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# Sex in Respiratory and Skin Allergies

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## Abstract

A bulk of literature demonstrated that respiratory allergy, and especially asthma, is prevalent in males during childhood, while it becomes more frequent in females from adolescence, i.e., after menarche, to adulthood. The mechanisms underlying the difference between females and males are the effects on the immune response of female hormones and in particular the modulation of inflammatory response by estrogens, as well as the result of the activity of various cells, such as dendritic cells, innate lymphoid cells, Th1, Th2, T regulatory (Treg) and B regulatory (Bregs) cells, and a number of proteins and cytokines, which include interleukin (IL)-4, IL-5, IL-10, and IL-13. As far as sexual dimorphism is concerned, a gender difference in the expression profiles of histamine receptors and of mast cells was demonstrated in experimental studies. A critical phase of hormone production is the menstrual cycle, which often is associated with asthma deterioration, as assessed by worsening of clinical symptoms and increase of bronchial hyperresponsiveness. In asthmatic woman, there is a high risk to develop more severe asthma during menstruation. The higher prevalence of asthma in females is confirmed also in the post-menopause age, but the underlying mechanisms are not yet understood. In pregnancy, asthma may worsen but may also improve or remain unchanged, with no significant difference in frequency of these three outcomes. For allergic rhinitis, the available studies indicate, likewise asthma, a male predominance in prevalence in childhood that shifts to a female predominance in adolescence and adulthood, but further investigation is needed.

**Keywords** Allergy · Asthma · Female sex · Hormones · Cytokines · Menstruation pregnancy · Menopause

**Abbreviations**

| | |
|---|---|
| AR | Allergic rhinitis |
| BHR | Bronchial hyperresponsiveness |
| Bregs | Regulatory B cells |
| DC | Dendritic cells |
| ED | Emergency department |
| HR | Histamine receptors |
| ICS | Inhaled corticosteroids |
| IFN | Interferon |
| IL | Interleukin |
| ILC2 | Group 2 innate lymphoid cells |
| iNKT | Invariant natural killer T |
| MC | Mast cells |
| NFA | Near-fatal attacks |
| OR | Odds ratio |
| PMA | Perimenstrual asthma |
| PSA | Mediated passive systemic anaphylaxis |
| SARP | Severe Asthma Research Program |
| SNPs | Single nucleotide polymorphisms |
| TGF | Transforming growth factor |
| Th | T helper |
| Treg | T regulatory |
| TSLP | Thymic stromal lymphopoietin |

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## Introduction

Despite a number of old reports drew the attention on possible differences between males and females in developing allergic

diseases, only the beginning of the scientific age of allergy, which was driven by the discovery of IgE antibodies, allowed to properly assess the issue. A first study from Johansson, the IgE discoverer, did not find any difference in IgE levels according to sex [1], but in the following years, epidemiologic studies provided the first data suggesting that differences do exist. For example, in 1974, the data from a study performed in London on the incidence of hay-fever highlighted that men had less tendency to asthma while less women had seasonal rhinitis [2]. In the latest decades, the global literature on sex differences in human diseases steadily expanded, but immunology ranked the lowest of 10 biological disciplines for reporting in published papers the sex of animals or human subjects [3]. A critical factor is the sexual dimorphism, the extent of which concerning the gene expression was demonstrated by microarray analysis to be very large, thousands of genes showing sexual dimorphism, though with a variable degree in different tissues, ranging from 14% in the brain to 70% in the liver [4]. Indeed, in a recent review, Klein and Flanagan emphasized that sex is a biological variable that should be considered in immunological studies [5]. Concerning allergic disorders, variable observations were reported thus far. For exercise-induced anaphylaxis, no sex difference was found; for atopic dermatitis and food allergy, there were conflicting results, while prevalence of males for insect venom allergy and of females for drug allergy was reported. However, for venom allergy, a degree of exposure to insect stings significantly greater for males was claimed to account for the difference [6]. Also, the higher prevalence of drug allergy in females was supposed to be related to the inclination to use more drugs compared with males and not to sex-related immunologic mechanisms [7]. Instead, there is abundant literature on the role of sex factors in respiratory allergy (Table 1), including allergic rhinitis (AR) and especially asthma, which is the most studied disease and was found to be different in females according to both prevalence and severity [8]. The investigations on the mechanisms underlying such differences provided data that improved the understanding of this issue.

