



## Editorial

## Sex and allergic diseases



Differences between women and men are pervasive in human biology, including the immune system.<sup>1</sup> The direct effects of sex hormones have not been comprehensively evaluated; however, lymphocytes, monocytes, eosinophils, basophils, and mast cells are known to express receptors for sex hormones.<sup>2</sup> There is also evidence to suggest that estrogens act as enhancers of humoral responses, autoimmunity, mast cell reactivity, and delayed type IV allergic reactions, whereas androgens, progesterone, and glucocorticoids may have an immunosuppressive effect. Furthermore, T-cell responses vary with the phase of the menstrual cycle, suggesting variability of allergic symptom expression in relation to menstrual cycle, pregnancy, administration of oral anti-contraceptive drugs, and hormone replacement therapy. Others have found that histamine response during skin prick testing is highest on days 12 and 16 of the menstrual cycle and comparable between allergic and nonallergic control groups.<sup>3</sup> These biologic differences translate into clinical differences between women and men regarding predisposition to immunologic disease, including allergic disorders, autoimmune conditions, and malignant tumors.

Furthermore, cultural and societal conditions affect the behavior, perception, and expression of disease. Allergic disorders are more common in males than females before puberty with a reversal after puberty, indicating dynamic changes of sex distribution in allergic disorders and the potential role of epigenetics. This trend has been documented in asthma, atopic dermatitis, allergic rhinitis, food allergy, drug allergy, and anaphylaxis. Eosinophilic esophagitis is the only exception, with a persistent predominance in males (3:1) at all ages. Investigations into sex and gender differences are critical to decipher the pathophysiology of allergic diseases. Research on genetic, epigenetic, and environmental factors, including differential hormonal exposures during the human life cycle, can provide the foundations of precision medicine optimally tailored to individual patients.

The current issue of the *Annals* features several articles that contribute to a better understanding of the diversity of several allergic conditions that predominantly affect females. Two reviews dissect the expression of female sex hormone hypersensitivity. Foer and Buchheit<sup>4</sup> discuss a rare condition of progesterone

hypersensitivity. Initially described as *autoimmune progesterone dermatitis*, the term *progesterone hypersensitivity* has recently been proposed because there is limited evidence that autoimmune progesterone dermatitis is an autoimmune condition and progesterone hypersensitivity may start after allergic sensitization to progestins. Affected patients are females of reproductive age (<200 cases reported in the literature), although 1 case of a male with rash and a positive skin test result to megestrol acetate (used as an appetite stimulant) has been reported. The new classification into endogenous (progesterone sensitization caused by natural cycles) and exogenous (extraphysiologic exposure to progesterone through *in vitro* fertilization and plan B) has helped personalize the management of symptoms and potential treatment with desensitization. Clinical manifestations are highly variable and may be cutaneous (eg, papular or vesicular rashes, eczema, purpura, urticaria), respiratory (bronchospasm), or systemic (anaphylaxis). Cyclical symptoms peak in the luteal phase in the 14 days preceding menses. Because of extraphysiologic progesterone exposure, progesterone hypersensitivity may become more common with the increased rates of *in vitro* fertilization. Desensitization has high success rates and has resulted in live births.

Bernstein and Lavery<sup>5</sup> report a case of a 16-year-old girl with 2-year history of cyclical anaphylaxis. Her symptoms typically began 2 to 3 days before the onset of menses. Her serum progesterone specific IgE level was elevated, and a trial of leuprolide resulted in resolution of symptoms, confirming the diagnosis of progesterone hypersensitivity. Progesterone hypersensitivity may be considered to be a form of catamenial anaphylaxis; however, the symptoms of catamenial anaphylaxis correlate with the onset of menses not with the progesterone surge of the luteal phase. A potential mechanism for catamenial anaphylaxis includes the release of prostaglandins from the endometrium, peaking on the first day of the menstrual cycle. Prostaglandin F<sub>2</sub> may cause uterine mast cell activation and release of mediators. Catamenial anaphylaxis may be prevented by nonsteroidal anti-inflammatory drugs, such as indomethacin, or in rare cases by hysterectomy with bilateral salpingo-oophorectomy. Another potential cause of catamenial anaphylaxis is endogenous and exogenous estrogen hypersensitivity. In addition, breastfeeding-associated anaphylaxis has been reported usually within a few days after delivery. One hypothesis attributes this condition to a decrease in progesterone levels after delivery, resulting in an exaggerated release of mediators from the mast cells that were suppressed by progesterone and cortisol during pregnancy and delivery.

Drug allergy has been typically found in higher frequency in women after the age of 20 years, and in the review “Drug Allergy in Children and Adults: Is It the Double X Chromosome?” Norton et al<sup>6</sup> describe the evidence for sex differences. The nonrandom inactivation of chromosome X has been associated with autoimmune

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disorders, and the ubiquitous expression of estrogen, progesterone, and testosterone receptors in all immune cells has been associated with modulation of immune responses. Cyclical changes in female hormones may modify the perception of danger signals, as found in mice with oophorectomy that presented with a significant decrease in anaphylaxis. Drug allergy is shown in multiple studies to have a 2:1 expression when compared with males, but that difference is not seen in children before puberty, but there is no differential sex expression of drug allergy or drug-induced anaphylaxis. Despite a clear increase in drug-induced anaphylaxis in females, death rates are higher in men, indicating a protective mechanism for female hormones, possibly modulating cardiovascular responses. The authors provide evidence that female sex is a risk factor for penicillin allergy and aspirin hypersensitivity. Moreover, radiocontrast media and antiepileptic drugs reactions as well as perioperative and anesthesia-induced anaphylaxis are skewed toward females. Whether cosmetics, household products, and work-related exposures influence drug allergy has not been established, and research is needed to unveil genetic, epigenetic, environmental, and cyclical exposures that can influence drug allergy in postpubertal females.

Asthma is described in women after the age of 20 as more frequent than in men, with many factors contributing to its frequency and severity. Louisias et al<sup>7</sup> analyzed the factors that affect the different expression of asthma in children and adults and across the society spectrum. Environmental exposures include the newly recognized cockroach and mouse allergens, pervasive in homes and schools in inner-city communities. The effect of ambient air pollution with increased nitric dioxide and sulfur dioxide levels is described as affecting minorities and low-income populations because of geography. Diet and obesity are important factors that affect black and Latino populations. Stress, racism, and discrimination are described as proinflammatory factors that can elicit and/or worsen asthma. The authors emphasize the lack of biomarkers to address social, racial, and sex disparities and the need to apply dissemination and implementation techniques to bring research advances to the forefront to force social changes that can improve asthma outcomes.

We hope you enjoy this sex and allergy themed issue of the *Annals*. We challenge you to look for these differences in your

practice and identify opportunities for your personalized medical approach to men and women.

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