



Gender differences in anaphylaxis

Lorenzo Salvati*, Gianfranco Vitiello*, and Paola Parronchi

Purpose of review

Is sexual dimorphism also true in anaphylaxis as described in other allergic diseases? Possible gender differences in the epidemiology, triggers, severity, outcomes of anaphylaxis as well as in the pathogenesis of the disease are discussed.

Recent findings

Hormonal status and the X-chromosome-coded factors deeply involved in the regulation of T-cell and B-cell responses may influence the gender difference noticed in allergic diseases, such as asthma and rhinitis. Little is known if sex is also relevant for anaphylaxis, although the description of catamenial anaphylaxis is intriguing. However, epidemiologic bias, lack of reliable animal models for the human disease, differences into diagnostic codes and not harmonized clinical grading unfortunately represent hurdles to obtain meaningful information on this topic.

Summary

The female sex predisposes to a dysregulation of the immune response as suggested by the increased prevalence of autoimmunity and atopy. In anaphylaxis, pathomechanisms are not fully disclosed, triggers are numerous and IgE-dependent mast cell degranulation only represents a part of the story. Improvement into the definition of the disease including a more careful coding system and better investigations about triggers seem the only way to allow a more precise assessment of the possible different risk for women to develop anaphylaxis.

Keywords

anaphylaxis, gender, hormones, mast cells, sex

INTRODUCTION

Each one of us, by our chemical make-up,
above all by our blood and probably also
by the protoplasm of each cell,
is himself and no one else.
In other words, he has a humoral personality.

Charles Richet

Nobel Lecture, 11 December 1913

Anaphylaxis is defined as a serious, potentially fatal generalized or systemic hypersensitivity reaction being typically rapid in onset and usually characterized by involvement of at least two different organs (skin, respiratory, cardiovascular or gastrointestinal systems). Although traditionally related to the rapid mediator release by mast cells in the context of an IgE-mediated type I hypersensitivity, anaphylaxis recognizes several other triggers, not strictly and necessarily allergen-dependent, so much that idiopathic anaphylaxis has also been described [1,2^{***},3]. Along with this, the sentence by the father of anaphylaxis, Charles Richet, is illuminating as referring to personality (individual triggers, different clinical symptoms, severity

and outcomes for each patient), chemical make-up and humoral state (different immunomechanisms, circulating immune modulators). In such a so 'personal' history, and way more in anaphylaxis, sex-dependent and hormonal-dependent factors might play a role. Some X-coded natural (e.g. TLR7 and 8, CXCR3) and adaptive (e.g. CD40 ligand, FoxP3, WAS, IL2RG) immune players and the expression of estrogen and androgen receptors on the majority of the immune cells, including mast cells, are involved into the regulation of the immune response [4,5]. Nonetheless, sex influence on the mechanisms of activation (classical or alternative) of MCs has not been fully clarified and the female predisposition towards immediate immune reactions, at least for human anaphylaxis, appears premature to be affirmed.

Department of Experimental and Clinical Medicine, University of Firenze, Firenze, Italy

Correspondence to Paola Parronchi, MD, Department of Experimental and Clinical Medicine, University of Firenze, Largo Brambilla 3, 50134 Firenze, Italy. Tel: +39 557947421; e-mail: paola.parronchi@unifi.it

*Lorenzo Salvati, Gianfranco Vitiello equally contributed to this work.

Curr Opin Allergy Clin Immunol 2019, 19:417–424

DOI:10.1097/ACI.0000000000000568

KEY POINTS

- In rodents, anaphylaxis is more severe in female than male animals and estrogen increase eNOS and mast cell degranulation with the consequence of increased vascular permeability and systemic manifestations.
- In humans, the possible role of sex hormones is indirectly indicated by the rare catamenial and breast-feeding anaphylaxis. Estrogen and progesterone affect mast cells *in vitro* but *in-vivo* effects are still unknown.
- Epidemiologic studies often conclude for an increased risk of anaphylaxis in women than in men but composition of the cohorts, definition of anaphylaxis, self-reported events, different coding system and lacking homogenous criteria about severity represent major biases and undermine the validity of the observations.
- It is hopeful that data coming from prospective large pooled cohort studies where definition and severity criteria are shared and possible (including hidden) triggers are adequately investigated, may finally confirm or exclude the gender influence on anaphylaxis.