## Immunologic Mechanisms Accounting for Sex-Related Differences in Allergy

In humans, but also in animals, it is known that males and females differ in the strength of immune responses, particularly concerning antibody production, cell-mediated responses, CD4+ T cell counts, C4/CD8 ratio, T-helper (Th) cells, including Th1 and Th2, and T regulatory (Treg) cells. Different sets of Th cells have essential roles in adaptive immunity, e.g., Th1 cells trigger type 1 responses, which are primarily cell-mediated, and Th2 cells trigger type 2

**Table 1** Differences between males and females in allergic disease

| | | Male | Female | Mechanisms underlying the different prevalence |
|---|---|---|---|---|
| Asthma | Prevalence | Higher in childhood (1.5 times) | Higher from adolescence to adulthood | Effects of female hormones on immune response, influencing the activity of cells (dendritic cells, innate lymphoid cells, Th1, Th2, Treg, and Breg cells), and the production of cytokines (IL) -4, IL-5, IL-10, IL-13). |
| | Features | More severe in young boys; frequently associated atopic status | • Higher airway responsiveness;<br>• PMA is usually severe;<br>• Non-atopic asthma is more frequent;<br>• In pregnancy, asthma may not only worsen but may also improve or remain unchanged, with no significant difference in frequency of these three outcomes. | |
| Rhinitis | Prevalence | Higher in childhood | Higher from adolescence to adulthood | Not sufficiently investigated |
| | Features | No reported differences | | |
| Atopic dermatitis | Prevalence | predominant in male after the age of 65 yrs | Predominant in females until the age of 65 years | Not investigated |
| | Features | No reported differences | | |
| Contact dermatitis | Prevalence | Overall higher prevalence in female | | |
| | Features | Balsam of Peru is the most frequent sensitizer | Nickel is the most frequent sensitizer | |
| Urticaria | Prevalence | Predominant in women | | |
| | Features | Acute urticaria is much more common, but no studies comparing the prevalence in males and females are available | | |

responses, which are primarily humoral responses (Table 1). Such immune modulation is influenced by sex hormones: the male sex hormone testosterone is usually immunosuppressive, while the female sex hormone estrogen has a tendency to be immunoenhancing [9]. Reviewing the literature, it is apparent that estrogen and progesterone enhance type 2 and suppress type 1 responses in females, while testosterone suppresses type 2 responses, but with an uneven pattern for type 1 responses in males [9]. Laffont et al. highlighted that estrogens contribute to the sex differences in immunity by regulating dendritic cells (DC) subsets, which both in early and mature phases express estrogen receptors and act as ligand-dependent transcription factors [10]. Figure 1 summarizes the actions of estrogens on the immune system. The same authors showed by an experimental study that group 2 innate lymphoid cells (ILC2s), which are key regulators of type 2 inflammatory responses (proposed as surrogate markers of airway eosinophilic inflammation in asthma), are negatively influenced by male sex hormones. In fact, male mice had decreased numbers of ILC2 progenitors and mature ILC2s in peripheral tissues compared with female mice. This resulted in reduced susceptibility to allergic airway inflammation in response to environmental allergens in males and less severe interleukin (IL)-33-driven lung inflammation [11]. Of interest, orchiectomy, but not ovariectomy, abolished the sex differences in ILC2 development and reinstated IL-33-mediated lung inflammation [11]. In addition, in experimental models of asthma, female mice have increased airway hyperresponsiveness, eosinophil influx, and increased type 2 cytokine production, including IL-4, IL-5, and IL-13, in the lungs after allergen challenge when compared with males. While $CD4^+$ Th2 cells are known to produce type 2 cytokines, the ILC2s were found to produce much larger quantities of IL-5 and IL-13 compared with Th2 cells [12]. Concerning IL-5, Okujama et al. studied splenocytes from wild-type mice and CD4+ T cell−, CD8+ T cell−, and iNKT (invariant natural killer T) cell-deficient mice stimulated with anti-CD3/CD28 antibodies for 3 days, measuring the concentrations of IL-4, IL-5, IL-13, and IFN-γ in the cultures. IL-5, but not IL-4 and IL-13, concentrations in culture derived from female wild-type mice were significantly higher than in male wild-type mice. The sex difference in IL-5 concentrations was not observed in the cultures of splenocytes from CD4+ and CD8+ T cell-deficient mice, this being attributable to a decrease in IL-5 concentration in female mice and an increase in IL-5 concentration in male mice [13]. In another experiment, the same authors stimulated, in the presence of CD8+ T cells, splenocytes from naive mice with anti-CD3/CD28 antibodies and analyzed the proportions of CD4+ and CD8+ T cells. The concentrations of interleukin IL-5, IL-10, and interferon (IFN)-gamma were measured, being possible to observe significantly higher concentration of IL-5, but not IFN-gamma, in female splenocytes than in male splenocytes. No sex differences in the proportions of CD4+ and CD8+ T cells in the splenocytes were found. Despite that the IL-5 levels in male and female CD4+ T cells were comparable, IL-5 production in male CD4+ T cells, but not female CD4+ T cells, was suppressed by both male and female CD8+ T cells [14]. Another very recent study investigated the immune mechanisms underlying the effects of asthma on pregnancy as well as the effects of pregnancy on asthma. In the study

