

# Perimenstrual Asthma in Adolescents

Subjects: **Pediatrics**

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Asthma is a frequent medical condition in adolescence. The worsening of the most common symptoms perimenstrually is defined as perimenstrual asthma (PMA). The cause of PMA remains unclear, but a role for hormonal milieu is plausible. Data on PMA in adolescents are limited, and its management is not fully established. The fluctuation of estrogens at ovulation and before menstruation and the progesterone secretion during the luteal phase and its subsequent withdrawal seem to be the culprits, because the deterioration of asthma is cyclical during the luteal phase and/or during the first days of the menstrual cycle.

perimenstrual asthma

sex hormones

adolescents

menstrual cycle

## 1. Asthma in Young Female Adolescents

Globally, in people aged 10 to 24 years, respiratory disorders are the sixth leading cause of disability; in 2011, it was estimated that asthma was responsible for 346,000 deaths worldwide each year <sup>[1][2]</sup>. In pediatric age, the prevalence of asthma is higher in males than in females; however, in adulthood, the prevalence is approximately 20% higher in females than in males, indicating a change that occurs during puberty <sup>[3][4]</sup>. The higher prevalence in boys is, in part due, to their smaller airways relative to lung size compared with young girls; however, this is a characteristic that reverses during adolescence <sup>[3]</sup>.

The Global Initiative for Asthma (GINA) guidelines describe asthma as a heterogeneous disease <sup>[5]</sup>, usually characterized by chronic airway inflammation <sup>[6]</sup>. Variability in symptoms and airflow limitation is a feature of asthma that can vary in time and intensity <sup>[5]</sup>. Clusters of demographic, clinical, and pathophysiologic characteristics identify asthma phenotypes and endotypes. No strong relationship has been found between specific pathological features and peculiar clinical patterns and treatment responses; however, in patients with more severe asthma, some phenotype guided treatments have become available <sup>[5][7][8][9]</sup>.

Epidemiologic evidences have shown that the overall prevalence and incidence of asthma are increased in obese individuals, and obesity is a risk factor for airway inflammation <sup>[1][10][11][12][13][14]</sup>. A recent meta-analysis, including six prospective cohort studies on the effect of body weight on future asthma risk, found a twice-higher risk in obese children compared with normal-weight ones, suggesting that obesity is an independent asthma risk factor for the youngest <sup>[15][16]</sup>. Clinical studies also suggest that obesity-related asthma is distinct from normal-weight asthma: it is associated to decreased responsiveness to medications <sup>[17]</sup> and poor disease control <sup>[14][15][18]</sup>, particularly among ethnic-minority children <sup>[18][19]</sup>, contributing to increased healthcare expenditures <sup>[15]</sup>. In terms of ethnic and gender differences, it has been observed that Hispanics and African Americans, who have a higher burden of

obesity-related asthma, tend to have central obesity more frequently, for the same body weight, than Caucasians [15][20], and obese girls are more symptomatic [21][22] than boys [23]. Visceral obesity is responsible for a picture of mechanical obstruction in the lungs, resulting in airflow obstruction and altered lung volumes [15]. The relationship between obesity and asthma is complex [10][24]. In the Severe Asthma Research Program, an age/phenotype-dependent association was found: children with early onset asthma became obese, whereas there was no significant relationship between overweight/obesity and asthma duration in cases of late-onset asthma [1][25]. In the Asthma Adiposity Study conducted by Kattan et al. [19] among 368 adolescents aged 12 to 20 years living in urban areas of the United States, the main finding was the association between adiposity and asthma morbidity [19]. In female adolescents, higher BMI and body fat correlated with worse asthma control, more disease exacerbations, and a lower Tiffenau index (forced expiration, FEV1/forced vital capacity, FVC) [19]. In addition, obese girls, in contrast to boys, lacked the anti-inflammatory properties of serum adiponectin. Indeed, although there were higher serum levels of adiponectin in females, its protective role was observed only in males: one plausible interpretation is that adiponectin receptors are downregulated with elevated adiposity in female adolescents [19]. Adipokines produced by the adipose tissue are likely to mediate the association between obesity and asthma in a gender-specific manner, and asthma outcome seems to be adversely influenced by obesity in girls but not in boys [1][19].

Despite a worldwide reduction in asthma mortality in adults and children over the past 25 years, largely attributable to increased use of inhaled corticosteroids, a wide global disparity in life years lost due to asthma remains [3].

It is much easier to diagnose asthma in teenagers than in younger children. A narrower range of conditions should be considered in the differential diagnosis of the adolescent who presents with recurrent cough, dyspnea, or wheezing [26]. In contrast to preschoolers, it is possible to assess lung function at baseline and in response to bronchodilators or exercise for objective evidence of reversible airway narrowing. However, both under-diagnosis and under-treatment are common [26][27]. Of note, in a Danish study, it has been shown that girls were 50% more likely to have underdiagnosed asthma than boys (69% vs. 33%), and coughing rather than wheezing or breathlessness was the major symptom [28].

Remission of asthma frequently occurs, especially in late adolescence, with reported rates of 16% to 60% [29]. In several population-based studies, remission probability of asthmatic disease in late adolescence was commonly observed and showed a relationship with mild disease, male sex, and absence of atopic trait, particularly sensitization to fur-bearing animals at the age of 7 or 8 years [1][30]. In a prospective study conducted in Sweden since 1996 in people followed from 7 or 8 to 19 years of age, 21% of those with asthma at age 7 were in remission at 19 years old, 38% had periodic asthma, and 41% had persistent asthma [30]; these results were similar to those of other studies [29][31][32][33][34]. Conversely, sensitization and female sex have been identified as important predictors of persistent asthma in several studies [31][35]. In addition, along with a higher incidence among girls [36], the higher remission rate among boys contributes to the change in asthma prevalence ratio between boys and girls. That notwithstanding, puberty is the turning point with male prevalence in early childhood and a more prevalent asthma among women later in life [30]. Other relevant risk factors for pubertal asthma include early airway obstruction, sensitization to fur-bearing animals, more severe asthma in childhood, family history of atopy, being the first-born child, perinatal family stress, extreme preterm birth (23–27 gestational weeks), and low birth weight

per gestational age [1][30][35][37][38][39][40]. In young females, early menarche (before 12 years of age) has been associated with an up to two-fold increased risk of new onset asthma [41][42]. However, the role of heredity, sex, smoking, and sensitization to specific allergens remains to be further investigated [1][43][44][45][46][47].

As far as the role of sex is concerned, both incidence and prevalence of asthma vary accordingly; in addition, age-related changes in sex prevalence are observed [1][48]. Sex differences play a key role in driving numerous conditions, including cardiovascular diseases and, specifically, atherosclerosis [49]; bone metabolism disorders, such as osteoporosis [50]; and some neurological pathologies [51]. Sex hormones are responsible for the expression of such gender differences at the phenotypic and genotypic level [52], including the regulation of airway function and inflammation [52]. Indeed, it has been observed that estrogens are able to prevent cholinergic constriction of asthmatic tracheal rings in vitro [53], and estrogen treatment decreases airway responsiveness to acetylcholine in ovariectomized rats [54]. Female rats appear to be more susceptible than males to allergen-induced airway inflammation [55][56][57]. By examining sex differences in a scenario of allergen exposure delivered exclusively through the airway and in the absence of systemic sensitization and adjuvant, thus dependent solely on IgE, Fc epsilon receptor (FcεRI), and mast cells [52], the inhibitory effects of estrogen on airway hyper-responsiveness (AHR) development are evident [53][54][58][59]. In contrast, when dual allergen sensitization with systemic adjuvant and airway sensitization occurs, female mice develop greater AHR, with estrogen increasing airway inflammation [56][57][60]. Carey et al. also demonstrated that estrogen receptor deficiency led to increased AHR [58].

Unquestionably, female sex hormones, particularly estrogens, play a key role in the pathophysiology of asthma and the development AHR.

Estrogens participate in various biological processes through different molecular actions. They may show either pro- or anti-inflammatory properties depending on the circumstances and the involved tissues.

Lowered levels of estrogens increase the concentration of reactive oxygen species, along with the inhibition of NF-κB transcription factor, indicating their prevalent anti-inflammatory properties.

On the other hand, estrogen therapy in ovariectomized mice reduces reactive oxygen species-induced by ovariectomy in bone marrow [61][62], attenuating the phosphorylation of PKC β (redox-sensitive cytoplasmic kinase) [61][62].

It is well-known that female patients of all ages endure remarkably lower rates of infection and resultant mortality than male subjects.

Immunological evidences suggest that female sex hormones are key factors in the etiology and course of chronic inflammatory diseases, being linked to significant influencing reproductive stages, such as menstrual cycle, pregnancy, perimenopause, and postmenopausal status [63][64][65][66]. Estrogens and their specific receptors influence systemic immune response by reducing the cytokine-driven cortisol and ACTH release, by increasing substance P signaling and responsiveness to noxious stimulation (increase of neurogenic inflammation).

Estrogen receptors  $\alpha$  and  $\beta$  could have different effects depending on the cell type. The connection between estrogens and their receptors acts on monocyte differentiation along with inflammatory mediator production by macrophages [67][68][69]. Estrogens, in particular, 17  $\beta$ -estradiol (E2), protect neuronal cells against toxic insults, inducing the expression of growth factors and their receptors, as well as proteins and cells involved in apoptosis [67][68][69].