DO IMMUNE CELLS HAVE SEX IN ANAPHYLAXIS? WHAT PATHOGENETIC STUDIES TELL

Animal models

In-vivo murine models of systemic anaphylaxis are ordinarily used to elucidate the pathological mechanisms involved in anaphylaxis, even if these observations have limitations when translated into humans' disorder [6]. To date, only few experimental studies have addressed the question about a possible difference in the intensity of anaphylaxis between female and male mice (Fig. 1). In these studies, C57Bl/6 mice have been used: experiments have been conducted on male mice at 10 weeks and female mice at 12–14 weeks [7^{***}], or male and female mice at 10–12 weeks of age [8^{***}]. Estrous cycle does not seem to influence mast cell responses in mice. No differences have been noticed in serum histamine levels following restrain stress or in histamine content of peritoneal mast cells in female mice during the stages of the estrous cycle [8^{***}]. Only a mild increase of peritoneal mast cells in C57Bl/6 female mice has been described in proestrous and estrus compared with metestrous/diestrous [8^{***}]. On the contrary, higher numbers of mast cells have been observed in the mammary glands of female rats in association with higher histamine levels during the estrous than in proestrous or diestrous stage [9].

In general, IgE-mediated passive systemic anaphylaxis is significantly more severe in female mice compared with age-matched males [7^{***},8^{***}]. A crucial role might be played by estradiol: sexual difference in anaphylaxis severity is abrogated when female mice are ovariectomized (compared with sham-operated mice) or estrogen receptor α (ER α) is blocked by hormonal antagonists (fulvestrant) and restored upon administration of estradiol in ovariectomized mice [7^{***}]. 17 β -estradiol does not significantly alter mast cell responsiveness in terms of preformed mediator release (histamine, mast cell protease 1 MCPT-1) in ovariectomized compared with sham-operated mice, as Hox *et al.* [7^{***}] recently demonstrated within 90s after anaphylaxis. However, histamine levels are higher in females than males when measured later (30 min) [8^{***}]. The effects of estradiol could be mediated by increased vascular permeability, as evidenced by the significantly increased hematocrit levels and the more severe lung edema in female mice undergoing anaphylaxis when compared with male mice. A first possible explanation lies in the upregulation of endothelial nitric oxide synthase (eNOS) whose levels and activity are enhanced by estradiol [7^{***}]. Indeed, the injection of NOS inhibitor L-NG-nitroarginine methyl ester (L-NAME) or genetic eNOS deficiency results in abolition of gender differences [7^{***}]. Furthermore, pretreatment with estrogen receptor antagonists prevents the protective effect of NOS inhibition in female mice [7^{***}]. *In-vitro* female primary bone marrow-derived mast cells (BMMCs) indeed exhibit increased releasability as they do synthesize and store larger amounts of granule mediators (β -hexosaminidase, TNF- α , tryptase and histamine) than male BMMCs [8^{***}]. The increased quantity of mediators has been also demonstrated in other districts, such as female peritoneal mast cells and across different animal species, such as mice and rats [8^{***}]. The enhanced degranulation response displayed by female BMMCs in comparison with males does not depend on Fc ϵ RI-mediated tyrosine phosphorylation signaling or intracellular calcium mobilization, but it results from the upregulated expression of a wide variety of genes, including *Tnf*, *Prps*, *Srm* and *Bhlha15*, which are involved in metabolic, biosynthetic and cellular processes leading to mast cells granules formation [8^{***}]. In unstimulated conditions, tumor necrosis factor (*Tnf*) gene is actually 3.5 times more expressed in female BMMCs than male BMMCs. Further, phosphoribosyl pyrophosphate synthetase 1 (*Prps1*) gene is 2.45 times more expressed in female BMMCs than in male BMMCs. This gene codifies for a key enzyme in histidine and tryptophan synthesis and its rate of transcription directly correlates with the rate of production for phosphoribosyl phosphate. Spermidine synthetase (*Srm*) gene, involved in polyamine