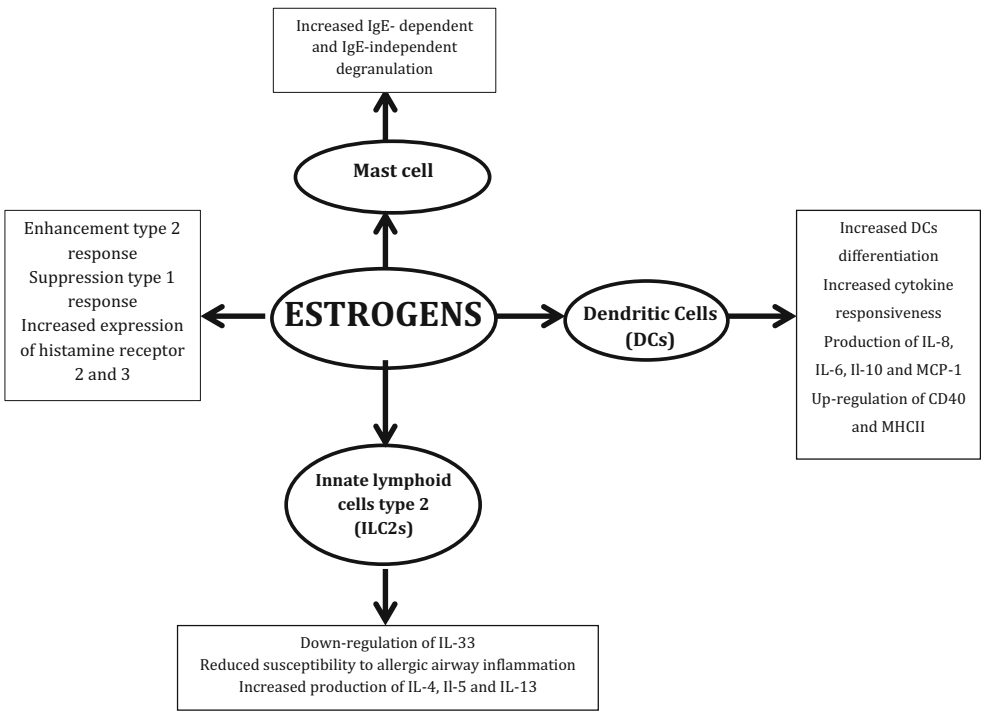


**Fig. 1** Estrogen actions on the immune system

were enrolled 23 asthmatic women, 43 healthy women, 33 third trimester-pregnant asthmatic women, and 35 healthy nonpregnant women. In all subjects, circulating Tregs and regulatory B cells (Bregs) were characterized, and Foxp3 expression was assessed in CD4DimCD25Hi Tregs. The results showed no significant variation in Tregs from pregnancy to postpartum in asthmatic or healthy women, while CD24HiCD38Hi Bregs declined in pregnancy and increased significantly postpartum. Also, Foxp3 expression in Tregs was reduced during pregnancy in both asthmatic and healthy women but was restored postpartum. The Foxp3 expression levels were significantly higher in asthmatic pregnant women than in healthy pregnant women but were likely due to the effect of drug treatment of asthma [15].