The prevalence of asthma is higher in males before puberty, with a reversal in adulthood, when it is more common in women, who have a higher risk of having severe asthma, as well as greater susceptibility to the harmful effects of smoking [1][70][74][72]. There is no single direct mechanism responsible for gender differences, but several etiologies have been proposed, including gender-specific dysinaptic lung growth, female and male hormonal influences, genetic susceptibility, immune response, and differences in consultation practices [1][58][73][74][75]. Studies showing changes in lung structure and function at key life stages, such as puberty, suggest a modulatory role of sex steroids in the phenomenon of asthma transitions [1]. Indeed, sex hormones are known to have both biological and pathophysiological actions on several non-reproductive organs, including the lung [76]. Moreover, pulmonary function appears to undergo alterations during the menstrual cycle, with worsening of asthma when sex hormones decline premenstrually [77][78]. Moreover, a number of women who have moderate asthma report relief of their premenstrual exacerbations by taking oral contraceptives, which suppress wide fluctuations in circulating sex hormones [75]. Although these preliminary clinical data seem to indicate that the hormonal milieu correlates with prevalence and severity of asthma, the role of specific hormones in determining these changes is unclear. In particular, the effects of estrogens in asthma have been discordant [56][57][58]. On one side, supplementation with estrogens has been used beneficially as sparing steroids in women with asthma. Conversely, postmenopausal estrogen therapy increased the subsequent risk of asthma, and several lines of evidence report worsening of asthma during the premenstrual and intra-menstrual periods [47][77][79][80][81][82].

Even progesterone may play a role in the exacerbation of asthma symptoms [83]. Indeed, progesterone can influence airway smooth muscle tone and inflammation. Moreover, a progestogen hypersensitivity, characterized by a spectrum of symptoms ranging from urticaria to asthma and systemic anaphylaxis, has been described [83].

In addition, from a therapeutic point of view, there is evidence suggesting that the response to inhaled corticosteroid may be gender-specific: in particular, women are less likely to have uncontrolled persistent asthma [84]; the underlying rationale is currently not understood [1][85].

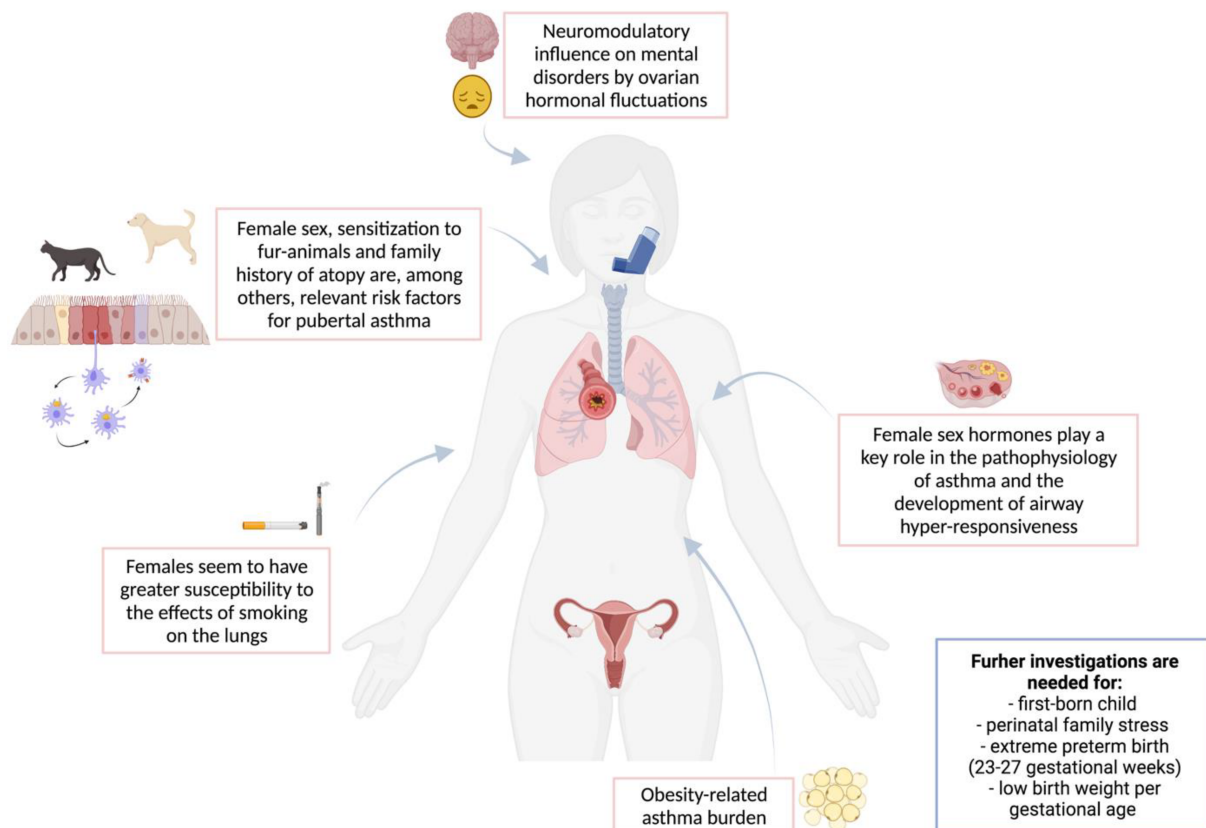
Besides the intrinsic risk factors mentioned above, extrinsic risk factors, such as environmental pollution and cigarette smoking, also play a major role on asthma incidence and severity [86][87][88]. Furthermore, females seem to have a greater susceptibility to the effects of smoking [1], which, whether occasional or not, is a serious risk factor for adolescents with asthma, and smoking rates in this vulnerable population remain high [1][89]. Early exposure to secondhand smoke, whether in utero or during childhood, influences the development of allergic disease into adolescence [90]. Guerra et al., who conducted a prospective study from birth to age 26, recently demonstrated that active and parental smoking act synergistically to influence early deficits in lung function in young adulthood [91]. In addition, in asthmatic individuals, tobacco smoking is associated with accelerated decline

in lung function, decreased disease control, and reduced benefit from corticosteroid treatment [92]. Although electronic cigarettes (e-cigs), as compared to traditional ones, contain fewer carcinogens and cause fewer acute lung effects in both healthy individuals and asthmatics, they are still not totally harmless, as they contain formaldehyde and other toxins that are still poorly understood [93][94]. Moreover, e-cigs could offer an alternative to cannabis use for youth [1][95]. However, due to the absence of complete scientific studies related to cannabinoid vaping, health consequences remain largely unknown and hypothetical; therefore, the most significant health concerns are for children and adolescents [95]. In addition, smoking cannabinoids could lead to environmental and passive contamination [95].

Adolescence is a period fraught with expectation for the youngest, in which social, sexual, and intellectual maturation occurs, followed by a progressive greater level of autonomy [96]. Nevertheless, this autonomy is frustrated by parental and physician dependence for asthma care, medication, and the need for continued follow-up [96]. Asthma, and how it is managed, can impede these processes and intensify the stress that is already an integral part of ordinary adolescence [26].

Anxiety and depression are clinically linked to asthma in this life period [97][98][99], being typically associated with lower adherence to daily monitoring of asthma symptoms [98][100][101]. Social anxiety disorder (SAD), one of the most common anxiety disorders in adolescents, is typically characterized by intense fear of social situations, anxiety, or avoidance; all of which lead to significant impairment (e.g., few friends, loneliness, depressed mood, poor school performance, and difficulty with interpersonal relationships) [101][102]. SAD can be particularly disabling during adolescence because peers play a critical role in social and identity development at this stage [101][103]. Adolescents with asthma are then at high risk for social anxiety. These youth report feeling different and isolated from their peers, fearing peer rejection and having poor social competence [102][104][105][106][107]. In addition, social anxiety may decrease compliance with treatment regimens that require taking medications in front of others (e.g., taking rapid-release medications before exercise or exposure to other triggers), because adolescents are worried about being accepted by peers [101]. Overall, anxiety disorders, such as panic disorder (PD), are up to twice as prevalent in females as in males [108], and it appears that a gender-specific susceptibility is responsible for their development. Sex hormonal changes occurring in the premenstrual phase represent a neuromodulatory signal in the onset and maintenance of maladaptive or clinical anxiety and other mental disorders in the female sex [109][110][111][112][113]. Indeed, in some [80][114][115] but not in all [77] studies, women with PMA showed a higher incidence of premenstrual syndrome if compared with a control asthma group [116]. Dysphoric symptoms or general discomfort preceding menstruation [114] could contribute to self-reported premenstrual worsening of asthma: women with PMS might have an altered perception of asthmatic symptoms in the premenstrual phase, and emotional changes may influence lung function up to precipitation of asthmatic attacks [116]. In a study conducted by Richardson et al. [98], involving subjects aged 11–17 years, youth with an anxiety or depressive disorder were, among other things, more frequently girls and had a more recent diagnosis of asthma. Furthermore, in the same research by Richardson et al. [98], youth with an anxiety or depressive disorder reported, on average, more days of symptoms than the other participants without either of these disorders (5.4 vs. 3.5 days). Among other factors significantly and independently associated with increased symptom days, there was the female sex.

**Figure 1** summarizes risk factors for asthma in young female adolescents.



**Figure 1.** Risk factors for asthma in young female adolescents.

## 2. Perimenstrual Asthma

PMA is usually defined as cyclical exacerbation of asthma symptoms during the luteal phase and/or during the first days of the menstrual cycle [\[117\]](#)[\[118\]](#).

