

Sex differences in asthma and immunological response: an overview

Elena Barbagelata¹, Catia Cilloniz², Antonello Nicolini³, Anna Maria Moretti⁴

¹Internal Medicine Department, General Hospital, Sestri Levante, Italy; ²Department of Pneumology, Institut Clinic del Tórax, Hospital Clinic of Barcelona - Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona - Ciber de Enfermedades Respiratorias (Ciberes) Barcelona, Spain; ³Respiratory Diseases Unit, General Hospital, Sestri Levante, Italy; ⁴Respiratory Diseases Unit, Policlinico University Hospital, Bari, Italy. Received 19 January 2019; accepted 8 March 2019.

Summary. Gender differences in asthma incidence, prevalence and clinical phenotypes have been extensively reported worldwide. A number of studies have shown that respiratory allergy, and especially asthma, is prevalent in males during childhood, whereas it becomes more frequent and severe in females between adolescence and adulthood, suggesting that sex hormones play a role as important modulators of immune response. The mechanisms underlying these differences between females and males are most likely the effects on the immune and inflammatory responses of female hormones and the result of the activity of various cells and cytokines. Understanding gender differences in respiratory allergies and asthma is important for providing effective education and personalized management plans for patients throughout their lives.

Key words. Gender differences, bronchial asthma, immune response, pregnancy, menopause.

Differenze sessuali nell'asma e nella risposta immunologica: una panoramica

Riassunto. Le differenze di genere nell'incidenza di asma, nella prevalenza e nei fenotipi clinici sono state ampiamente riportate in tutto il mondo. Numerosi studi hanno dimostrato che l'allergia respiratoria, e in particolare l'asma, è prevalente nei maschi durante l'infanzia, mentre diventa più frequente e grave nelle donne dall'adolescenza all'età adulta, suggerendo un ruolo per gli ormoni sessuali come importanti modulatori delle risposte immunitarie. I meccanismi alla base di queste differenze tra femmine e maschi sono probabilmente gli effetti sulle risposte immunitarie e infiammatorie degli ormoni femminili e il risultato dell'attività di varie cellule e citochine. Comprendere le differenze di genere nelle allergie respiratorie e nell'asma è importante per fornire un'educazione efficace e piani di gestione personalizzati per i pazienti nel corso della vita.

Parole chiave. Differenze di genere, asma bronchiale, risposta immunitaria, gravidanza, menopausa.

Introduction

Nearly 40 million people in the United States are diagnosed with asthma¹. This chronic inflammatory airway disease results in a cost to society of ~\$50 billion per

year, in addition to the significant loss of productivity of individuals who suffer from asthma^{1,2}.

In recent decades, international literature on sex differences in human diseases has grown steadily, but immunology ranked the lowest of 10 biological disciplines for reporting on the sex of animals or human subjects in published papers³. In a recent review, Klein and Flanagan emphasized that sex is a biological variable that should be considered in immunological studies⁴. There is, on the other hand, abundant literature on the role of sex factors in respiratory allergy, including allergic rhinitis (AR) and especially asthma, which is the most studied disease and was found to be different in females in terms of both prevalence and clinical severity⁵.

Epidemiological data show that overall asthma prevalence, severity, exacerbation rate, hospitalizations and mortality are higher amongst women than men; however, asthma-related office and emergency room visits and hospitalizations are higher among boys than girls in the 0 to 14 years age range^{6,7}.

The reasons for this gender difference are unknown, but have been linked to immunological and hormonal factors, and/or to differences in gender-specific responses to environmental or occupational exposure⁸.

The purpose of this concise review is to better identify and understand gender differences in asthma and respiratory allergy conditions, in order to provide more appropriate and personalized management plans for these patients. Figure 1 summarizes the potential factors contributing to the gender difference in respiratory allergies and asthma.

Sex differences in immune response

Males and females differ in the strength of immune response and these effects have been verified in humans and other animals. Sex hormones act as important modulators of immune response; the male sex hormone testosterone is generally immunosuppressive, whereas the female sex hormone estrogen tends to be immunoenhancing. Different sets of T-helper cells (Th) play important roles in adaptive immunity, e.g. Th1 cells trigger type 1 responses that are primarily cell-mediated, and Th2

cells trigger type 2 responses that are primarily humoral responses⁹. Reviewing the literature, it is apparent that in females estrogen (at periovulatory to pregnancy levels) and progesterone enhance type 2 and suppress type 1 responses, whereas in males testosterone suppresses type 2 responses and shows an inconsistent pattern for type 1 responses. Thus, the sex differences in immune response should be particularly strong in immune functions associated with type 2 responses, and less pronounced with type 1 responses. In general, the hormone-mediated sex differences in immune response may lead to genetic sexual conflicts on immunity. Finally, behavioral and ecological contexts can play a role in sex hormone-induced effects on immune response, considering the social mating system, sexual selection, geographical distribution of hosts, and parasite abundance⁹.