Concerning genetics, Mayne et al. performed meta-analyses of sex-biased gene expression in multiple human tissues, analyzing 22 human gene expression microarray data sets including over 2500 samples from 15 different tissues and 9 different organs. The effect size difference of gene expression between males and females was measured. The greatest sex differences in gene expression were found in the brain (1818 genes), followed by the heart (375 genes), and the kidney (224 genes), colon (218 genes), and thyroid (163 genes). For the lungs, most sex-biased genes were on the sex chromosomes or involved in sex hormone production, though about two thirds of autosomal genes that were sex-biased were not under direct influence of sex hormones [16]. Other studies assessed by experimental models the potential mechanisms for sexual dimorphism in asthma. The gender difference in expression profiles of histamine receptors (HR) was explored, being possible to observe that H2R and H3R were highly expressed in female rats compared with males and downregulated in ovariectomized females, while H1R was equally expressed in both sexes [17]. Moreover, the role of sex on mast cells (MC), which have a pivotal role in allergic reaction, was investigated in C57BL/6 male and female mice exposed to IgE-mediated passive systemic anaphylaxis (PSA) or psychological stress, performing primary bone marrow-derived MC from male and female mice and analyzing MC degranulation, signaling pathways, and RNA transcriptome analysis. Sexually dimorphic responses were observed in both models of PSA and stress, and in primary MC, female mice exhibited amplified clinical scores, hypothermia, and serum histamine levels in response to PSA compared with male mice. Primary bone marrow-derived MC showed increased release of β-hexosaminidase, histamine, tryptase, and TNF-α upon stimulation [18].

Also, researches on particular regulatory proteins are available. A study on single nucleotide polymorphisms (SNPs) in thymic stromal lymphopoietin (TSLP), a cytokine that is known to play an important role in the maturation of T cells through activation of antigen presenting cells, detected an association with IgE production in young women and with asthma in general. Two SNPs in TSLP (rs1837253 and rs2289276) were significantly associated with a globally reduced risk of asthma, whereas in a sex-stratified analysis, a significant association of the T allele of rs1837253 with a decreased risk of asthma only in males and a significant association of the T allele of rs2289276 with a decreased risk of asthma only in females was found [19]. Periostin is another protein under investigation, which is not only named after its expression in the periosteum of long bones, but also present in many other tissues and organs, including the heart, kidney, skin, and lungs, being enhanced by mechanical stress or injury [20]. In a distinct subtype of asthma defined by the expression of genes inducible by Th2 cytokines in bronchial epithelium, including periostin, which is detected in around half of asthmatic patients and correlates with eosinophilic airway inflammation, serum periostin levels were significantly increased in asthmatic patients with eosinophilic airway inflammation and were found to the single best predictors of airway eosinophilia [21]. Because periostin also plays a role in normal gestation and pregnancy, a study investigated periostin during pregnancy in asthmatic patients. Plasma periostin levels were measured in patients with asthma non-pregnant, and in pregnant patients with asthma, compared with healthy non-pregnant controls and healthy pregnant women, also evaluating the relationship between periostin levels and asthma control. Plasma periostin levels were comparable in asthmatic non-pregnant and healthy non-pregnant controls, while they were significantly higher in healthy pregnant compared with healthy non-pregnant and asthmatic pregnant groups. Periostin levels of the two pregnant groups were similar, and in asthmatic pregnant women, periostin correlated negatively with FEV1. The authors concluded that though periostin correlates with lung function in asthmatic pregnancy, periostin as a biomarker should be handled with prudence in pregnant patients based on the influence of pregnancy on its plasma level [22].

## Clinical Data on Asthma in Female Sex

The first epidemiologic report on a difference between males and females concerning asthma dates back to 1980, when Dodge and Burrows examined the prevalence of incidence of asthma and other wheezing syndromes in a general population sample. Table 1 summarizes the essential findings in terms of asthma-related. In an overall prevalence of 6.6%, the incidence of asthma was 1.5 times greater in young boys than in young girls, but was much greater in women older than 40 years of age. The authors suggested that the findings perhaps reflected the diagnostic biases of physicians [23], but subsequent studies confirmed and strengthened the observation. In fact, asthma was more prevalent in boys than in girls during childhood [24–26], but in adolescence became more