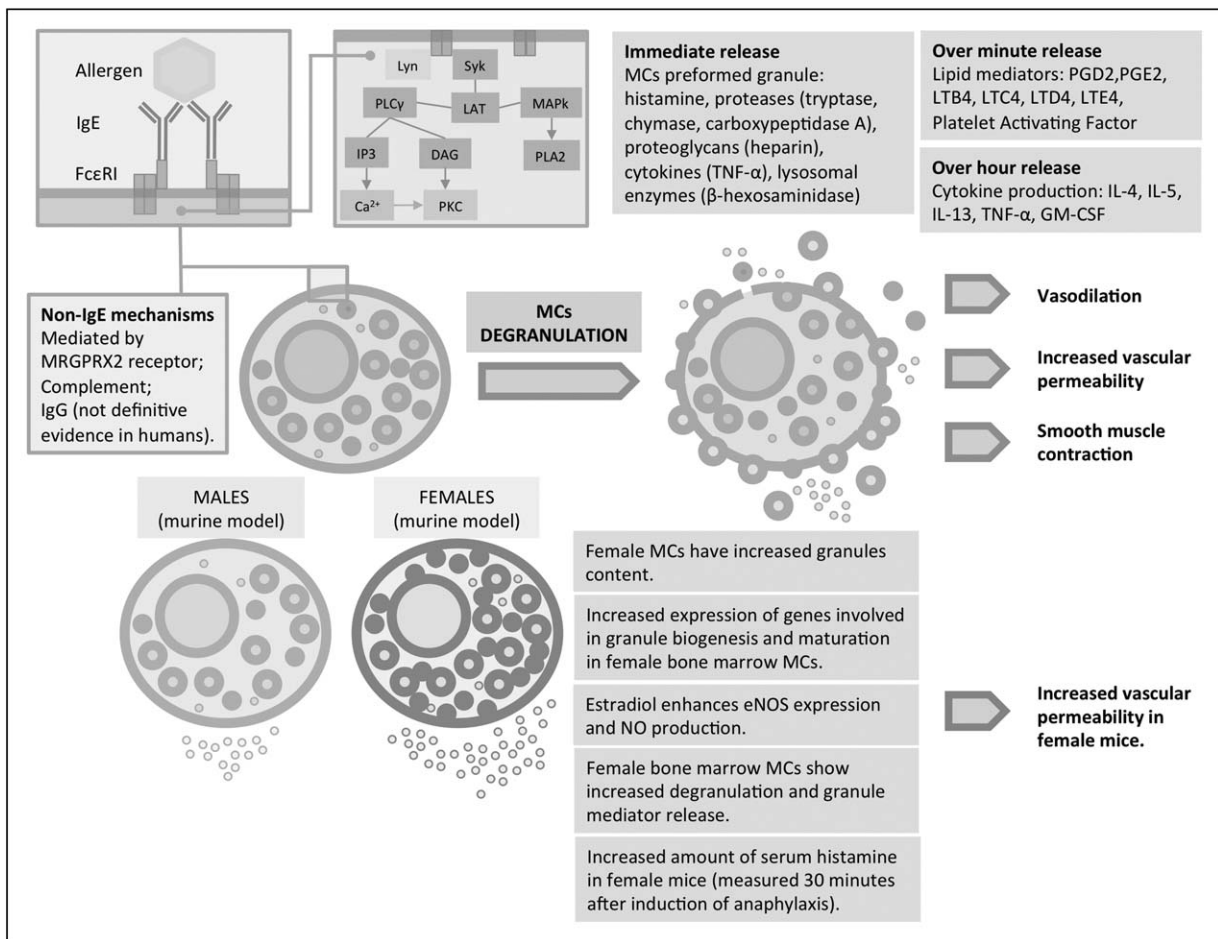


FIGURE 1. Gender differences in degranulation of mast cells. Anaphylaxis results from the effects of mediators released by the degranulation of mast cells, which can be activated by either IgE-dependent or IgE-independent pathways. After prior sensitization to a specific antigen, antigen-specific IgE are produced and bound to high-affinity receptor FcεRI expressed on the surface of mast cells. Re-exposure to that specific antigen or a cross-reactive antigen cross-links FcεRI-bound IgE consequently aggregating surface FcεRI and triggering the signaling pathway. Once the tyrosine kinase Lyn phosphorylates the immunoreceptor tyrosine-based activation motifs (ITAM) of the β and γ chains of the FcεRI, Syk is recruited to the ITAMs of the γ chain. The nonreceptor tyrosine kinase Syk is activated and phosphorylates linker activation of T cells (LAT). LAT phosphorylates phospholipase Cγ (PLCγ), which catalyzes the formation of inositol trisphosphate (IP3) and diacylglycerol (DAG) from membrane phosphatidylinositol biphosphate (PIP2). IP3 determines intracellular calcium release from the endoplasmic reticulum, whereas calcium and DAG activate protein kinase C (PKC). PKC and calcium contribute to exocytosis of preformed granules. Lipid mediator synthesis is controlled by phospholipase A2 (PLA2), which is activated by extracellular receptor-activated kinase (ERK) that derives from mitogen-activated protein (MAP) kinase signaling pathway. Some of the mast cell granule mediators (summarized in the figure) are released within minutes of antigen exposure accounting for the immediate biologic effects of anaphylaxis (vasodilation, vascular permeability and bronchoconstriction), others (cytokines and growth factors) are newly synthesized from gene transcripts whose expression is promoted by MAP kinases, PKC and calcium. In passive systemic anaphylaxis murine models, gender differences in mast cell disorder have been described. LT, leukotriene; MRGPRX2, Mas-related G-protein coupled receptor member X2; PG, prostaglandin.

synthesis, and Basic helix-loop-helix family member A15 (*Bhlha15*) gene, which is an important transcription factor in granules maturation, have higher (3.7-fold and 3.4-fold, respectively) expression in female BMMCs than in male BMMCs [8^{***}]. Hence, in addition to direct stimulation mediated by sex hormones, male and female mast cell phenotype might be intrinsically different.