In experimental animal models of asthma, female mice have increased airway hyper-responsiveness, eosinophilic influx, and increased production of type 2 cytokines (i.e. interleukin [IL]-4, IL-5, and IL-13) in the lungs after allergen challenge compared to males. Although CD4⁺ TH2 cells are known to produce type 2 cytokines, type 2 innate lymphoid cells (ILC2s) have been described as producing far larger quantities of IL-5 and IL-13 than TH2 cells¹⁰.

Moreover, estrogens contribute to the sex differences in immunity by regulating dendritic cell (DC) subsets, which express estrogen receptors and act as ligand-dependent transcription factors¹¹. Laffont et al. showed, in an experimental study, that group 2 innate lymphoid cells (ILC2s), which are key regulators of type 2 inflammatory responses, are negatively influenced by male sex

hormones. Indeed, male mice had fewer ILC2 progenitors and mature ILC2s in peripheral tissues than 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 inflammation¹². Interestingly, orchiectomy, but not ovariectomy, abolished the sex differences in ILC2 development and reinstated IL-33-mediated lung inflammation¹².

Estrogen's influences on immune cells favor the allergic response, promoting Th2 polarization, encouraging class switching of B cells to IgE production and prompting mast cell and basophil degranulation¹³.

Sex differences in genetics

As regards genetics, other studies used experimental models to analyze the potential mechanisms involved in the sexual dimorphism of asthma. The gender difference in the expression profiles of histamine receptors (HR) was explored, making it possible to observe that H2R and H3R expression was higher in female rats than in males and was down-regulated in ovariectomized females, whereas H1R expression was equal across both sexes¹⁴.

Genetic polymorphisms are also influenced by gender. Immunoglobulin E (IgE) levels and asthma have been associated with 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 the activation of antigen-presenting cells. In humans, there are increased

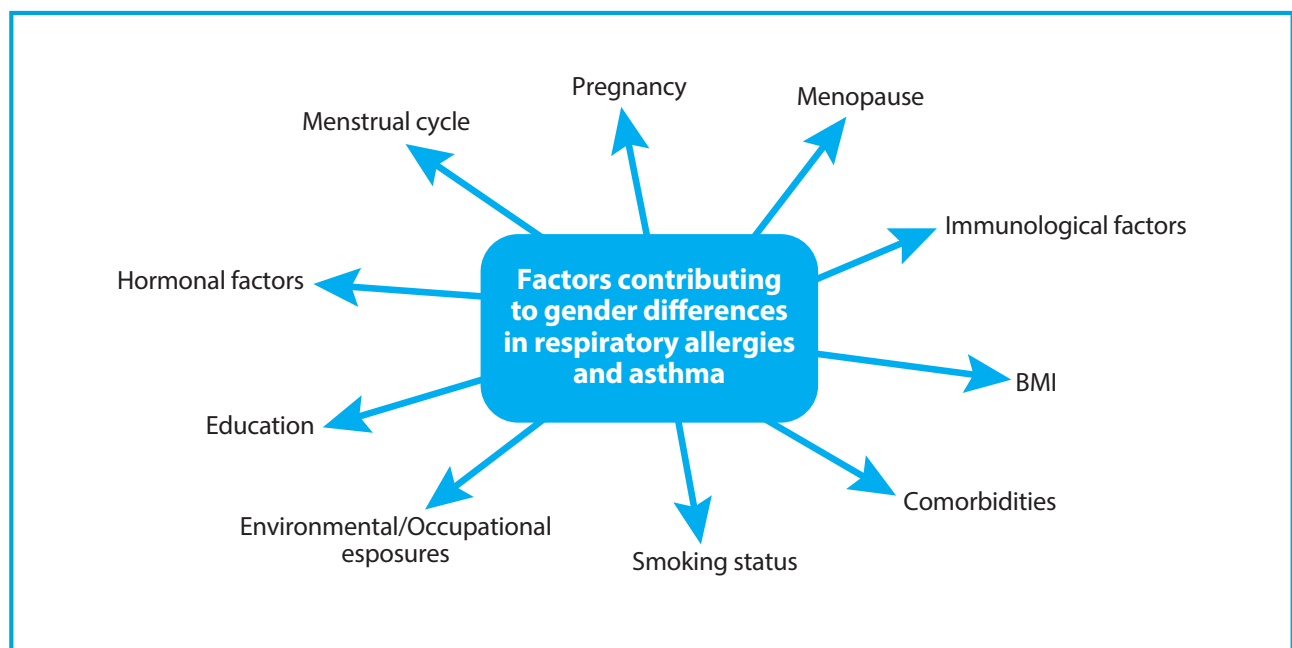


Figure 1. The potential factors contributing to gender difference in respiratory allergies and asthma.

numbers of TSLP mRNA⁺ bronchial epithelial cells in asthmatics vs. controls, and this correlates with the degree of airflow obstruction. Two SNPs in TSLP (rs1837253 and rs2289276) are of particular interest. The first is associated with a lower risk of asthma in men, but the second is associated with a higher risk of asthma in women. Whether this differential effect is regulated by gender or by sex-related differences in the hormonal profile is unknown¹⁵.

