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Gender-medicine aspects in allergology

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Abstract

Despite the identical immunological mechanisms activating the release of mediators and consecutive symptoms in immediate-type allergy, there is still a clear clinical difference between female and male allergic patients. Even though the risk of being allergic is greater for boys in childhood, almost from adolescence onwards it seems to be a clear disadvantage to be a woman as far as atopic disorders are concerned. Asthma, food allergies and anaphylaxis are more frequently diagnosed in females. In turn, asthma and hay fever are associated with irregular menstruation. Pointing towards a role of sex hormones, an association of asthma and intake of contraceptives, and a risk for asthma exacerbations during pregnancy have been observed. Moreover, peri- and postmenopausal women were reported to increasingly suffer from asthma, wheeze and hay fever, being even enhanced by hormone replacement therapy. This may be on account of the recently identified oestradiol-receptor-dependent mast-cell activation. As a paradox of nature, women may even become hypersensitive against their own sex hormones, resulting in positive reactivity upon intradermal injection of oestrogen or progesterone. More importantly, this specific hypersensitivity is associated with recurrent miscarriages. Even though there is a striking gender-specific bias in IgE-mediated allergic diseases, public awareness of this fact still remains minimal today.

Keywords

allergy; gender; hormone allergy; mast cell; oestrogen

Limited predictability of allergic reactions

Sensitization towards allergens occurs silently and without awareness of the patient, whereas the effector phase is associated with defined symptoms like rhinoconjunctivitis, asthma, skin rashes, gastrointestinal symptoms or even an anaphylactic shock. This course of the disease is because of the underlying pathophysiology; in an appropriate cytokine milieu, e.g. on account of genetic predis-position, allergen-specific B lymphocytes switch on to the production of IgE antibodies, which only then arm the diverse effector cells. Binding of IgE occurs via the high-affinity-receptor FcεRI expressed on the mast cells, basophils, and eosinophils, which are mostly responsible for the immediate reactions. Both, the IgE-FcεRI (1, 2) as well as the IgE-allergen (3, 4) interactions are characterized by high affinity. Therefore, the presence of IgE is an indicator for possible clinical reactivity of this potent system upon a next contact with a multivalent allergen, which enables cross-linking of at least two IgE – FcεRI complexes. Consecutive activation of the effector cells is characterized by calcium influx and degranulation with expulsion of potent inflammatory

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mediators causing immediate and delayed-type allergic reactions. Furthermore, the dendritic cells express FcεRI (5, 6), which participate in antigen-trapping, -focussing and transportation to secondary lymph organs, often enhancing the effector response.

However, the anaphylactic reaction is not as static and predictable as it may appear at first sight. Since long, it is well recognized that allergen contact can elicit symptoms at higher or lower dose at different time points, exhibiting different thresholds in allergen-provocation tests within the very same individual. Several criteria influencing the releasability of the effector cells and the amounts of allergens needed to trigger mediator-release were already in the focus of interest. For example, elevated allergen concentration in pollen on account of UV exposure (7), allergen modifications through chemical processes like nitration (8), or processing of food allergens (9-11) may directly affect the allergen cross-linking capacity by favouring oligomerization or even aggregation (12). In these settings IgE cross-linking is facilitated and the extent of allergic reactivity enhanced. It is further known that the presence of IgE is a positive regulator for FcεRI expression and enhancing the density of IgE on the effector cell surface again increases the likelihood of cross-linking (13, 14). Whereas the affinity of IgE to FcεRI is constant (2, 15, 16), the binding strength of IgE to its allergen, although being already extraordinarily high, may vary to a certain extent (3, 4). However, none of these mechanistic principles are capable of explaining the reason behind a statistically higher risk for adult females to suffer from allergies.

Truly gender-specific aspects in allergy

As an exception, only in patients below the age of 15 years, allergies are more frequently diagnosed in males (17, 18). The higher susceptibility for eczema in 5- to 7-year-old was explained by a tendency for indoor playing associated with lower endotoxin exposure (19). At a later stage in life, female adolescents clearly suffer more often from respiratory allergies and asthma (20, 21). Moreover, there has been observed a 60 : 40 ratio for female to male patients of severe food allergy (22-29). Also in anaphylaxis, female patients predominate with more than 60% of the documented cases (30). Nevertheless, these numbers can hardly be explained by a female dominance in self-reporting (31).