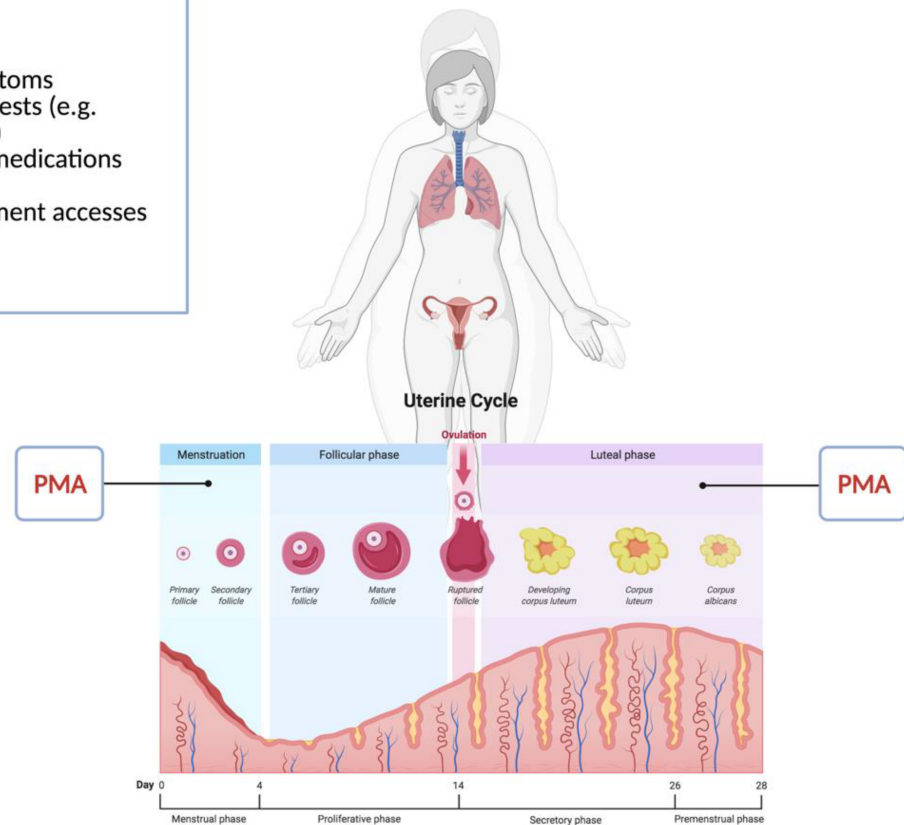
The first case of a woman with serious recurrent PMA exacerbations was described in 1931 [\[119\]](#). Inhibition of ovarian function stopped the symptoms; nevertheless, with the return of hormonal function, they reappeared. These observations revealed the relevance of menstrual-cycle-related variations of sex hormones in the pathogenesis of PMA.

The worsening of asthma is defined as a reactivation of symptoms and/or impairment of lung function tests, such as a decrease of  $\geq 20$ –40% in the peak expiratory flow (PEF) [\[120\]](#)[\[121\]](#)[\[80\]](#) (see **Figure 2**).



**Perimenstrual asthma (PMA):**

- reactivation of asthma symptoms
- impairment of lung function tests (e.g. decrease  $\geq 20$ –40% in the PEF)
- increased use of quick-relief medications
- increased oral corticosteroid
- increased emergency department accesses



**Figure 2.** Perimenstrual asthma in young female adolescents.

A straight definition of PMA in the literature is still lacking, and discrepancies in PMA definition highly influence data recall in different studies and prevalence in different populations [\[122\]](#).

PMA incidence is reported to be between 19 and 40% of asthmatic women [\[117\]](#). In population-based studies, asthma hospitalization rates are similar by sex in early adolescence [\[70\]\[117\]\[123\]\[124\]](#), although they are up to three times higher in women than in men aged 20–50 years. Following menopause, the asthma incidence drops, and the return equals that of men [\[70\]\[117\]\[123\]\[124\]](#). The occurrence of PMA has been correlated with an increase in the number of asthma-related emergency-room visits, hospital admissions, and emergency treatment. Emergency-room admissions most commonly occur among women in the preovulatory and perimenstrual phases [\[125\]](#).

These data, together with abundant evidence on sex differences in asthma [\[123\]\[126\]](#), support the hypothesis that hormonal status may influence asthma in women, focusing on the role of sex hormones, and particularly the impact of estrogen fluctuations at ovulation and before menstruation [\[123\]](#).

Perimenstrual fluctuations of sex hormones in women are considered responsible for the specific worsening of many different perimenstrual symptoms and specific inflammatory [\[127\]](#), autoimmune [\[128\]\[129\]](#), and pain-related conditions [\[117\]](#), thus confirming their pathogenic role.

### 3. Perimenstrual Asthma and Sex Hormones

Various studies, including the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study, have shown that there is a gender difference in asthma that varies with age [\[130\]](#).

The PIAMA study [\[112\]](#) enlisted 4146 pregnant women and assessed 3308 of their children yearly for wheezing and asthma, using questionnaires. Males showed an increased incidence of wheezing compared to females. At the age of 8, 15.1% of the male patients and 10.8% of the female patients had asthma, suggesting that the gender difference in asthma could begin early in infancy. Males also showed more atopic symptoms, measured by specific IgE or skin-prick testing to common allergens, compared to female patients prior to adolescence [\[48\]\[130\]\[131\]\[132\]\[133\]\[134\]](#). Another study showed that phytohemagglutinin-induced mononuclear cells from males, compared to females, have remarkably increased IFN- $\gamma$ , IL-5, and IL-13 in children that showed wheezing at 3 years of life. Increased rates of sensitization, total IgE levels, and blood eosinophil counts were higher in males. The disproportionate growth between lung size and airway caliber has also been detected more often in male patients [\[132\]\[135\]](#). Therefore, a more robust immune response and a decreased airway size likely contribute to increased wheezing in young males compared to females.

Various studies have shown that hospital admissions for asthma are similar by sex in the early teenage years (10 to 13 years of age), but they are up to three times higher in females than males between 20 to 50 years. It is also reported that, after menopause, the incidence of asthma decreases balancing again with men [\[70\]\[123\]\[124\]](#).

Sex hormones are known to be effective modulators of immune responses and inflammatory-associated diseases [\[136\]\[137\]\[138\]](#).

Estrogens play a key role in influencing the course of various autoimmune diseases, as well as infectious processes (viral, bacterial, and others), exerting their actions through the estrogen receptor alpha and beta, as ultimately expressed by several immune cells [\[138\]](#).

Classical estrogen receptors (ER) ER $\alpha$  and ER $\beta$  are members of the superfamily of nuclear receptors. The binding of a ligand to ER $\alpha$  or ER $\beta$  triggers receptor activation, dimerization, and translocation from the cytoplasm to the nucleus. Here, the hormone-receptor complex recruits co-regulators and binds to estrogen receptor elements (ERE) of targeted genes, thus modulating gene transcription (genomic mechanism) [\[139\]](#). More recently, researchers identified the membrane estrogen receptor GPR30 or GPER, a 7-transmembrane G-protein-coupled receptor that activates intracellular signaling cascades, including MAPK, ERK1/2, and PI3K pathways [\[76\]\[140\]](#). Thus, rapid nongenomic mechanisms through secondary messengers determine variations in cellular enzymatic pathways, ion channel, and intracellular calcium levels, and they also result in transcriptional modulation [\[76\]\[141\]](#).

Experimental evidence suggests that ERs are involved in lung development [\[141\]](#). Indeed, ER $\alpha$  modulates alveolar regeneration and alveolar size and number, while ER $\beta$  induces normal elastic tissue recoil through regulation of extracellular matrix [\[142\]](#). In human lung tissue, ER $\alpha$  and ER $\beta$  are expressed in bronchial epithelial cells [\[76\]](#), as well as in various immune cells, including macrophages, lymphocyte, and dendritic cells [\[143\]](#). It has been demonstrated that ER $\beta$  activation modulates airway inflammation and negatively regulates eosinophilic airway infiltration during



asthma [144]. GPER also exerts a negative control on airway inflammation through IL-10 [145]. ERs activation in both vascular endothelial cells (especially ER $\alpha$ ) and bronchial epithelial cells (especially ER $\beta$ ) leads to nitric oxide synthesis and subsequent vasodilation or bronchodilation, respectively [76]. ER $\alpha$  and ER $\beta$  are expressed also in human airway smooth muscle (ASM) cells: it was observed that asthmatic subjects manifest an increased ERs expression in ASM which concerns especially ER $\beta$  subtype [146]. A murine model of asthma revealed pronounced airway fibrosis and ASM hypertrophy, leading to airway hyper-reactivity (AHR) and remodeling. Interestingly, this condition reversed with ER $\beta$  activation [144][147] and downregulation of extracellular matrix proteins [148]. Furthermore, it was observed that ER $\beta$  activation diminishes ASM thickness through the negative regulation of PDGF (platelet derived growth factor)-induced proliferation in human ASM cells [147]. According to these evidences, in a recent study on mice, it was confirmed that asthmatic phenotype was associated to airway remodeling and subsequent AHR. In that context, ERs may play a major downregulating role, in which the activation of ER $\beta$  (but not ER $\alpha$ ) resulted in decreased remodeling and AHR [144].

Patients with asthma generally show allergic airway inflammation characterized by type-2-mediated airway inflammation, but some patients show low type-2-mediated airway inflammation with increased neutrophils concentration caused by type 1 or IL17-mediated airway inflammation [149][150]. Type 2 allergic airway inflammation starts with exposures to allergens, including dust, pollen, mammalian antigens, cockroach antigens, and others, resulting in increased production of inflammatory cytokines, such as thymic IL-4, IL-25, and IL-33. Increased concentration of these co-stimulatory cytokines results in enhanced expression of proinflammatory cytokines; IL-4, IL-5, IL-13, and IL-9 produced by TCD4<sup>+</sup> cells helper; group-2 innate lymphoid cells (ILCs); eosinophils; basophils; mast cells; macrophages; and others. The release of these cytokines leads to increased IgE-triggered hypersensitivity to allergens, activation of airway epithelial cells, activation and infiltration of eosinophils, mucus production, and AHR. Increased secretion of IL-17A, a cytokine secreted by CD4<sup>+</sup> Th17 cells and other cell types, also leads to increased airway inflammation and hyper-responsiveness [151].