Humans

The role of gender on the pathogenetic mechanisms of human anaphylaxis is still largely unknown. Human anaphylaxis is per se difficult to be studied because of the nature and the timing of the reaction, indeed justifying the numerous yet unanswered questions about the effector mechanisms involved [1]. Hypotheses on biological gender diversity in

human anaphylaxis are mainly derived from immunohistochemical and in-vitro studies [10] aimed at identifying the expression of sex hormones receptors on human mast cells and analyzing human mast cell cultures under hormonal stimulation [11,12].

In vivo, women may suffer from a peculiar form of monthly anaphylaxis recurring during the time of menstruation, called as catamenial or cyclical anaphylaxis, which may underscore the role of progesterone in inducing anaphylaxis [13]. In healthy children, serum basal tryptase levels tend to be higher, although not significantly, in boys than girls [14], whereas among healthy adults the mean tryptase level is increased by 0.2 ng/ml in women and reduced by 0.2 ng/ml in men [15].

As the effects of sex hormones in anaphylaxis are numerous and potentially different in experimental animals and humans, a summary is reported in Table 1.

DOES THE EPIDEMIOLOGY OF ANAPHYLAXIS RECOGNIZE A SEX EFFECT? THE INFLUENCE OF AGE AND TRIGGERS

Anaphylaxis has been the subject of countless epidemiologic studies, most focusing on the rising incidence through years, the recognition of triggers as well as the standardization of treatment, but few

and conflicting data are available regarding gender differences and influence of sex on the incidence and outcomes.

Stratifying data according to age, during childhood, boys have higher incidence of anaphylaxis for all causes [22,23[¶]] because of the higher prevalence of food allergy in male individuals in this period of life [24,25]. As the children grow older (>10 years of age), girls have reported comparable or even higher anaphylaxis rates [26[¶]], because of the increased prevalence of food allergies in women after puberty [27]. However, these data have not been confirmed by other authors who found a significant higher incidence of anaphylaxis in male individuals aged 10–19 years and only a trend towards increased incidence in boys aged 0–9 years, which does not reach statistical significance [28^{¶¶}] (Fig. 2).