Truly gender-specific seem the documented associations between menstruation, pregnancy, and hormone therapies, and the severity of allergic reactions. Today, too little public awareness is evinced on this topic, and unfortunately the objective symptoms are often attributed to psychical imbalances in the investigated female patients. On the contrary, the exacerbation of atopic dermatitis around menstruation is a rather common and measurable event (32). In asthmatic females, pre- and perimenstrual asthma have been observed in up to 40% of cases (33). Since the first report in 1938 (34) the underlying cause for perimenstrual asthma has not been clarified and the exacerbation of the disease was projected all the time as hormone-induced changes of smooth muscle and β-adrenergic receptor function (33, 35, 36). Interestingly, asthma and hay fever were even found to be associated with irregular menstruation, uninfluenced by medications (37). With these reports, the need for clinical studies to enable conclusions for evidence-based medicine became apparent. Consecutively, a case–control study analyzed more than 100 sex-matched adults and 450 children recruited from six clinical chest centres and revealed premenstrual exacerbation in asthmatic women to be associated with eosinophilia ($P = 0.01$) (38). Further, it was found that independent of age and smoking habits, intake of oral contraceptive enhanced the IgE levels, indicating a direct relation between hormone levels and allergic reactions. Even near-fatal asthma (NFA) episodes related to menstruation have been repeatedly reported (39, 40), and the results of a multicentre study on NFA were published in 2004 (41). Enrolling 44 cases of NFA revealed finally the menstruation to be a significant trigger of NFA prompting the authors to express the demand for educational programs and better information of female asthma patients in the

reproductive age. These findings are supported by a recent study from Japan, which also concluded that attention should be paid to the deficiency in knowledge regarding peri-menstrual asthma (PMA) in patients with asthma (42). However, only a single report is available on the pharmacological treatment of PMA episodes (43).

Nonphysiological changes in the female hormone status: contraceptives and HRT

The intake of contraceptives in reproductive females, and of hormone-replacement therapy (HRT) in perimenopausal women, has several side-effects such as growth support of hormone receptor-positive malignant cells (44, 45), an enhanced risk for thrombosis and stroke (46), and an enhancement of allergic reactions. Already in healthy women without a history of asthma an elevated risk of wheeze was revealed to be associated with the intake of oral contraceptives (47). From a Medline analysis, Haggerty et al. (48) concluded that pulmonary function decreases and asthma exacerbations increase in the pre- and menstrual phase of pre-menopausal women. Their recommendation prescribing oestrogen- and progesterone replacement therapy to these women to improve pulmonary function should be critically reconsidered based on data from a consecutive study. Hendler et al. (49) assessed a larger cohort of peri-menopausal women by postal questionnaires. From 8568 responding women, 2206 were included and analyzed in the study revealing an interesting correlation between HRT, body mass index (BMI) and asthma. While on the one hand a high BMI increased the risk of asthma (49), the protective effect of a lower BMI was found to have weakened in women treated with HRT (50). Likewise, in a recently published mouse model, progesterone was found to have exacerbated asthma, an effect which could be enhanced by additional tobacco-smoke exposure (51). Taken together, HRT-treated women have a higher risk for experiencing asthma, irrespective of their body weight, but most likely worsened by smoking.

Physiological changes in the female hormone status: pregnancy

During pregnancy, not only extensive hormonal changes occur, but also the abdominal volume increases substantially resulting in a reduced chest volume. Thus, respiration functions under more constraints, even though it is substantial not only for the mother but also for the foetus. Clinically, the functional residual capacity decreases, which is compensated by an up to 50% increase in minute ventilation resulting in hyperventilation in 60–70% of the pregnancies (52). Moreover, nasal congestion is observed in 22–72% of pregnant women in the second trimester. In this situation, acute asthma is a further common negative factor of the respiratory condition. It affects 3–8% of pregnancies in the US, among them hospital visits are required in 9–11% of the women in pregnancy. Most of the attacks occur in the second trimester and as usual, there is a higher risk for patients already with pre-existing severe asthma (53, 54). However, in pregnancy, asthmatic exacerbation is a severe risk factor associated with maternal morbidities like preeclampsia, preterm delivery with low birth weight and bronchiolitis of the child (55-57). Thus, it is crucial for the health of both the mother and the unborn child to optimize asthma therapy during pregnancy by inhaled corticosteroids, which were revealed to be safe and helpful for the management of asthma in pregnant women (58).