Such an immune response can be modulated by hormonal milieu during different stages in life, from puberty to menopause [136][137][138]. Thus, sex-hormone fluctuations seem to play a key role in respiratory health, leading to asthma exacerbations, suggesting the need of monitoring hormonal changes in asthmatic female patients.

During puberty, testes increase testosterone production, along with adrenal glands producing androgens, leading reproductive organs to mature and muscle and bone to grow. For what concerns females, there is an increase in the production of estrogen from the ovaries (driving thelarche and menarche), along with FSH and LH, and androgens (androstenedione and DHEA-S) from the adrenal glands.

Hyperandrogenism may be present in some adolescents more likely suffering from polycystic ovary syndrome (PCOS), a medical condition showing a certain degree of comorbidity with asthma [152], especially in overweight and obese adolescents [153].

The androgen overproduction with puberty seems to confer protection on lung growth in both males and females, while estrogens may well have negative effects in females extending into adulthood.

It has been observed that progesterone is the pivotal hormone in the perimenstrual phase, which is also when this specific asthma phenotype occurs [\[154\]](#). Patients with PMA frequently show impairment in periodic fluctuations in serum progesterone concentrations [\[155\]\[156\]](#). Progesterone, as well as all other steroid hormones, is synthesized from pregnenolone. Progesterone is an aldosterone precursor, which, in turn, can be converted into testosterone [\[157\]](#). Some data have shown that low testosterone levels can significantly impair immune responses and airway smooth-muscle reactivity, either through genomic or non-genomic mechanisms [\[125\]\[158\]](#).

De Boer et al. [\[125\]](#) studied 116 males and 71 females, showing that female patients had post-bronchodilator FEV1% and FVC% significantly lower (by 8.9% and 9.1% respectively) than the same values seen in male patients from pre-/early to mid-/late puberty, as determined by breast development (differences attributed by Tanner stage). For what concerned female patients between 6 and 18 years of age, androgens correlated positively with lung function, whereas estrogens did not. Free testosterone had a favorable connection with post-bronchodilator FEV1%. On the other hand, estradiol showed negative coefficients for pre- and post-bronchodilator FEV1% and FVC%.

Moreover, DHEAS, which works as an inhibitor of the airway smooth muscle and fibroblast proliferation, influences airway epithelial-to-mesenchymal transition and even prevents airway remodeling observed in severe asthma. All of these effects, in association with the increased levels of DHEA-S reported in male subjects during late adolescence, may explain lower symptoms in case of hyperandrogenism.

These data suggest that the high rate of asthma exacerbations in females during late adolescence is due to the negative role of estradiol; it also consolidates the benefit of androgens, which are quite low in females [\[125\]](#).

Studies showed reactivation of asthma symptoms, reduced peak flow rates, and increased use of quick-relief medications in nearly 40% of female patients with asthma during the pre- or perimenstrual phase of the cycle [\[77\]\[78\]\[115\]\[159\]\[160\]](#).

As far as the use of contraceptive measures is concerned, some studies, such as the SAPALDIA (Swiss cohort study on Air Pollution And Lung Disease in Adults) [\[161\]](#), showed a reduction in methacholine-induced airway hyper-responsiveness in pill users. DHEA, which is ultimately converted into androgens and estrogens, has been tested in animal studies in order to explore its asthma-related role. It happened to lower the airway eosinophils, along with IL-4 and -5 serum levels in mice fed with it [\[162\]\[163\]](#). Nebulized dehydroepiandrosterone-3-sulfate, when used as a medication in moderate-to-severe asthmatic patients seemed to improve asthma control. Surely, further studies are needed in order to evaluate the possible therapeutic use of such hormonal compounds in asthmatic patients [\[164\]](#).

It appears clear that sex hormones have an important role in the immune system in many autoimmune and/or allergic diseases, including asthma. Therefore, gender differences in asthma prevalence coincide with modifications in sex hormones levels, highlighting their key role in regulating PMA asthma pathogenesis.

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## References

1. de Benedictis, D.; Bush, A. Asthma in Adolescence: Is There Any News?: Asthma in Adolescence. *Pediatr. Pulmonol.* 2017, 52, 129–138.
2. Gore, F.M.; Bloem, P.J.N.; Patton, G.C.; Ferguson, J.; Joseph, V.; Coffey, C.; Sawyer, S.M.; Mathers, C.D. Global Burden of Disease in Young People Aged 10–24 Years: A Systematic Analysis. *Lancet* 2011, 377, 2093–2102.
3. Papi, A.; Brightling, C.; Pedersen, S.E.; Reddel, H.K. Asthma. *Lancet* 2018, 391, 783–800.
4. Leynaert, B.; Sunyer, J.; Garcia-Esteban, R.; Svanes, C.; Jarvis, D.; Cerveri, I.; Dratva, J.; Gislason, T.; Heinrich, J.; Janson, C.; et al. Gender Differences in Prevalence, Diagnosis and Incidence of Allergic and Non-Allergic Asthma: A Population-Based Cohort. *Thorax* 2012, 67, 625–631.
5. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention; GINA: London, UK, 2021.
6. Chipps, B.E.; Bacharier, L.B.; Farrar, J.R.; Jackson, D.J.; Murphy, K.R.; Phipatanakul, W.; Szeffler, S.J.; Teague, W.G.; Zeiger, R.S. The Pediatric Asthma Yardstick: Practical Recommendations for a Sustained Step-up in Asthma Therapy for Children with Inadequately Controlled Asthma. *Ann. Allergy Asthma Immunol.* 2018, 120, 559–579.e11.
7. Akar-Ghibril, N.; Casale, T.; Custovic, A.; Phipatanakul, W. Allergic Endotypes and Phenotypes of Asthma. *J. Allergy Clin. Immunol. Pract.* 2020, 8, 429–440.
8. Licari, A.; Castagnoli, R.; Brambilla, I.; Marseglia, A.; Tosca, M.A.; Marseglia, G.L.; Ciprandi, G. Asthma Endotyping and Biomarkers in Childhood Asthma. *Pediatr. Allergy Immunol. Pulmonol.* 2018, 31, 44–55.
9. Di Cicco, M.; D’Elios, S.; Peroni, D.G.; Comberiati, P. The Role of Atopy in Asthma Development and Persistence. *Curr. Opin. Allergy Clin. Immunol.* 2020, 20, 131–137.
10. Calcaterra, V.; Verduci, E.; Ghezzi, M.; Cena, H.; Pascuzzi, M.C.; Regalbuto, C.; Lamberti, R.; Rossi, V.; Manuelli, M.; Bosetti, A.; et al. Pediatric Obesity-Related Asthma: The Role of Nutrition and Nutrients in Prevention and Treatment. *Nutrients* 2021, 13, 3708.
11. Beuther, D.A.; Sutherland, E.R. Overweight, Obesity, and Incident Asthma: A Meta-Analysis of Prospective Epidemiologic Studies. *Am. J. Respir. Crit. Care Med.* 2007, 175, 661–666.
12. Thomsen, S.F.; Ulrik, C.S.; Kyvik, K.O.; Sørensen, T.I.A.; Posthuma, D.; Skadhauge, L.R.; Steffensen, I.; Backer, V. Association between Obesity and Asthma in a Twin Cohort. *Allergy* 2007, 62, 1199–1204.
13. Cibella, F.; Cuttitta, G.; La Grutta, S.; Melis, M.R.; Bucchieri, S.; Viegi, G. A Cross-Sectional Study Assessing the Relationship between BMI, Asthma, Atopy, and ENO among Schoolchildren. *Ann. Allergy Asthma Immunol.* 2011, 107, 330–336.

14. Quinto, K.B.; Zuraw, B.L.; Poon, K.-Y.T.; Chen, W.; Schatz, M.; Christiansen, S.C. The Association of Obesity and Asthma Severity and Control in Children. *J. Allergy Clin. Immunol.* 2011, 128, 964–969.
15. Vijayakanthi, N.; Grealley, J.M.; Rastogi, D. Pediatric Obesity-Related Asthma: The Role of Metabolic Dysregulation. *Pediatrics* 2016, 137, e20150812.
16. Chen, Y.C.; Dong, G.H.; Lin, K.C.; Lee, Y.L. Gender Difference of Childhood Overweight and Obesity in Predicting the Risk of Incident Asthma: A Systematic Review and Meta-Analysis. *Obes. Rev.* 2013, 14, 222–231.
17. Forno, E.; Lescher, R.; Strunk, R.; Weiss, S.; Fuhlbrigge, A.; Celedón, J.C. Childhood Asthma Management Program Research Group Decreased Response to Inhaled Steroids in Overweight and Obese Asthmatic Children. *J. Allergy Clin. Immunol.* 2011, 127, 741–749.
18. Belamarich, P.F.; Luder, E.; Kattan, M.; Mitchell, H.; Islam, S.; Lynn, H.; Crain, E.F. Do Obese Inner-City Children with Asthma Have More Symptoms than Nonobese Children with Asthma? *Pediatrics* 2000, 106, 1436–1441.
19. Kattan, M.; Kumar, R.; Bloomberg, G.R.; Mitchell, H.E.; Calatroni, A.; Gergen, P.J.; Kerckmar, C.M.; Visness, C.M.; Matsui, E.C.; Steinbach, S.F.; et al. Asthma Control, Adiposity, and Adipokines among Inner-City Adolescents. *J. Allergy Clin. Immunol.* 2010, 125, 584–592.
20. Messiah, S.E.; Arheart, K.L.; Lipshultz, S.E.; Miller, T.L. Ethnic Group Differences in Waist Circumference Percentiles among U.S. Children and Adolescents: Estimates from the 1999–2008 National Health and Nutrition Examination Surveys. *Metab. Syndr. Relat. Disord.* 2011, 9, 297–303.
21. Huang, S.L.; Shiao, G.; Chou, P. Association between Body Mass Index and Allergy in Teenage Girls in Taiwan. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* 1999, 29, 323–329.
22. Schachter, L.M.; Peat, J.K.; Salome, C.M. Asthma and Atopy in Overweight Children. *Thorax* 2003, 58, 1031–1035.
23. Jensen, M.E.; Gibson, P.G.; Collins, C.E.; Wood, L.G. Airway and Systemic Inflammation in Obese Children with Asthma. *Eur. Respir. J.* 2013, 42, 1012–1019.
24. Ali, Z.; Ulrik, C.S. Obesity and Asthma: A Coincidence or a Causal Relationship? A Systematic Review. *Respir. Med.* 2013, 107, 1287–1300.
25. Holguin, F.; Bleecker, E.R.; Busse, W.W.; Calhoun, W.J.; Castro, M.; Erzurum, S.C.; Fitzpatrick, A.M.; Gaston, B.; Israel, E.; Jarjour, N.N.; et al. Obesity and Asthma: An Association Modified by Age of Asthma Onset. *J. Allergy Clin. Immunol.* 2011, 127, 1486–1493.e2.
26. Couriel, J. Asthma in Adolescence. *Paediatr. Respir. Rev.* 2003, 4, 47–54.