Periostin is another protein under investigation for its relationship with the immune system. It is expressed in the periosteum of long bones but also in many other tissues and organs, including the heart, kidney, skin and lungs, and is enhanced by mechanical stress or injury. Periostin has a relevant physiological function in promoting injury repair in a large number of tissues. However, its over-expression was observed in different diseases characterized by inflammation, fibrosis and tumor genesis.

A specific focus regards the correlation between the level of periostin and lung diseases and the identification of periostin as an inflammatory key effector in asthma, where it is closely associated with airway eosinophilia. Indeed, periostin seems to be a useful biomarker of the "Th2-high" asthma rather than the "Th2-low" asthma phenotype and a predictor of response to therapeutic agents¹⁶. In a certain subtype of asthma defined by Th2 cytokine-induced expression of genes in bronchial epithelium, including periostin, which is detected in approximately half of all 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 be the single best predictors of airway eosinophilia¹⁷. As periostin also plays a role in normal gestation and pregnancy, a recent study investigated plasma periostin levels in non-pregnant and pregnant asthmatic patients compared to healthy pregnant and non-pregnant women, also evaluating the relationship between periostin levels and asthma control. Plasma periostin levels were similar in asthmatic non-pregnant patients and healthy non-pregnant controls, whereas they were significantly higher in the two pregnant groups (asthmatic and healthy) than in the control groups, and in asthmatic pregnant women periostin correlated negatively with FEV₁¹⁸.

Epidemiology and clinical features

Asthma in early childhood is generally associated with male gender, poor socioeconomic status, and exposure to soot, exhaust and/or household tobacco, wood or oil smoke^{19,20}. However, asthma in early childhood was only seen to be associated with obesity in young girls,

not in young boys, in two large cross-sectional series from China and the Netherlands^{21, 22}, and in two longitudinal cohorts from the United Kingdom and Taiwan. In adolescence, asthma becomes more severe and prevalent in girls²³.

This gender-switch after puberty has been related to the increase in sex hormones²⁴⁻²⁶. The transition from childhood to adulthood is characterized by a higher odds ratio of persistence of wheezing in females^{27,28}, and by asthma improvement in males but worsening in females²⁹. In two cohorts of patients followed longitudinally until the age of 18 years, male gender was independently associated with asthma remission³⁰⁻³². After the age of 11 years, the provocative concentration of methacholine necessary to cause a 20% decrement in FEV₁ (PC20) increased in adolescent boys, suggesting an improvement in airway responsiveness during puberty in boys, but not in girls³³.

By contrast, in adult women with stable well-controlled asthma, PC20 decreases by more than half over the course of the menstrual cycle, with the lowest PC20 occurring at peak estrogen and progesterone levels in the luteal phase³⁴. The cyclic changes in PC20 have been attributed to abnormal β 2 adrenoceptor regulation in premenstrual asthma³⁴.

It has been suggested that β 2 adrenoceptors are influenced by ovarian sex-steroid hormones, and that this is the mechanism underlying the gender differences in β 2 bronchodilator responses³⁵. This concept is supported by the paradoxical down-regulation of β 2 adrenoceptors when progesterone is given during the follicular phase to women with premenstrual asthma^{35,36}. On the other hand, estrogen supplementation during the follicular phase had no effect on β 2 adrenoceptor responses or airway reactivity³⁷. Interestingly, whereas a higher progesterone to estrogen ratio occurs during the luteal phase of fertile cycles^{38,39}, the opposite occurs during the menopausal transition, where women are exposed to unopposed estrogen stimulation⁴⁰. Thus, it remains unclear as to whether progesterone and/or estrogen or a balance between the sex hormones is responsible for the premenstrual worsening of asthma.

Sex hormones have a wide variety of effects beyond the β 2 adrenoceptor: for example, they alter epithelial cell function. The progesterone receptor is expressed in airway epithelium and progesterone inhibits the beat frequency of cilia, which may impact mucociliary clearance during the menstrual cycle among women⁴¹.

Many reports have linked female sex hormones to asthma severity. Women with premenstrual asthma are at a higher risk of severe asthma, required more bursts of corticosteroid therapy, and have a higher risk of emergency room visits, hospitalization, and admission to the intensive care unit⁴². Interestingly, asthmatic women receiving oral contraceptives have attenuated cyclical

changes in airway reactivity associated with a suppression of the upsurge in progesterone and estradiol during the luteal phase⁴³. In multiparous women, asthma prevalence increases linearly with the number of births⁴⁴.