severe and prevalent in girls [27]. Also airway hyperresponsiveness, which is clearly related to asthma, was investigated in women. In a first study, no significant differences were detected in the effect of methacholine on FEV1 value during menstrual cycle compared with the out of cycle period [28]. However, in a prospective study on 1041 children, initially aged 5–12 years, with mild to moderate persistent asthma who were evaluated for 8.6 ± 1.8 years with methacholine challenges yearly, the findings were apparent. In fact, postpubertal girls had significantly higher airway responsiveness than males even after adjustment for FEV1 and other potential confounders [29]. Perimenstrual increase of bronchial hyperresponsiveness (BHR) was also studied in 143 pre-menopausal women undergoing methacholine challenge within the risk window (defined by 3 days before and after the first day of menstruation). A significant increase, as assessed by a odds ratio (OR) of 2.3, in BHR within the window of risk was found, with effect modification in asthma status when oral contraceptive were used [30]. Actually, in a survey on 681 women aged 29–32 years, the risk to have asthma decreased by 7% per year of oral contraceptive use [31]. In a small study on 28 premenopausal women with asthma prospectively followed for 12 weeks over two to four consecutive menstrual cycles, no significant difference was found in premenstrual asthma between women using oral contraceptives (55%) and women not using oral contraceptives (59%) [32]. Murphy and Gibson studied 792 women aged 18–54 years presenting to the emergency department with a diagnosis of acute asthma exacerbation, who were classified by menstrual phase based on both date of symptom onset. Of them, 28% were preovulatory, 25% were periovulatory, 21% were postovulatory, and 27% were perimenstrual. These findings suggested that acute asthma exacerbations do not markedly increase during the perimenstrual phase [33]. More recently, Rao et al., in the frame of the National Heart, Lung and Blood Institute Severe Asthma Research Program, recruited women with asthma who reported perimenstrual asthma (PMA) by clinical questionnaire data, immunoinflammatory markers, and physiologic parameters. A severity-adjusted model predicting PMA was created. Additional models addressed the role of PMA in asthma control. PMA was reported in 92 women (17%), and 52% of them met the criteria for severe asthma compared with 30% of the non-PMA group. The authors concluded that PMA is common in women with severe asthma and associated with poorly controlled disease [34]. This confirmed a previous report on 44 women of reproductive age with near-fatal attacks (NFA), in whom significantly more NFA occurred on the first day of menstruation than on the remaining days ($P = 0.022$), and patients on the first day of menstruation used more inhaled salbutamol as rescue medication during the 7 days before the asthma exacerbation ($P = 0.003$). Based on this observation, the authors recommended that educational programs and self-management plans of asthmatic women of reproductive age should include particular care in the perimenstrual phase [35]. Another period at risk for asthma is menopause. The Respiratory Health in Northern Europe study provided questionnaire data concerning respiratory and reproductive health at baseline (1999–2001) from a cohort of 2322 women aged 45 to 65 years, without asthma at baseline, and not using exogenous hormones. Menopausal status was defined as nonmenopausal, transitional, early postmenopausal, and late postmenopausal. The risk of new-onset asthma was increased in women who were transitional (OR 2.40, early postmenopausal (OR 2.11, and late postmenopausal (OR 3.44) at follow-up compared with non-menopausal women, regardless smoking status [36]. The same group of authors investigated by measuring FEV1 and FVC the lung function decline in menopause. The population-based longitudinal European Community Respiratory Health Survey provided serum samples, spirometry, and questionnaire data about respiratory and reproductive health, and follicle-stimulating hormone and luteinizing hormone were also measured. Menopausal status was associated with accelerated lung function decline, as shown by an increased FVC decline by − 10.2 ml/year adjusted mean in transitional women and − 12.5 ml/year postmenopausal women, compared with women with regular menstruations. For FEV1, the adjusted mean increased by − 3.8 ml/year in transitional women and − 5.2 ml/year in postmenopausal women [37]. In a cross-sectional study on severe asthmatic outpatients, evaluating functional and inflammatory markers, health-related quality of life, clinical control status, and characteristics related to atopy and age of asthma onset, the cohort was mostly formed (85%) by women, frequently with a body mass index higher than 31, atopy (60%), early-onset disease (50%), and sputum eosinophilia (80%) [38]. The prevalence of atopy is in contrast with another cohort study, in which asthma was 20% more frequent in women than in men aged more than 35 years, whereas more than 60% of women, compared with 30% of men, with new-onset asthma were non-atopic [39]. Instead, the observation by de Carvalho-Pinto et al. about the association with obesity was confirmed in a retrospective analysis of chart review of patients with mild, moderate, and severe persistent asthma, which yielded five clusters similar to Severe Asthma Research Program (SARP). Subjects in cluster 1 and cluster 2 had early-onset atopic asthma and reduced lung function but differed in medication requirement and healthcare utilization; subjects in cluster 3 were older obese women with late-onset asthma, less atopy, and slightly reduced FEV1; and patients of cluster 4 and cluster 5 had atopic asthma with severe obstruction but differed in bronchodilator response, age of onset and oral corticosteroid use. [40]. Another study under the SARP endorsement that analyzed 372,685 hospitalizations for asthma found distinct bimodal distributions for hospitalization age, with an initial peak at 5 years and a second at 50 years. Most subjects