27. Kaur, B.; Anderson, H.R.; Austin, J.; Burr, M.; Harkins, L.S.; Strachan, D.P.; Warner, J.O. Prevalence of Asthma Symptoms, Diagnosis, and Treatment in 12–14 Year Old Children across Great Britain (International Study of Asthma and Allergies in Childhood, ISAAC UK). *BMJ* 1998, 316, 118–124.
28. Siersted, H.C.; Boldsen, J.; Hansen, H.S.; Mostgaard, G.; Hyldebrandt, N. Population Based Study of Risk Factors for Underdiagnosis of Asthma in Adolescence: Odense Schoolchild Study. *BMJ* 1998, 316, 651–655; discussion 655–656.
29. Burgess, J.A.; Matheson, M.C.; Gurrin, L.C.; Byrnes, G.B.; Adams, K.S.; Wharton, C.L.; Giles, G.G.; Jenkins, M.A.; Hopper, J.L.; Abramson, M.J.; et al. Factors Influencing Asthma Remission: A Longitudinal Study from Childhood to Middle Age. *Thorax* 2011, 66, 508–513.
30. Andersson, M.; Hedman, L.; Bjerg, A.; Forsberg, B.; Lundbäck, B.; Rönmark, E. Remission and Persistence of Asthma Followed from 7 to 19 Years of Age. *Pediatrics* 2013, 132, e435–e442.
31. Roorda, R.J.; Gerritsen, J.; van Aalderen, W.M.; Schouten, J.P.; Veltman, J.C.; Weiss, S.T.; Knol, K. Follow-up of Asthma from Childhood to Adulthood: Influence of Potential Childhood Risk Factors on the Outcome of Pulmonary Function and Bronchial Responsiveness in Adulthood. *J. Allergy Clin. Immunol.* 1994, 93, 575–584.
32. Sears, M.R.; Greene, J.M.; Willan, A.R.; Wiecek, E.M.; Taylor, D.R.; Flannery, E.M.; Cowan, J.O.; Herbison, G.P.; Silva, P.A.; Poulton, R. A Longitudinal, Population-Based, Cohort Study of Childhood Asthma Followed to Adulthood. *N. Engl. J. Med.* 2003, 349, 1414–1422.
33. Phelan, P.D.; Robertson, C.F.; Olinsky, A. The Melbourne Asthma Study: 1964–1999. *J. Allergy Clin. Immunol.* 2002, 109, 189–194.
34. Sekerel, B.E.; Civelek, E.; Karabulut, E.; Yildirim, S.; Tuncer, A.; Adalioglu, G. Are Risk Factors of Childhood Asthma Predicting Disease Persistence in Early Adulthood Different in the Developing World? *Allergy* 2006, 61, 869–877.
35. Vink, N.M.; Postma, D.S.; Schouten, J.P.; Rosmalen, J.G.M.; Boezen, H.M. Gender Differences in Asthma Development and Remission during Transition through Puberty: The TRacking Adolescents' Individual Lives Survey (TRAILS) Study. *J. Allergy Clin. Immunol.* 2010, 126, 498–504.e1–6.
36. Anderson, H.R.; Pottier, A.C.; Strachan, D.P. Asthma from Birth to Age 23: Incidence and Relation to Prior and Concurrent Atopic Disease. *Thorax* 1992, 47, 537–542.
37. Hovland, V.; Riiser, A.; Mowinckel, P.; Carlsen, K.-H.; Lødrup Carlsen, K.C. Early Risk Factors for Pubertal Asthma. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* 2015, 45, 164–176.
38. Andersson, M.; Bjerg, A.; Forsberg, B.; Lundbäck, B.; Rönmark, E. The Clinical Expression of Asthma in Schoolchildren Has Changed between 1996 and 2006. *Pediatr. Allergy Immunol.* 2010, 21, 859–866.

39. Crump, C.; Winkleby, M.A.; Sundquist, J.; Sundquist, K. Risk of Asthma in Young Adults Who Were Born Preterm: A Swedish National Cohort Study. *Pediatrics* 2011, 127, e913–e920.
40. Johnson, C.C.; Peterson, E.L.; Joseph, C.L.M.; Ownby, D.R.; Breslau, N. Birth Weight and Asthma Incidence by Asthma Phenotype Pattern in a Racially Diverse Cohort Followed through Adolescence. *J. Asthma* 2015, 52, 1006–1012.
41. McCleary, N.; Nwaru, B.I.; Nurmatov, U.B.; Critchley, H.; Sheikh, A. Endogenous and Exogenous Sex Steroid Hormones in Asthma and Allergy in Females: A Systematic Review and Meta-Analysis. *J. Allergy Clin. Immunol.* 2018, 141, 1510–1513.e8.
42. Salam, M.T.; Wenten, M.; Gilliland, F.D. Endogenous and Exogenous Sex Steroid Hormones and Asthma and Wheeze in Young Women. *J. Allergy Clin. Immunol.* 2006, 117, 1001–1007.
43. Bjerg-Bäcklund, A.; Bäcklund, A.B.; Perzanowski, M.S.; Platts-Mills, T.; Sandström, T.; Lundbäck, B.; Rönmark, E. Asthma during the Primary School Ages--Prevalence, Remission and the Impact of Allergic Sensitization. *Allergy* 2006, 61, 549–555.
44. Vonk, J.M.; Boezen, H.M. Predicting Adult Asthma in Childhood. *Curr. Opin. Pulm. Med.* 2006, 12, 42–47.
45. Rönmark, E.; Lindberg, A.; Watson, L.; Lundbäck, B. Outcome and Severity of Adult Onset Asthma--Report from the Obstructive Lung Disease in Northern Sweden Studies (OLIN). *Respir. Med.* 2007, 101, 2370–2377.
46. Arshad, S.H.; Raza, A.; Lau, L.; Bawakid, K.; Karmaus, W.; Zhang, H.; Ewart, S.; Patil, V.; Roberts, G.; Kurukulaaratchy, R. Pathophysiological Characterization of Asthma Transitions across Adolescence. *Respir. Res.* 2014, 15, 153.
47. Goksör, E.; Åmark, M.; Alm, B.; Ekerljung, L.; Lundbäck, B.; Wennergren, G. High Risk of Adult Asthma Following Severe Wheezing in Early Life. *Pediatr. Pulmonol.* 2015, 50, 789–797.
48. Almqvist, C.; Worm, M.; Leynaert, B.; Working group of GA2LEN WP 2.5 Gender. Impact of Gender on Asthma in Childhood and Adolescence: A GA2LEN Review. *Allergy* 2008, 63, 47–57.
49. Meyer, M.R.; Haas, E.; Barton, M. Gender Differences of Cardiovascular Disease: New Perspectives for Estrogen Receptor Signaling. *Hypertens. Dallas Tex* 2006, 47, 1019–1026.
50. Most, W.; van der Wee-Pals, L.; Ederveen, A.; Papapoulos, S.; Löwik, C. Ovariectomy and Orchidectomy Induce a Transient Increase in the Osteoclastogenic Potential of Bone Marrow Cells in the Mouse. *Bone* 1997, 20, 27–30.
51. Gillies, G.E.; Murray, H.E.; Dexter, D.; McArthur, S. Sex Dimorphisms in the Neuroprotective Effects of Estrogen in an Animal Model of Parkinson's Disease. *Pharmacol. Biochem. Behav.* 2004, 78, 513–522.