Immunological facts for gender differences in immunity

There are several immunological facts that point towards gender differences in immune functions. Receptors for sex steroids were detected on lymphocytes, and monocytes with possible interference in type and extent of immune responses. Peripheral blood leucocytes respond to oestrogens through oestrogen-receptors alpha and beta (59), whereas

progesterone may preferentially act as a negative regulator of mast cell degranulation (60). Indeed, oestrogens were shown to act as immunomodulators (61) by suppressing T-lymphocyte effector function, and enhancing Th2 cell function and consecutive antibody production (62-64), but also delayed type hypersensitivity responses (65). These facts are reflected by relatively higher antibody responses upon vaccinations in women with the exception for IgG titers (66). Oestrogens are, thus, natural enhancers of the humoral immunity and support autoimmunity, whereas androgens and progesterone (and glucocorticoids) physiologically function as immune-suppressors (67). At least in animal models for lupus erythematosus, pathologically increased antibody production could be ascribed to an elevation in oestrogen or prolactin levels promoting the survival and activation of autoreactive B cells (68). Moreover, ovarectomized or oestradiol-antagonist-treated mice developed less IL-5-dependent eosinophilia in allergic inflammation (69).

Oestrogen receptors on mast cells

In various tissues such as related to the upper airway or the gastrointestinal tract, mast cells express oestrogen receptors (63, 70-72). It is generally accepted that oestrogen treatment stimulates mast cells to release mediators (73, 74), which have also been reported to affect the clinical outcome of hereditary angio-oedema (75). In allergy, oestrogen receptor polymorphism was associated with a hyper responsiveness in female asthmatics (76). It has been shown earlier that pre-incubation of mast cells with oestrogens had a priming effect leading to increased release of histamines upon IgE cross-linking (77, 78). More recently the direct biological function of oestrogen receptors on mast cells was evaluated. When the mast cell/basophil cell lines RBL2H3, BMMC and the bone marrow derived HMC-cells were exposed to 17β-oestrogen, Ca^{2+}-influx occurred, followed by β-hexosaminidase and leucotriene C4 release, already measurable at physiological oestrogen concentrations. Oestrogen stimulation potentiated an IgE-induced degranulation, providing evidence that allergen thresholds can be downregulated upon oestrogen stimulation (79). These data indicated that effective triggering of symptoms may occur at lower allergen doses in the presence of oestrogens.

Thus, endogenous oestrogens may support allergic reactivity in females by acting via the oestrogen alpha receptor on mast cells, which might explain the peaking allergic reactions in females around menstruation and pregnancy, under anti-contraceptive and HRT treatment. Interestingly, even exogenous or xeno-oestrogens imitate or support the action of the oestrogens. Environmental oestrogens like Lindan accumulate in pollutants and may affect the development of the female reproductive system by acting as a so-called endocrine disrupter (80). For allergy it is important to note that xeno-oestrogens do interact equally well with the oestrogen alpha and beta receptors and, thus, may either directly or in conjunction with an allergic reaction support the release of histamine (81, 82).

Additionally, it may be noted in this context that on account of structural homology, phyto-oestrogens might also interfere with oestrogen receptors and consequently influence mast cell mediator release (80, 83, 84).

Allergy to sex hormones: a paradox of nature

From the data reviewed above, it becomes evident that the likelihood and extent of allergic reactions in females peak in situations with elevated oestrogen levels. Why then should not the hormone itself be the allergen responsible? In fact, when 270 patients suffering from peri-menstrual symptoms such as asthma, migraine or joint pains were investigated for antibodies to oestrogen and progesterone, elevated titers of specific IgE, IgG, and IgM were detected in serological analysis (85). It is likely that the hormones could act as haptens, gaining sensitizing potency in context with self-proteins like albumin or with their

pharmaceutical formulation. Itsekson et al. (86) examined whether hypersensitivity to sex hormones could be a cause for recurrent pregnancy loss. By intradermal tests they identified oestrogen hypersensitivity in 20 of 23 patients with a history of miscarriages (86). Thus, adverse reactions to sex hormones are documented and have major clinical and personal implications for affected female patients.

Conclusion

From clinical observations, the association of hormone status and allergic reactivity has been known since several decades. Only during the recent years, the mechanistic involvement of sex hormones in immune reactions has been acknowledged. In allergy, sex hormone receptors on lymphocytes and leucocytes may modulate the type of immune reaction and regulate inflammation. Oestrogens were revealed to have a receptor-mediated effect on the releasability of mast cells influencing the threshold levels in the effector phase of allergy. These findings have wide gender-specific implications on the prevention and treatment of allergies in female patients. Moreover, adequate patient information about female aspects in allergy should be designed to enhance the awareness of this evidence-based correlation. On the other hand in the case of sex hormone allergy, specific desensitization might represent a novel treatment option for the future.

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Abbreviations

BMI	body mass index
HRT	hormone-replacement therapy
NFA	near fatal asthma
PMA	perimenstrual asthma

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