In adulthood, it seems not to be any gender influence on the overall incidence of anaphylaxis [23[¶]]. However, outdated and past clinical observations highlighted a female prevalence of anaphylaxis generally related to the increased sex-associated prevalence of atopic disorders and asthma [29]. In this context, a female prevalence of systemic reactions, including anaphylaxis, to subcutaneous allergen immunotherapy has been also described [30]. In a recent retrospective population-based study, an increased incidence of anaphylaxis rate was observed in men between 30 and 39 years, whereas 40–49 years old women were more

Table 1. Effects of sex hormones relevant for anaphylaxis

Hormone	Experimental models (animal)	Ref.	Humans	Ref.
Estrogen	↑ vascular permeability in females (mouse)	[7 ^{¶¶}]	ER expressed by MCs	[12]
	↑↑ eNOS activity and NO production in female MCs (mouse)	[7 ^{¶¶}]	↑ β-Hexosaminidase release in HMC-1	[11]
	ERα expressed by MCs and BMMC (mouse)	[7 ^{¶¶} ,11,12]	↑ Tryptase expression in HMC-1	[12]
	↑ histamine release in female pMCs (mouse and rat)	[8 ^{¶¶} ,16]		
	↑ degranulation and LTC4 production	[11]		
Progesterone	↓ histamine release in pMCs (rat)	[16,17]	PR expressed by MCs	[18]
			↑ Tryptase expression in HMC-1	[12]
			catamenial anaphylaxis ^a	[13]
Prolactin	Unknown effect in anaphylaxis		Anaphylaxis associated with breast-feeding or lactation anaphylaxis ^a	[13,19]
Androgens	↑ IL-33 in male MCs by testosterone (mouse)	[20]	AR expressed by skin MCs (10-fold in foreskin MCs than female breast skin MCs)	[10,21]
	↑ Histamine release in female pMCs but not in males by testosterone and DHT (rat)	[16]	↓ IL-6 production in female breast skin MCs by DHT	

AR, androgen receptor; DHT, dihydrotestosterone; eNOS, endothelial NO synthase; ER, estrogen receptor; HMC-1, human mast cell line; MCs, mast cells; pMCs, peritoneal mast cells.

^aCause is still unknown.