52. Matsubara, S.; Swasey, C.H.; Loader, J.E.; Dakhama, A.; Joetham, A.; Ohnishi, H.; Balhorn, A.; Miyahara, N.; Takeda, K.; Gelfand, E.W. Estrogen Determines Sex Differences in Airway Responsiveness after Allergen Exposure. *Am. J. Respir. Cell Mol. Biol.* 2008, 38, 501–508.
53. Dimitropoulou, C.; White, R.E.; Ownby, D.R.; Catravas, J.D. Estrogen Reduces Carbachol-Induced Constriction of Asthmatic Airways by Stimulating Large-Conductance Voltage and Calcium-Dependent Potassium Channels. *Am. J. Respir. Cell Mol. Biol.* 2005, 32, 239–247.
54. Degano, B.; Prévost, M.C.; Berger, P.; Molimard, M.; Pontier, S.; Rami, J.; Escamilla, R. 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, 1849–1854.
55. Melgert, B.N.; Ray, A.; Hylkema, M.N.; Timens, W.; Postma, D.S. Are There Reasons Why Adult Asthma Is More Common in Females? *Curr. Allergy Asthma Rep.* 2007, 7, 143–150.
56. Corteling, R.; Trifilieff, A. Gender Comparison in a Murine Model of Allergen-Driven Airway Inflammation and the Response to Budesonide Treatment. *BMC Pharmacol.* 2004, 4, 4.
57. Riffo-Vasquez, Y.; Ligeiro de Oliveira, A.P.; Page, C.P.; Spina, D.; Tavares-de-Lima, W. Role of Sex Hormones in Allergic Inflammation in Mice. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* 2007, 37, 459–470.
58. Carey, M.A.; Card, J.W.; Bradbury, J.A.; Moorman, M.P.; Haykal-Coates, N.; Gavett, S.H.; Graves, J.P.; Walker, V.R.; Flake, G.P.; Voltz, J.W.; et al. Spontaneous Airway Hyperresponsiveness in Estrogen Receptor-Alpha-Deficient Mice. *Am. J. Respir. Crit. Care Med.* 2007, 175, 126–135.
59. Taube, C.; Wei, X.; Swasey, C.H.; Joetham, A.; Zarini, S.; Lively, T.; Takeda, K.; Loader, J.; Miyahara, N.; Kodama, T.; et al. Mast Cells, Fc Epsilon RI, and IL-13 Are Required for Development of Airway Hyperresponsiveness after Aerosolized Allergen Exposure in the Absence of Adjuvant. *J. Immunol. Baltim. Md* 2004, 172, 6398–6406.
60. Melgert, B.N.; Postma, D.S.; Kuipers, I.; Geerlings, M.; Luinge, M.A.; van der Strate, B.W.A.; Kerstjens, H.A.M.; Timens, W.; Hylkema, M.N. Female Mice Are More Susceptible to the Development of Allergic Airway Inflammation than Male Mice. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* 2005, 35, 1496–1503.
61. Almeida, M.; Han, L.; Martin-Millan, M.; Plotkin, L.I.; Stewart, S.A.; Roberson, P.K.; Kousteni, S.; O'Brien, C.A.; Bellido, T.; Parfitt, A.M.; et al. Skeletal Involution by Age-Associated Oxidative Stress and Its Acceleration by Loss of Sex Steroids. *J. Biol. Chem.* 2007, 282, 27285–27297.
62. Almeida, M.; Han, L.; Ambrogini, E.; Bartell, S.M.; Manolagas, S.C. Oxidative Stress Stimulates Apoptosis and Activates NF- $\kappa$ B in Osteoblastic Cells via a PKC $\beta$ /P66shc Signaling Cascade: Counter Regulation by Estrogens or Androgens. *Mol. Endocrinol.* 2010, 24, 2030–2037.
63. Olsen, N.J.; Kovacs, W.J. Gonadal Steroids and Immunity. *Endocr. Rev.* 1996, 17, 369–384.

64. Talal, N. Sex Steroid Hormones and Systemic Lupus Erythematosus. *Arthritis Rheum.* 1981, 24, 1054–1056.
65. Bijlsma, J.W.J.; Van Den Brink, H.R. Estrogens and Rheumatoid Arthritis. *Am. J. Reprod. Immunol.* 1992, 28, 231–234.
66. Cutolo, M.; Wilder, R.L. Different roles for androgens and estrogens in the susceptibility to autoimmune rheumatic diseases. *Rheum. Dis. Clin. N. Am.* 2000, 26, 825–839.
67. Lang, T.J. Estrogen as an Immunomodulator. *Clin. Immunol.* 2004, 113, 224–230.
68. Carruba, G.; D'Agostino, P.; Miele, M.; Calabrò, M.; Barbera, C.; Bella, G.D.; Milano, S.; Ferlazzo, V.; Caruso, R.; Rosa, M.L.; et al. Estrogen Regulates Cytokine Production and Apoptosis in PMA-Differentiated, Macrophage-like U937 Cells: Estrogen Regulates Cytokine Production in U937 Cells. *J. Cell. Biochem.* 2003, 90, 187–196.
69. Mor, G.; Sapi, E.; Abrahams, V.M.; Rutherford, T.; Song, J.; Hao, X.-Y.; Muzaffar, S.; Kohen, F. Interaction of the Estrogen Receptors with the Fas Ligand Promoter in Human Monocytes. *J. Immunol.* 2003, 170, 114–122.
70. Skobeloff, E.M.; Spivey, W.H.; St Clair, S.S.; Schoffstall, J.M. The Influence of Age and Sex on Asthma Admissions. *JAMA* 1992, 268, 3437–3440.
71. Hyndman, S.J.; Williams, D.R.; Merrill, S.L.; Lipscombe, J.M.; Palmer, C.R. Rates of Admission to Hospital for Asthma. *BMJ* 1994, 308, 1596–1600.
72. Bloomberg, G.R.; Trinkaus, K.M.; Fisher, E.B.; Musick, J.R.; Strunk, R.C. Hospital Readmissions for Childhood Asthma: A 10-Year Metropolitan Study. *Am. J. Respir. Crit. Care Med.* 2003, 167, 1068–1076.
73. Postma, D.S. Gender Differences in Asthma Development and Progression. *Gend. Med.* 2007, 4 (Suppl. B), S133–S146.
74. Dratva, J.; Schindler, C.; Curjuric, I.; Stolz, D.; Macsali, F.; Gomez, F.R.; Zemp, E. SAPALDIA Team Perimenstrual Increase in Bronchial Hyperreactivity in Premenopausal Women: Results from the Population-Based SAPALDIA 2 Cohort. *J. Allergy Clin. Immunol.* 2010, 125, 823–829.
75. Liptzin, D.R.; Landau, L.I.; Taussig, L.M. Sex and the Lung: Observations, Hypotheses, and Future Directions. *Pediatr. Pulmonol.* 2015, 50, 1159–1169.
76. Townsend, E.A.; Miller, V.M.; Prakash, Y.S. Sex Differences and Sex Steroids in Lung Health and Disease. *Endocr. Rev.* 2012, 33, 1–47.
77. Gibbs, C.J.; Coutts, I.I.; Lock, R.; Finnegan, O.C.; White, R.J. Premenstrual Exacerbation of Asthma. *Thorax* 1984, 39, 833–836.

78. Pauli, B.D.; Reid, R.L.; Munt, P.W.; Wigle, R.D.; Forkert, L. Influence of the Menstrual Cycle on Airway Function in Asthmatic and Normal Subjects. *Am. Rev. Respir. Dis.* 1989, 140, 358–362.
79. Ensom, M.H.H.; Chong, G.; Beaudin, B.; Bai, T.R. Estradiol in Severe Asthma with Premenstrual Worsening. *Ann. Pharmacother.* 2003, 37, 1610–1613.
80. Ensom, M.H.; Chong, E.; Carter, D. Premenstrual Symptoms in Women with Premenstrual Asthma. *Pharmacotherapy* 1999, 19, 374–382.
81. Oguzulgen, I.K.; Turktas, H.; Erbas, D. Airway Inflammation in Premenstrual Asthma. *J. Asthma* 2002, 39, 517–522.
82. Jung, W.J.; Lee, S.Y.; Choi, S.I.; Kim, B.-K.; Lee, E.J.; Choi, J. Population-Based Study of the Association between Asthma and Exogenous Female Sex Hormone Use. *BMJ Open* 2021, 11, e046400.
83. Bernstein, J.A. Progestogen Sensitization: A Unique Female Presentation of Anaphylaxis. *Curr. Allergy Asthma Rep.* 2020, 20, 4.
84. Pedersen, S.E.; Bateman, E.D.; Bousquet, J.; Busse, W.W.; Yoxall, S.; Clark, T.J. Gaining Optimal Asthma control Steering Committee and Investigators Determinants of Response to Fluticasone Propionate and Salmeterol/Fluticasone Propionate Combination in the Gaining Optimal Asthma Control Study. *J. Allergy Clin. Immunol.* 2007, 120, 1036–1042.
85. Tse, S.M.; Coull, B.A.; Sordillo, J.E.; Datta, S.; Gold, D.R. Gender- and Age-Specific Risk Factors for Wheeze from Birth through Adolescence. *Pediatr. Pulmonol.* 2015, 50, 955–962.
86. Rosewich, M.; Schulze, J.; Eickmeier, O.; Adler, S.; Rose, M.A.; Schubert, R.; Zielen, S. Early Impact of Smoking on Lung Function, Health, and Well-Being in Adolescents. *Pediatr. Pulmonol.* 2012, 47, 692–699.
87. Yoo, S.; Kim, H.B.; Lee, S.Y.; Kim, B.S.; Kim, J.H.; Yu, J.; Kim, B.J.; Lee, D.H.; Seong, M.W.; Hong, S.J. Effect of Active Smoking on Asthma Symptoms, Pulmonary Function, and BHR in Adolescents. *Pediatr. Pulmonol.* 2009, 44, 954–961.
88. Silvestri, M.; Franchi, S.; Pistorio, A.; Petecchia, L.; Rusconi, F. Smoke Exposure, Wheezing, and Asthma Development: A Systematic Review and Meta-Analysis in Unselected Birth Cohorts. *Pediatr. Pulmonol.* 2015, 50, 353–362.
89. Hedman, L.; Bjerg, A.; Sundberg, S.; Forsberg, B.; Rönmark, E. Both Environmental Tobacco Smoke and Personal Smoking Is Related to Asthma and Wheeze in Teenagers. *Thorax* 2011, 66, 20–25.
90. Thacher, J.D.; Gruzieva, O.; Pershagen, G.; Neuman, Å.; Wickman, M.; Kull, I.; Melén, E.; Bergström, A. Pre- and Postnatal Exposure to Parental Smoking and Allergic Disease through Adolescence. *Pediatrics* 2014, 134, 428–434.

