Takeoka K, Hidaka Y, Hanada H, Nomura T, Tanaka S, Takano T, et al. Increase in serum levels of autoantibodies after attack of seasonal allergic rhinitis in patients with Graves' disease. Int Arch Allergy Immunol 2003;132:268-76.
133. Hidaka Y, Masai T, Sumizaki H, Takeoka K, Tada H, Amino N. Onset of Graves' thyrotoxicosis after an attack of allergic rhinitis. Thyroid 1996;6:349-51.
134. American Academy of Dermatology Association. Eczema types: nummular eczema overview. Accessed February 7, 2022. https://www.aad.org/public/diseases/eczema/types/nummular-dermatitis
135. Lugović-Mihić L, Bukvić I, Bulat V, Japundžić I. Factors contributing to chronic urticaria/angioedema and nummular eczema resolution – which findings are crucial? Clin Croat 2019;58:595-603.
136. Patrizi A, Gurioli C, Tengattini V, Bardazzi F. Eczema craquele, an uncommon clinical manifestation of myxedema. J Dtsch Dermatol Ges 2015;13:453-4.
137. Fatourechi V. Pretibial myxedema: pathophysiology and treatment options. Am J Clin Dermatol 2005;6:295-309.
138. Miyasaka T, Dobashi-Okuyama K, Takahashi T, Takayanagi M, Ohno I. The interplay between neuroendocrine activity and psychological stress-induced exacerbation of allergic asthma. Allergol Int 2018;67:32-42.
139. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. Brain Behav Immun 2007;21:993-9.
140. Marshall GD. Neuroendocrine mechanisms of immune dysregulation: applications to allergy and asthma. Ann Allergy Asthma Immunol 2004;93:S11-7.
141. Rosa MJ, Lee AG, Wright RJ. Evidence establishing a link between prenatal and early-life stress and asthma development. Curr Opin Allergy Clin Immunol 2018;18:148-58.
142. Medsker B, Forno E, Simhan H, Celedon JC. Prenatal stress, prematurity, and asthma. Obstet Gynecol Surv 2015;70:773-9.
143. Trikojat K, Luksch H, Rosen-Wolff A, Plessow F, Schmitt J, Buske-Kirschbaum A. "Allergic mood" - depressive and anxiety symptoms in patients with seasonal allergic rhinitis (SAR) and their association to inflammatory, endocrine, and allergic markers. Brain Behav Immun 2017;65:202-9.
144. Fang SY, Shen CL. Neuropeptide innervation and neuroendocrine cells in allergic rhinitis and chronic hypertrophic rhinitis. Clin Exp Allergy 1998;28:228-32.
145. Rupprecht M, Hornstein OP, Schluter D, Schafers HJ, Koch HU, Beck G, et al. Cortisol, corticotropin, and beta-endorphin responses to corticotropin-releasing hormone in patients with atopic eczema. Psychoneuroendocrinology 1995;20:543-51.
146. Rupprecht M, Salzer B, Raum B, Hornstein OP, Koch HU, Riederer P, et al. Physical stress-induced secretion of adrenal and pituitary hormones in patients with atopic eczema compared with normal controls. Exp Clin Endocrinol Diabetes 1997;105:39-45.
147. Buske-Kirschbaum A, Trikojat K, Tesch F, Schmitt J, Roessner V, Luksch H, et al. Altered hypothalamus-pituitary-adrenal axis function: a relevant factor in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder? Psychoneuroendocrinology 2019;105:178-86.
148. Heubeck B, Schonberger A, Hornstein OP. Are shifts in circadian cortisol rhythm an endocrine symptom of atopic eczema? [in German]. Hautarzt 1988;39:12-7.
149. Cydulka RK, Emerman CL. Adrenal function and physiologic stress during acute asthma exacerbation. Ann Emerg Med 1998;31:558-61.
150. Gurnell M, Heaney LG, Price D, Menzies-Gow A. Long-term corticosteroid use, adrenal insufficiency and the need for steroid-sparing treatment in adult severe asthma. J Intern Med 2021;290:240-56.
151. Ahmet A, Mokashi A, Goldbloom EB, Huot C, Jurencak R, Krishnamoorthy P, et al. Adrenal suppression from glucocorticoids: preventing an iatrogenic cause of morbidity and mortality in children. BMJ Paediatrics Open 2019;3:e000569.
152. Spry C. Eosinophilia in Addison's disease. Yale J Biol Med 1976;49:411-3.
153. Nanzer AM, Chowdhury A, Raheem A, Roxas C, Fernandes M, Thomson L, et al. Prevalence and recovery of adrenal insufficiency in steroid-dependent asthma patients receiving biologic therapy. Eur Respir J 2020;56:1902273.
154. Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, et al. Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2016;101:364-89.
155. Samprón N, Undabeitia J, Torres-Bayona S, Úrculo E. Asthma relapse after surgical treatment of Cushing's syndrome [in Spanish]. Neurocirugia (Astur) 2015;26:205-6.
156. Krysiak R, Kedzia A, Okopien B. Relapse of asthma after surgical treatment of Cushing's syndrome. Acta Clin Belg 2013;68:218-9.