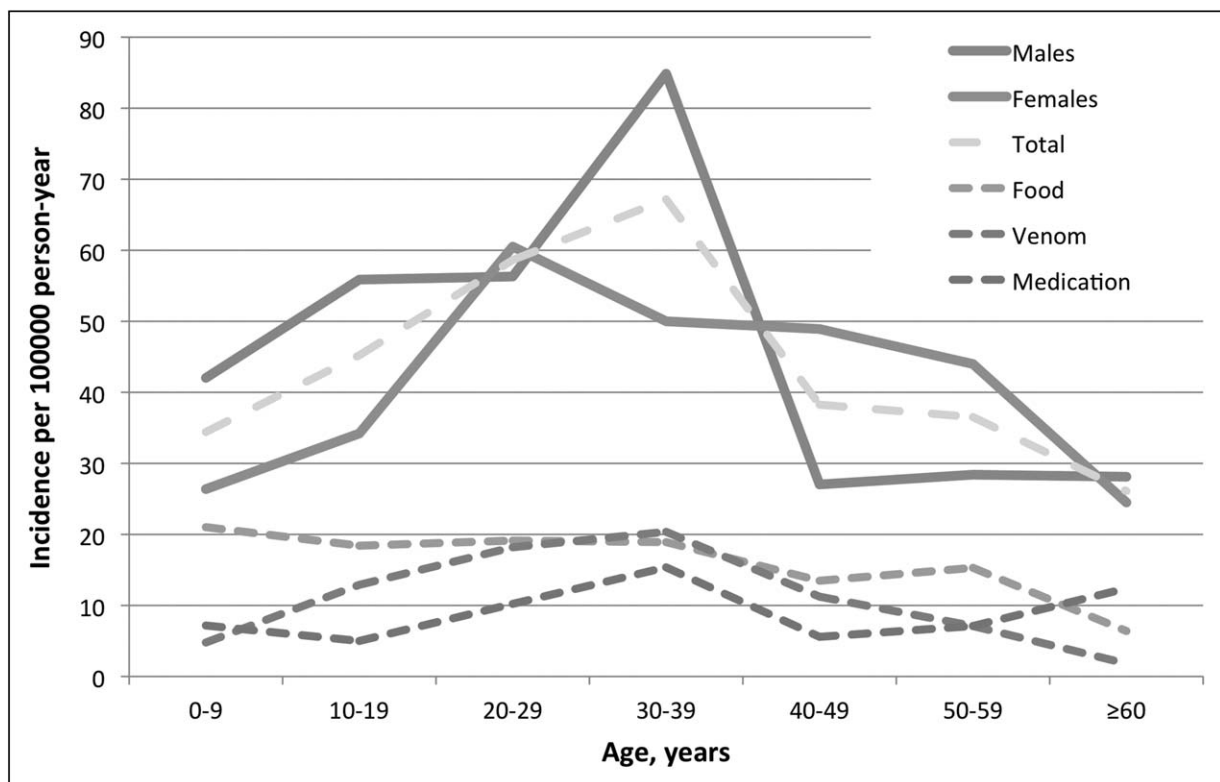


FIGURE 2. Incidence of anaphylaxis through age, sex and triggers. Data were pooled together from Lee *et al.* [28^{***}]. In the original article, the population-based study incidence rate and causes of anaphylaxis were evaluated during a 10-year period (2001-2010) in Olmsted County, Minnesota, USA. With permission from Elsevier via Copyright Clearance Center's RightsLink.

likely to experience anaphylaxis than same aged men [28^{***}] (Fig. 2).

Interestingly, notable sex differences become evident stratifying data accordingly to the triggers of anaphylaxis. Nonfatal and fatal insect-venom anaphylaxis is way more frequent in male individuals [31^{*},32]. In this case, the occupational exposure plays a major role as more than 80% of beekeepers are men [33^{***}]. In addition, mastocytosis, a well known risk factor of venom allergy, prevails in male individuals rather than in female individuals [31^{*}].

Mixed results can instead be found regarding drug-induced and food-induced anaphylaxis. Two survey-based studies reported a female prevalence for drugs [34,35]. However, when the 10th clinical modification of the *International Classification of Diseases* (ICD) system diagnostic codes was used, data from National databases failed to identify any gender difference either in the incidence or the fatalities [31^{*}].

Cancer drug anaphylaxis, both involving chemotherapies and targeted monoclonal antibodies (MoAbs), has been recently recognized as a worldwide problem that impacts on the quality of life and survival of patients [36]. Platins, taxanes and MoAbs are the most common drugs involved and for whom

a desensitization protocol has been developed [37]. Data extracted from centers performing desensitizations have shown that 91% of protocols are performed in women (mean age 57 years), mainly affected by ovarian cancer and treated with carboplatin, paclitaxel or doxorubicin [38]. It has been reported that up to 27% of women with ovarian and breast cancer develop carboplatin allergy after several exposures [37]. In addition, female patients presenting BRCA1 and BRCA2 mutations are at increased risk of earlier and more severe carboplatin-induced reactions [39].

For food-induced anaphylaxis, ICD-based studies conducted in adults referring to public hospitals all the same identified the female sex as a risk factor [26^{*},27]. Interestingly, a personal history of allergy was recorded for less than 1% of the studied cohort in New Zealand, which is in contrast with recent reports [23^{*},27]. However, conflicting results are provided by the literature on this point. Focusing on fatalities because of food-related anaphylactic events, a slight male prevalence was reported [31^{*}] but others failed to confirm these data [26^{*}]. It is important to underline that none of these studies have approached the conflicting gender-related results into the discussion section.

Only one study reported a gender difference in exercise-induced anaphylaxis (EIA), with a 2:1 female to male ratio [40]. However, the survey-based design of this study may have deeply conditioned these results, in as much as only about one half of the patients (54%) reached with the questionnaire actually completed the study. In line with this, the authors did not further discuss this finding throughout the article.