91. Guerra, S.; Stern, D.A.; Zhou, M.; Sherrill, D.L.; Wright, A.L.; Morgan, W.J.; Martinez, F.D. Combined Effects of Parental and Active Smoking on Early Lung Function Deficits: A Prospective Study from Birth to Age 26 Years. *Thorax* 2013, 68, 1021–1028.
92. Chalmers, G.W.; Macleod, K.J.; Little, S.A.; Thomson, L.J.; McSharry, C.P.; Thomson, N.C. Influence of Cigarette Smoking on Inhaled Corticosteroid Treatment in Mild Asthma. *Thorax* 2002, 57, 226–230.
93. Cooke, A.; Fergeson, J.; Bulkhi, A.; Casale, T.B. The Electronic Cigarette: The Good, the Bad, and the Ugly. *J. Allergy Clin. Immunol. Pract.* 2015, 3, 498–505.
94. Polosa, R.; Morjaria, J.; Caponnetto, P.; Caruso, M.; Strano, S.; Battaglia, E.; Russo, C. Effect of Smoking Abstinence and Reduction in Asthmatic Smokers Switching to Electronic Cigarettes: Evidence for Harm Reversal. *Int. J. Environ. Res. Public. Health* 2014, 11, 4965–4977.
95. Giroud, C.; de Cesare, M.; Berthet, A.; Varlet, V.; Concha-Lozano, N.; Favrat, B. E-Cigarettes: A Review of New Trends in Cannabis Use. *Int. J. Environ. Res. Public. Health* 2015, 12, 9988–10008.
96. Randolph, C.C.; Fraser, B. Stressors and Concerns in Teen Asthma. *Allergy Asthma Proc.* 1998, 19, 193–203.
97. Bender, B.; Zhang, L. Negative Affect, Medication Adherence, and Asthma Control in Children. *J. Allergy Clin. Immunol.* 2008, 122, 490–495.
98. Richardson, L.P.; Lozano, P.; Russo, J.; McCauley, E.; Bush, T.; Katon, W. Asthma Symptom Burden: Relationship to Asthma Severity and Anxiety and Depression Symptoms. *Pediatrics* 2006, 118, 1042–1051.
99. Vila, G.; Nollet-Cléménçon, C.; de Blic, J.; Falissard, B.; Mouren-Simeoni, M.C.; Scheinmann, P. Assessment of Anxiety Disorders in Asthmatic Children. *Psychosomatics* 1999, 40, 404–413.
100. Burkhart, P.V.; Rayens, M.K. Self-Concept and Health Locus of Control: Factors Related to Children's Adherence to Recommended Asthma Regimen. *Pediatr. Nurs.* 2005, 31, 404–409.
101. Bruzzese, J.-M.; Fisher, P.H.; Lemp, N.; Warner, C.M. Asthma and Social Anxiety in Adolescents. *J. Pediatr.* 2009, 155, 398–403.
102. Vila, G.; Nollet-Clemençon, C.; de Blic, J.; Mouren-Simeoni, M.C.; Scheinmann, P. Prevalence of DSM IV Anxiety and Affective Disorders in a Pediatric Population of Asthmatic Children and Adolescents. *J. Affect. Disord.* 2000, 58, 223–231.
103. Buhrmester, D.; Furman, W. The Development of Companionship and Intimacy. *Child Dev.* 1987, 58, 1101–1113.
104. Kyngäs, H. Support Network of Adolescents with Chronic Disease: Adolescents' Perspective. *Nurs. Health Sci.* 2004, 6, 287–293.

105. KyngAs, H.A.; Kroll, T.; Duffy, M.E. Compliance in Adolescents with Chronic Diseases: A Review. *J. Adolesc. Health* 2000, 26, 379–388.
106. Price, J.F. Issues in Adolescent Asthma: What Are the Needs? *Thorax* 1996, 51 (Suppl. 1), S13–S17.
107. Fitzgerald, D. Non-Compliance in Adolescents with Chronic Lung Disease: Causative Factors and Practical Approach. *Paediatr. Respir. Rev.* 2001, 2, 260–267.
108. McLean, C.P.; Anderson, E.R. Brave Men and Timid Women? A Review of the Gender Differences in Fear and Anxiety. *Clin. Psychol. Rev.* 2009, 29, 496–505.
109. Breier, A.; Charney, D.S.; Heninger, G.R. Agoraphobia with Panic Attacks. Development, Diagnostic Stability, and Course of Illness. *Arch. Gen. Psychiatry* 1986, 43, 1029–1036.
110. Freeman, E.W. Premenstrual Syndrome and Premenstrual Dysphoric Disorder: Definitions and Diagnosis. *Psychoneuroendocrinology* 2003, 28 (Suppl. 3), 25–37.
111. Gonda, X.; Telek, T.; Juhász, G.; Lazary, J.; Vargha, A.; Bagdy, G. Patterns of Mood Changes throughout the Reproductive Cycle in Healthy Women without Premenstrual Dysphoric Disorders. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 2008, 32, 1782–1788.
112. Kaspi, S.P.; Otto, M.W.; Pollack, M.H.; Eppinger, S.; Rosenbaum, J.F. Premenstrual Exacerbation of Symptoms in Women with Panic Disorder. *J. Anxiety Disord.* 1994, 8, 131–138.
113. Kornstein, S.G.; Harvey, A.T.; Rush, A.J.; Wisniewski, S.R.; Trivedi, M.H.; Svikis, D.S.; McKenzie, N.D.; Bryan, C.; Harley, R. Self-Reported Premenstrual Exacerbation of Depressive Symptoms in Patients Seeking Treatment for Major Depression. *Psychol. Med.* 2005, 35, 683–692.
114. Rees, L. An Aetiological Study of Premenstrual Asthma. *J. Psychosom. Res.* 1963, 7, 191–197.
115. Agarwal, A.K.; Shah, A. Menstrual-Linked Asthma. *J. Asthma* 1997, 34, 539–545.
116. Vrieze, A.; Postma, D.S.; Kerstjens, H.A.M. Perimenstrual Asthma: A Syndrome without Known Cause or Cure. *J. Allergy Clin. Immunol.* 2003, 112, 271–282.
117. Graziottin, A.; Serafini, A. Perimenstrual Asthma: From Pathophysiology to Treatment Strategies. *Multidiscip. Respir. Med.* 2016, 11, 30.
118. Rao, C.K.; Moore, C.G.; Bleecker, E.; Busse, W.W.; Calhoun, W.; Castro, M.; Chung, K.F.; Erzurum, S.C.; Israel, E.; Curran-Everett, D.; et al. Characteristics of Perimenstrual Asthma and Its Relation to Asthma Severity and Control: Data from the Severe Asthma Research Program. *Chest* 2013, 143, 984–992.
119. Frank, R.T. The Hormonal Causes of Premenstrual Tension. *Arch. Neurol. Psychiatry* 1931, 26, 1053–1057.

120. Chandler, M.H.; Schuldheisz, S.; Phillips, B.A.; Muse, K.N. Premenstrual Asthma: The Effect of Estrogen on Symptoms, Pulmonary Function, and Beta 2-Receptors. *Pharmacotherapy* 1997, 17, 224–234.
121. Nakasato, H.; Ohrui, T.; Sekizawa, K.; Matsui, T.; Yamaya, M.; Tamura, G.; Sasaki, H. Prevention of Severe Premenstrual Asthma Attacks by Leukotriene Receptor Antagonist. *J. Allergy Clin. Immunol.* 1999, 104, 585–588.
122. Murphy, V.E.; Gibson, P.G. Premenstrual Asthma: Prevalence, Cycle-to-Cycle Variability and Relationship to Oral Contraceptive Use and Menstrual Symptoms. *J. Asthma* 2008, 45, 696–704.
123. Brenner, B.E.; Holmes, T.M.; Mazal, B.; Camargo, C.A. Relation between Phase of the Menstrual Cycle and Asthma Presentations in the Emergency Department. *Thorax* 2005, 60, 806–809.
124. Becklake, M.R.; Kauffmann, F. Gender Differences in Airway Behaviour over the Human Life Span. *Thorax* 1999, 54, 1119–1138.
125. DeBoer, M.D.; Phillips, B.R.; Mauger, D.T.; Zein, J.; Erzurum, S.C.; Fitzpatrick, A.M.; Gaston, B.M.; Myers, R.; Ross, K.R.; Chmiel, J.; et al. Effects of Endogenous Sex Hormones on Lung Function and Symptom Control in Adolescents with Asthma. *BMC Pulm. Med.* 2018, 18, 58.
126. Zein, J.G.; Erzurum, S.C. Asthma Is Different in Women. *Curr. Allergy Asthma Rep.* 2015, 15, 28.
127. Heitkemper, M.M.; Cain, K.C.; Jarrett, M.E.; Burr, R.L.; Hertig, V.; Bond, E.F. Symptoms across the Menstrual Cycle in Women with Irritable Bowel Syndrome. *Am. J. Gastroenterol.* 2003, 98, 420–430.
128. Rubtsova, K.; Marrack, P.; Rubtsov, A.V. Sexual Dimorphism in Autoimmunity. *J. Clin. Investig.* 2015, 125, 2187–2193.
129. Zandman-Goddard, G.; Peeva, E.; Shoenfeld, Y. Gender and Autoimmunity. *Autoimmun. Rev.* 2007, 6, 366–372.
130. Wijga, A.; Tabak, C.; Postma, D.S.; Kerkhof, M.; Wieringa, M.H.; Hoekstra, M.O.; Brunekreef, B.; de Jongste, J.C.; Smit, H.A. Sex Differences in Asthma during the First 8 Years of Life: The Prevention and Incidence of Asthma and Mite Allergy (PIAMA) Birth Cohort Study. *J. Allergy Clin. Immunol.* 2011, 127, 275–277.
131. Sears, M.R.; Burrows, B.; Flannery, E.M.; Herbison, G.P.; Holdaway, M.D. Atopy in Childhood. I. Gender and Allergen Related Risks for Development of Hay Fever and Asthma. *Clin. Exp. Allergy J. Br. Soc. Allergy Clin. Immunol.* 1993, 23, 941–948.
132. Johnson, C.C.; Peterson, E.L.; Ownby, D.R. Gender Differences in Total and Allergen-Specific Immunoglobulin E (IgE) Concentrations in a Population-Based Cohort from Birth to Age Four Years. *Am. J. Epidemiol.* 1998, 147, 1145–1152.