in the first peak were males, while women prevailed in the second. The risk of respiratory failure increased with aging up to 60 years, after which it continued to rise in men, but not in women. The authors concluded that severe asthma is primarily a disease of young boys and middle age women [41]. A factor of pivotal importance in developing severe asthma is airway remodeling, which is driven by immunologic and inflammatory mechanisms. In particular, remodeling may result from persistent inflammation and/or aberrant tissue repair mechanisms. Important candidate mediators of remodeling include transforming growth factor (TGF)-beta and Th2 cytokines, such as IL-5 and IL-13, as well as vascular endothelial growth factor, metalloproteinase 33, and matrix metalloproteinase 9 [42]. The influence of sex difference in airway remodeling was investigated in an animal model. Following induced sensitization to ovalbumin, male or female BALB/c mice were challenged with aerosolized ovalbumin on 3 days/week for 5 weeks, measuring BHR, airway inflammation, and airway remodeling. In ovalbumin-sensitized and challenged female mice, there was a higher increase of total and ovalbumin-specific IgE eosinophils, lymphocytes, T-helper type 2 cytokines, and growth factors in bronchoalveolar lavage compared with male mice. The histological features of airway remodeling were also increased in female mice [43]. Studies comparing the airway remodeling in patients with asthma according to sex are warranted. A further issue in asthma in female sex is pregnancy. In the late 1980s, some studies argued about an apparent improvement or worsening of asthma in pregnant women. In a survey on 366 pregnancies, asthma was unchanged in 33% of women, worsened in 35%, and improved in 28%. Based on diary cards, asthma was significantly less frequent and less severe during the last 4 weeks of pregnancy. Throughout the 3 months post-partum, asthma had returned to its pre-pregnancy course in 73% of women [44]. In the same year, another study monitored 181 pregnant women, using a control group of 198 non-asthmatic pregnant women matched for age and parity. During pregnancy, 40% of the patients did not need modification of drug therapy of asthma, 18% needed less drugs, and 42% more drugs [45]. Juniper et al. followed 20 non-pregnant asthmatic women every 3 months until conception, repeating the assessment in the 16 women who became pregnant once during the second and third trimesters and 1 month after delivery. There was an improvement in asthma severity as indicated by a significant reduction in medication need ($p = 0.03$) and a 2-fold improvement in airway responsiveness as well during pregnancy. Of interest, changes in responsiveness were not closely related to progesterone or estriol, suggesting that other non-hormonal factors may contribute to the improvement during pregnancy [46]. In 2003, in a US study according to the National Asthma Education Program Working Group on Asthma and Pregnancy, which defined asthma severity as mild, moderate, or severe as assessed by symptoms and spirometry, the initial asthma classification was found to be significantly related to subsequent asthma morbidity during pregnancy, including hospitalizations, unscheduled visits, corticosteroid requirements, and asthmatic symptoms during labor and delivery. Exacerbations during pregnancy concerned 12.6% of patients initially classified as mild, 25.7% of patients classified as moderate, and 51.9% of patients classified as severe ($p < 0.001$), with 30% of initially mild patients reclassified as moderate-severe during pregnancy, and 23% of the initially moderate-severe patients reclassified as mild later in pregnancy [47]. In a review, Gluck summarized that the course of asthma during pregnancy is variable, with about one third women improving, one third experiencing increased symptoms, and one third remaining unchanged. A number of physiologic changes during pregnancy as well as the severity of the pre-existing asthma may influence the course of asthma. Women with severe asthma have more exacerbations during pregnancy than mild asthmatics. The second and third trimesters have more potential for worsening of asthma and the need of drug treatment. After childbirth, most women revert to their pre-pregnant state within 3 months [48]. Recent investigations reappraised the issue. A prospective study followed 189 asthmatic women during pregnancy, with visits at 12, 20, 28, and 36 weeks gestation. Data on loss of disease control, recurrent uncontrolled asthma, and moderate/severe exacerbations were collected at each visit and their relationship to perinatal outcomes was analyzed; 50% of asthmatic women showed a loss of control or moderate/severe exacerbations during pregnancy. Factors associated with an increased risk of uncontrolled asthma during pregnancy included smoking, inhaled corticosteroid use at the beginning of pregnancy, and higher maternal age. No such association was detected for moderate/severe exacerbations [49]. Murphy et al. reviewed the recent publications on the effects of exacerbations on maternal and neonatal health, the use of asthma medications during pregnancy, and the novel management approaches for asthma in pregnancy. Pregnancy results in unpredictable changes in the disease; therefore, regular monitoring of symptoms is recommended. Uncontrolled asthma is frequently described in cohorts of pregnant women with asthma, and some recent studies showed associations with adverse perinatal outcomes. Guidelines for the management of asthma recommend the continued use of inhaled corticosteroids (ICS) in pregnancy, with a particularly good safety profile for budesonide. New management strategies are required to address the multifaceted needs of pregnant women with asthma, which include nonadherence to treatment and the presence of comorbidities affecting asthma, as rhinitis, cigarette smoking, obesity, and mental health issues [50]. Table 2 shows the characteristics of asthma in relation to menstrual cycle, menopause, and pregnancy. In recent years, vitamin D was defined as a potent immunomodulator capable of inhibiting inflammatory signals in a number of cell types involved in the asthmatic response. Associations were reported