Occupational-related anaphylaxis seems to prevail in men [33²²] but this may most likely be because of gender-specific professional exposure. Indeed, occupational anaphylaxis has been reported especially for beekeepers, as already cited. In addition, to be a cook is another high-risk job with, unexpectedly since more recent years, a clear male prevalence [33²²]. No gender-related data for occupational latex allergy, chemicals and medications exposure are available.

Finally, idiopathic anaphylaxis from hidden allergens or unexplained increased sensitivity to histamine has been described more commonly in women, even though no clear pathogenetic explanation for this phenomenon is provided [41²¹].

On the whole, studies that investigated the prevalence of anaphylaxis present several limitations (Table 2). First, it is difficult to assess the gender influence on the epidemiology of anaphylaxis as none of the studies mentioned above has been powered to study this item. Moreover, differences residing in the presence of beekeepers, the age of the studied cohorts, the access to healthcare system and the classification system used for the definition of anaphylaxis (either if ICD-defined or guidelines-defined) are all conditioning factors of

these epidemiologic investigations. Prospective, world-wide, pooled cohorts are needed to definitively confirm or exclude the gender influence on the incidence of anaphylaxis. This approach may also have a crucial influence on the diagnostic and therapeutic approach to anaphylaxis, especially in the current tendency towards a personalized approach in allergy. In this regard, gender differences are neither mentioned in the latest review focused on precision medicine applied to anaphylaxis [42].

DOES GENDER CORRELATION EXIST IN CLINICAL FEATURES, SEVERITY AND MORTALITY OF ANAPHYLAXIS?

The efforts to compare sexual dimorphism in clinical presentation and outcome of anaphylaxis are crucially important in order to identify specific traits that can orientate both clinicians and researchers to unveil gender peculiarities in this serious potentially life-threatening or fatal immune reaction. Data available from epidemiological studies exhibit critical limitations as described above (Table 2) but, and nonetheless, unlike the own experience of each clinician, they represent the only way to currently understand potential gender differences or similarities.

Analyzing the pooled data from the Anaphylaxis Registry, acquiring voluntary contributions from European tertiary allergy centers with particular expertise, cardiovascular and/or respiratory symptoms of anaphylaxis seemed not to differ between males and female individuals (Fig. 3a) [43²³]. In particular, male sex was not found to be associated with an increased risk of hypotension (SBP <90 mmHg),

Table 2. Main limitations of the epidemiological studies about gender-correlation in anaphylaxis	
Items or types of the study	Issues
Public and private health service	Different Economic conditions Education Presence of ethnic minorities Gender accessibility
ICD-based studies	Different definition of anaphylaxis between ICD-9 and ICD-10 Few encoded causes of anaphylaxis included (e.g. food, drug and serum) Less specific codes for bee sting-related reactions
Retrospective cohort studies	Numbers of beekeepers included
Definition of anaphylaxis	Changes throughout the years of publication No shared items among Scientific Associations/Societies (American vs. Australasian vs. European vs. World Allergy Organization)
Self-reported event studies	Selection bias Lack of confirmatory tests
Survey-based studies	Election bias Self-reported events

ICD, International classification of diseases.