133. Kulig, M.; Tacke, U.; Forster, J.; Edenharter, G.; Bergmann, R.; Lau, S.; Wahn, V.; Zepp, F.; Wahn, U. Serum IgE Levels during the First 6 Years of Life. *J. Pediatr.* 1999, 134, 453–458.
134. Mohammad, H.R.; Belgrave, D.; Kopec Harding, K.; Murray, C.S.; Simpson, A.; Custovic, A. Age, Sex and the Association between Skin Test Responses and IgE Titres with Asthma. *Pediatr. Allergy Immunol.* 2016, 27, 313–319.
135. Uekert, S.J.; Akan, G.; Evans, M.D.; Li, Z.; Roberg, K.; Tisler, C.; Dasilva, D.; Anderson, E.; Gangnon, R.; Allen, D.B.; et al. Sex-Related Differences in Immune Development and the Expression of Atopy in Early Childhood. *J. Allergy Clin. Immunol.* 2006, 118, 1375–1381.
136. Douin-Echinard, V.; Calippe, B.; Billon-Galès, A.; Fontaine, C.; Lenfant, F.; Trémollières, F.; Bayard, F.; Guéry, J.-C.; Arnal, J.-F.; Gourdy, P. Estradiol Administration Controls Eosinophilia through Estrogen Receptor-Alpha Activation during Acute Peritoneal Inflammation. *J. Leukoc. Biol.* 2011, 90, 145–154.
137. Huygen, K.; Palfliet, K. Strain Variation in Interferon Gamma Production of BCG-Sensitized Mice Challenged with PPD II. Importance of One Major Autosomal Locus and Additional Sexual Influences. *Cell. Immunol.* 1984, 85, 75–81.
138. Phiel, K.L.; Henderson, R.A.; Adelman, S.J.; Elloso, M.M. Differential Estrogen Receptor Gene Expression in Human Peripheral Blood Mononuclear Cell Populations. *Immunol. Lett.* 2005, 97, 107–113.
139. Björnström, L.; Sjöberg, M. Mechanisms of Estrogen Receptor Signaling: Convergence of Genomic and Nongenomic Actions on Target Genes. *Mol. Endocrinol.* 2005, 19, 833–842.
140. Filardo, E.J.; Quinn, J.A.; Frackelton, A.R.; Bland, K.I. Estrogen Action Via the G Protein-Coupled Receptor, GPR30: Stimulation of Adenylyl Cyclase and CAMP-Mediated Attenuation of the Epidermal Growth Factor Receptor-to-MAPK Signaling Axis. *Mol. Endocrinol.* 2002, 16, 70–84.
141. Fuentes, N.; Silveyra, P. Endocrine Regulation of Lung Disease and Inflammation. *Exp. Biol. Med.* 2018, 243, 1313–1322.
142. Massaro, D.; Massaro, G.D. Estrogen Regulates Pulmonary Alveolar Formation, Loss, and Regeneration in Mice. *Am. J. Physiol.-Lung Cell. Mol. Physiol.* 2004, 287, L1154–L1159.
143. Straub, R.H. The Complex Role of Estrogens in Inflammation. *Endocr. Rev.* 2007, 28, 521–574.
144. Ambhore, N.S.; Kalidhindi, R.S.R.; Loganathan, J.; Sathish, V. Role of Differential Estrogen Receptor Activation in Airway Hyperreactivity and Remodeling in a Murine Model of Asthma. *Am. J. Respir. Cell Mol. Biol.* 2019, 61, 469–480.
145. Itoga, M.; Konno, Y.; Moritoki, Y.; Saito, Y.; Ito, W.; Tamaki, M.; Kobayashi, Y.; Kayaba, H.; Kikuchi, Y.; Chihara, J.; et al. Correction: G-Protein-Coupled Estrogen Receptor Agonist Suppresses Airway Inflammation in a Mouse Model of Asthma through IL-10. *PLoS ONE* 2015, 10, e0136326.

146. Aravamudan, B.; Goorhouse, K.J.; Unnikrishnan, G.; Thompson, M.A.; Pabelick, C.M.; Hawse, J.R.; Prakash, Y.S.; Sathish, V. Differential Expression of Estrogen Receptor Variants in Response to Inflammation Signals in Human Airway Smooth Muscle: Expression of estrogen receptor variants in the airway. *J. Cell. Physiol.* 2017, 232, 1754–1760.
147. Ambhore, N.S.; Katragadda, R.; Raju Kalidhindi, R.S.; Thompson, M.A.; Pabelick, C.M.; Prakash, Y.S.; Sathish, V. Estrogen Receptor Beta Signaling Inhibits PDGF Induced Human Airway Smooth Muscle Proliferation. *Mol. Cell. Endocrinol.* 2018, 476, 37–47.
148. Hocking, D.C. Fibronectin Matrix Deposition and Cell Contractility. *Chest* 2002, 122, 275S–278S.
149. Fahy, J.V. Type 2 Inflammation in Asthma--Present in Most, Absent in Many. *Nat. Rev. Immunol.* 2015, 15, 57–65.
150. Ray, A.; Raundhal, M.; Oriss, T.B.; Ray, P.; Wenzel, S.E. Current Concepts of Severe Asthma. *J. Clin. Investig.* 2016, 126, 2394–2403.
151. Fahy, J.V. Eosinophilic and Neutrophilic Inflammation in Asthma: Insights from Clinical Studies. *Proc. Am. Thorac. Soc.* 2009, 6, 256–259.
152. Htet, T.D.; Teede, H.J.; de Courten, B.; Loxton, D.; Real, F.G.; Moran, L.J.; Joham, A.E. Asthma in Reproductive-Aged Women with Polycystic Ovary Syndrome and Association with Obesity. *Eur. Respir. J.* 2017, 49, 1601334.
153. Leon, G.; de Klerk, E.; Ho, J.; Jackman, M.; Reimer, R.A.; Connors, K.E.; Luca, P. Prevalence of Comorbid Conditions Pre-Existing and Diagnosed at a Tertiary Care Pediatric Weight Management Clinic. *J. Pediatr. Endocrinol. Metab.* 2018, 31, 385–390.
154. Maybin, J.A.; Critchley, H.O.D. Progesterone: A Pivotal Hormone at Menstruation: Progesterone and Menstruation. *Ann. N. Y. Acad. Sci.* 2011, 1221, 88–97.
155. Rubio Ravelo, L.; Gago Rodríguez, B.; Almirall Collazo, J.J.; Bell Heredia, L.; Fernández Fernández, L. Comparative Study of Progesterone, Estradiol and Cortisol Concentrations in Asthmatic and Non-Asthmatic Women. *Allergol. Immunopathol.* 1988, 16, 263–266.
156. Davis, C.H. *Gynecology and Obstetrics*. Vol. II, Chap. 3; W. F. Prior Co. Inc.: Hagerstown, MD, USA; pp. 17–50.
157. Nieschlag, E.; Behre, H.M.; Nieschlag, S. *Testosterone: Action, Deficiency, Substitution*; Cambridge University Press: Cambridge, UK, 2012; ISBN 1-107-01290-2.
158. Kouloumenta, V.; Hatziefthimiou, A.; Paraskeva, E.; Gourgoulisanis, K.; Molyvdas, P.A. Non-Genomic Effect of Testosterone on Airway Smooth Muscle. *Br. J. Pharmacol.* 2006, 149, 1083–1091.
159. Eliasson, O.; Scherzer, H.H.; DeGraff, A.C. Morbidity in Asthma in Relation to the Menstrual Cycle. *J. Allergy Clin. Immunol.* 1986, 77, 87–94.

160. Shames, R.S.; Heilbron, D.C.; Janson, S.L.; Kishiyama, J.L.; Au, D.S.; Adelman, D.C. Clinical Differences among Women with and without Self-Reported Perimenstrual Asthma. *Ann. Allergy Asthma Immunol.* 1998, 81, 65–72.
161. Leuenberger, P.; Künzli, N.; Ackermann-Liebrich, U.; Schindler, C.; Bolognini, G.; Bongard, J.P.; Brändli, O.; Defila, C.; Domenighetti, G.; Karrer, W.; et al. Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA). *Schweiz. Med. Wochenschr.* 1998, 128, 150–161.
162. Liou, C.-J.; Huang, W.-C. Dehydroepiandrosterone Suppresses Eosinophil Infiltration and Airway Hyperresponsiveness via Modulation of Chemokines and Th2 Cytokines in Ovalbumin-Sensitized Mice. *J. Clin. Immunol.* 2011, 31, 656–665.
163. Espinoza, J.; Montaña, L.M.; Perusquía, M. Nongenomic Bronchodilating Action Elicited by Dehydroepiandrosterone (DHEA) in a Guinea Pig Asthma Model. *J. Steroid Biochem. Mol. Biol.* 2013, 138, 174–182.
164. Wenzel, S.E.; Robinson, C.B.; Leonard, J.M.; Panettieri, R.A. 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, 461–471.

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