**Table 2** Main issues related to sexual physiology and asthma in females

| Physiologic issue | Effects on asthma |
|---|---|
| Menstrual cycle | Worsening of clinical symptoms and increase of bronchial hyperresponsiveness. |
| | High risk to develop more severe asthma during menstruation, also with potential near-fatal asthma attacks |
| Pregnancy | No significant difference in worsening, improving, or staying |
| Menopause | Higher prevalence compared to matched-age male subjects |

between its deficiency and augmented inflammation, exacerbations, and poor outcomes in asthmatic patients. Low serum levels of vitamin D (< 20 ng/mL) were found to be related to increased exacerbations and airway inflammation. Several studies, both experimental and clinical, have suggested that supplementation with vitamin D may improve many features of asthma, though the results from clinical trials are still arguable in supporting a beneficial role of vitamin D in asthma [51]. However, there is substantial agreement on the capacity of higher maternal 25OHD levels at early pregnancy to decrease the associated risk of uncontrolled asthma status during pregnancy, such effect being weakened by obesity [52].

## Clinical Data on Allergic Rhinitis According to Sex

The sex-related differences concerning AR are still unclear (Table 1). In fact, yet in early investigation, there were studies reporting higher prevalence rates of AR in females while other studies found a higher prevalence in males [53–55]. Such variability persisted in more recent surveys, with a possible role for geographical factors, as shown by studies in children and adolescents detecting higher AR prevalence in males in Kuwait [56] and Iran [57] but higher prevalence in females in Brazil [58] and Saudi Arabia [59]. To shed light on this issue, Pinart et al. recently performed a systematic review and meta-analysis. A systematic search of MEDLINE and Embase for population-based cross-sectional studies, regardless the language of publication, but limited to the present millennium was performed. The inclusion of studies in the meta-analysis was driven by sampling method, sample size and data collection methods. The sex differences in the prevalence of self-reported or parent-reported (for children aged less than 11 years) rhinitis symptoms were calculated by pooled estimates of the male-female ratio (MFR) obtained using random-effects model meta-analyses. Table 3 shows the main data from the analysis. In children, significantly more males than females had rhinitis symptoms, while in adolescents (aged 11 to 18 years), males were significantly less often affected than females. The findings were steady worldwide except for Asia, where a male predominance persisting beyond childhood was observed. Based on the large number of subjects included, this meta-analysis makes clear, as concluded by the authors, that there is a sex-related difference in AR prevalence switching from male to female predominance around puberty, with the exception of Asiatic countries. In adulthood, no prevalence in either males or females was found, but the number of studies (12) was lower compared with those on children (46) and adolescents (43). The authors suggested that longitudinal studies with follow-up prolonged into adulthood are mandatory to obtain definite data about the influence of sex on AR. Also, the possible determinants and mechanisms underlying the differences warrant to be investigated [60].