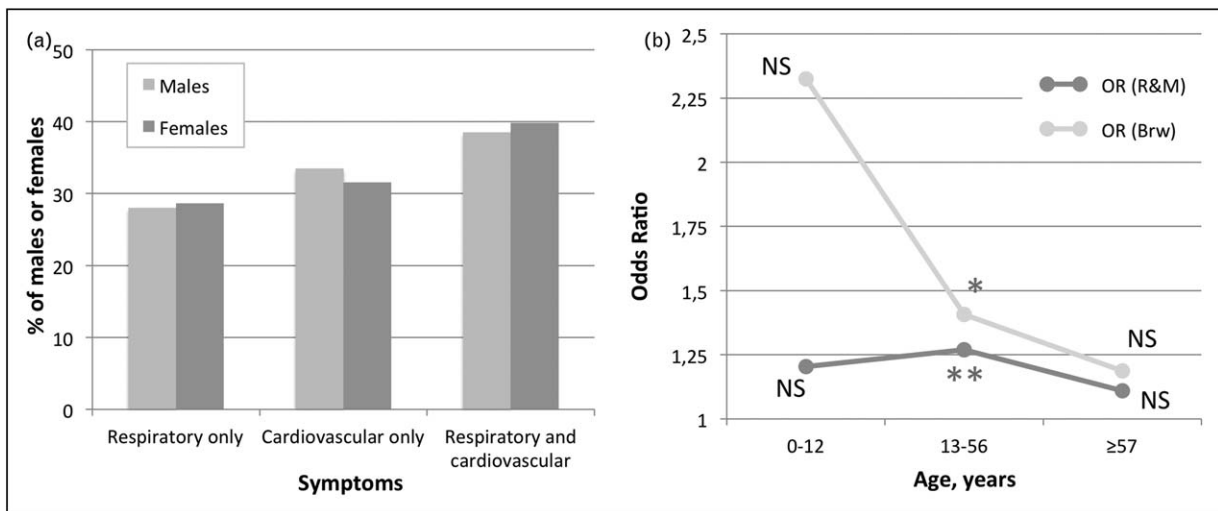


FIGURE 3. Gender, clinical symptoms and age according to the Anaphylaxis Registry. (a) Data were pooled from Worm *et al.* 2012 [43[•]]. The authors analyzed 950 male and 1062 female individuals of all ages with history of severe allergic reaction acquired into the Anaphylaxis Registry from 2006 to 2010. Respiratory symptoms included dyspnoea, stridor, apnoea with dyspnoea and stridor as more common. Cardiovascular symptoms included decreased alertness, tachycardia, decrease of blood pressure, loss of consciousness, collapse and cardiac arrest with dizziness and hypotension as more common. No significant gender difference in clinical presentations was found. (b) Data were pooled from Francuzik *et al.* 2015 [45]. The authors used the Anaphylaxis Registry, analyzing severity of anaphylaxis in 5765 patients (2792 male patients and 2973 female patients) stratified by age group and gender according to Ring & Messmer (R&M) or Brown (Brw) grading scales. Odds ratio (OR) for male gender as a predictor of anaphylaxis has been calculated by the authors finding that male patients aged 13–56 years are at increased risk for more severe anaphylaxis (OR = 1.3 and OR = 1.4 when considering Ring & Messmer and Brown scales, respectively) than age-matched female patients. NS, not significant, * $P=0.025$, ** $P=0.005$.

hypoxemia (oxygen saturation by pulse oximetry $\leq 92\%$) or delayed clinical deterioration [44]. About the relationship between gender and anaphylaxis severity, an analysis of the Anaphylaxis Registry was performed with details reported in Fig. 3b [45]. In prepubertal children, severity is similar in boys and girls [45]. Conversely, male patients aged 13–56 years exhibit a slightly increased risk for severe anaphylaxis when compared with female patients of the same age group [45], particularly for venom [2^{••}] and drug-induced anaphylaxis [3]. Same severity has been described in adult men and women older than 56 years [45]. About geographically distributed access to care, female individuals are more frequently admitted to the hospital in England and Wales when compared with male individuals [26[•]], while they are less likely to be hospitalized in the USA [46]. Also accounting mortality, the rate does not differ in boys and girls [47] and there are no significant gender differences in all-causes anaphylaxis-related fatalities among adults, even if men are at increased risk for fatal venom anaphylaxis and African American men for fatal food anaphylaxis [2^{••}, 31[•]].

Finally, the incidence of biphasic anaphylaxis is similar between male and female individuals [48, 49].

CONCLUSION

In allergology, being a woman or a man makes the difference in the prevalence, clinical presentation or course of bronchial asthma and rhinitis. Regarding anaphylaxis, female rodents develop more severe manifestations than male rodents and estrogens exert proactive effects favouring eNOS upregulation and mast cell degranulation. In human beings, on the contrary, sex, hormones and immediate severe hypersensitivity seem not to be so strictly connected, although catamenial and breast-feeding anaphylaxis have been described. Epidemiologic studies may help to better define this point but sharing a common method of selection, disease items and severity criteria represent a crucial issue.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interests.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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