**Table 3** Systematic review and meta-analysis of studies on sex-related differences in allergic rhinitis [60]

| Number of publications identified | Number of studies included | Global population | Differences according to male-female ratio |
|---|---|---|---|
| 6539<br>The study selection was made in accordance with the recommendations set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement | 86 (all studies were cross-sectional)<br>5 from Africa<br>35 from Asia<br>8 from North/Central America<br>8 from South America<br>28 from Europe<br>2 from Oceania<br>Sample size<br>10 studies < 1000<br>34 studies 1001–5000<br>23 studies 5001–10,000<br>18 studies 10,001–100,000<br>1 study > 100,000 | 291,726 males<br>301,781 females<br>Aged 11 to 17 years<br>137,443 males<br>142,939 females | In children, significantly more males than females had rhinitis (male-female ratio 1.21, 95% CI 1.17.1.25)<br>In adolescents, significantly less males than females had rhinitis (male-female ratio 0.90, 95% CI 0.85–0.95)<br>No sex-specific difference in adults (male-female ratio 0.96, 95% CI 0.83–1.17) |

## Clinical Data on Skin Allergic Disorders According to Sex

As hinted in the Introduction, the data on differences between males and females in atopic dermatitis are contrasting, some studies reporting a female predominance but others disagreeing with such finding (Table 1). A multinational study on 9803 infants comparing European and Central American countries found higher prevalence of atopic dermatitis in the latter, but no difference between males and female was detected [61]. Instead, concerning adults, a recent review concluded that with regard to sex, atopic dermatitis predominantly affects women, while this trend is reversed in individuals aged over 65 years, when more men are diagnosed [62]. No suggestion on the role of immunologic or hormonal factors in this changing prevalence is available. The observations on contact dermatitis are less conflicting. In a study performed in Israel by standard patch test results, positive reactions to nickel, which is the most common cause of contact dermatitis, were more frequent in women, whereas positive reactions to balsam of Peru were more common in men [63]. In a Spanish study also performed with standard patch test series, women had a higher overall frequency of sensitization than men, nickel being the most common causative hapten, followed by potassium dichromate, thiomersal, and cobalt chloride [64]. However, the number of available studies is too low to draw reliable conclusions. As far as urticaria is concerned, there are data suggesting that at least in chronic urticaria, a predominance of women is apparent [65–67] (Table 1). In particular, in the recent nationwide, population-based study in Italy on epidemiology of chronic spontaneous urticaria (CSU), the annual prevalence of CSU ranged from 0.02% in 2002 to 0.38% in 2013, and the incidence was 0.10–1.50 per 1000 person-years. Prevalence and incidence rates were higher in female patients [66]. Indeed, CSU does not belong to allergic diseases, the type of urticaria mostly associated with allergy being acute urticaria. An epidemiologic study performed in Germany reported a lifetime prevalence rate of all types of urticaria of 8.8%, while the lifetime prevalence for chronic urticaria was 1.8% [68]. Therefore, acute urticaria is much more common, but no studies comparing the prevalence in males and females are available. Also, for contact dermatitis and urticaria, no mechanism associated with the female prevalence was hypothesized.

## Conclusions

An increasing mass of literature shows that respiratory allergy, and especially asthma, following a prevalence of males in childhood, shifts to a higher rate of occurrence in female sex in adulthood.

The mechanisms underlying such difference between females and males are the immunologic effects of female hormones, particularly the modulation of inflammatory response by estrogens [59], and the result of the actions of a number of regulatory proteins and cytokines, as depicted in Fig. 1.

The menstrual cycle is a critical instance for asthma deterioration, as assessed by worsening of clinical symptoms and increase of bronchial hyperresponsiveness, with a high risk to develop more severe asthma during menstruation.

However, the higher prevalence of asthma in females is confirmed also in the post-menopause age, the underlying mechanisms being not yet understood, with a possible role for airway remodeling.

In pregnancy, asthma may not only worsen but may also improve or remain unchanged, with no significant difference in frequency of these three outcomes.

Concerning allergic rhinitis, the studies available thus far indicate, similarly to asthma, a male predominance in prevalence in childhood that changes to a female predominance in adolescence and adulthood, but further research is needed.

The data on influence of sex on skin allergic disorders are inconclusive.

#### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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