The role of pregnancy

During pregnancy asthma may worsen, improve or remain unchanged, with no significant difference in frequency of these three outcomes. In a survey on 366 pregnancies, asthma was unchanged in 33% of women, worsened in 35%, and improved in 28%. Based on diary sheets, asthma was significantly less frequent and less severe during the last 4 weeks of pregnancy. In the 3 months post-partum, asthma returned to its pre-pregnancy course in 73% of women⁴⁵. 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 pregnancy⁴⁶. A review by Gluck et al. concluded that the course of asthma during pregnancy is variable, with about one third of 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. Factors associated with an increased risk of uncontrolled asthma during pregnancy included smoking, inhaled corticosteroid use at the beginning of pregnancy, and higher maternal age⁴⁷.

One new interesting factor linked to the risk of asthma severity in pregnant women is the sex of the fetus.

Whereas many reports have reported that carrying a female fetus during pregnancy is associated with increased asthma symptoms, greater use of asthma medications and a higher risk of asthma-related hospitalization^{48,49}, a larger Canadian study did not confirm this finding⁵⁰. Recent reports have demonstrated sex-specific alterations in the expression of placental genes of pregnant women with asthma compared to the placenta of non-asthmatic mothers. Six genes were seen to have altered expression in the placenta of asthmatic women

carrying male fetuses, compared to 59 genes with altered expression in the placenta of asthmatic mothers carrying female fetuses. The genes were linked to growth, inflammation and immune pathways and might contribute to the fetal-sex dimorphic differences in asthma severity and fetal growth during pregnancy⁵¹.

The role of menopause

Another period at risk for asthma is the menopause and menopausal status has been associated with accelerated lung function decline⁵². Although the underlying mechanisms are not yet understood, it is possible that a role is played by airway remodeling, which is driven by immunologic and inflammatory mechanisms.

The influence of sex difference on 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, and BHR, airway inflammation, and airway remodeling were measured. 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 than in male mice. The histological features of airway remodeling were also increased in female mice⁵³.

Key messages

- Gender differences in asthma and respiratory allergy condition incidence, prevalence and clinical phenotypes are extensively reported in medical literature.
- Asthma is prevalent in males during childhood, but becomes more frequent and severe in females between adolescence and adulthood, suggesting that a role is played by sex hormones as important modulators of immune response.
- Like asthma, allergic rhinitis has a male predominance in prevalence during childhood that switches to a female predominance in adolescence and adulthood.
- Males and females differ in the strength of immune responses. Sex hormones act as important modulators of immune response; the male sex hormone testosterone is generally immunosuppressive, whereas the female sex hormone estrogen tends to be immunoenhancing.
- Sex differences in immune response are particularly strong in immune functions associated with type 2 responses, and less pronounced with type 1 responses.

Conclusions

There is solid evidence in favor of gender effects on asthma incidence and severity throughout the course of life. Whereas the clinical and epidemiological data support the role of sex hormones on asthma incidence and severity, the data are confounded by many internal and external factors, such as aging, obesity, atopy, and gender differences in behavior and exposure⁵⁴. Further work is needed to establish the gender impact on asthma *in utero*, in early life, puberty, adulthood and the menopause transition and to provide new insights for pathway-based therapies.

As regards allergic rhinitis, the studies available thus far indicate, as for asthma, a male predominance in prevalence during childhood that switches to a female predominance in adolescence and adulthood, but further research is needed.

References

1. CDC. National Health Interview Survey (NHIS) data. <http://www.cdc.gov/asthma/nhis/2012/data.htm>
2. Sullivan PW, Ghushchyan VH, Slejko JF, Belozeroff V, Globe DR, Lin SL. The burden of adult asthma in the United States: evidence from the medical Expenditure Panel Survey. *J Allergy Clin Immunol*. 2011;127(2):363-9.
3. Arnold AP. Conceptual framework and mouse models for studying sex differences in physiology and disease: why compensation changes the game. *Exp Neurol*. 2014;259:2-9.
4. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16(10):626-38.
5. Zein JG, Erzurum SC. Asthma is different in women. *Curr Allergy Asthma Rep*. 2015;15(6):28.
6. Moorman JE, Akinbami LJ, Bailey CM, Zahran HS, King ME, Johnson CA, Liu X. National surveillance of asthma: United States 2001-2010. *Vital Health Stat*. 2012;3(35):1-67.
7. Akinbami LJ, Moorman JE, Bailey C, Zahran HS, King M, Johnson CA, Liu X. Trends in asthma prevalence, health care use, and mortality in United States 2001-2010. *NCHS Data Brief*. 2012;94:1-8.
8. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax*. 1999;54(12):1119-38.
9. Roved J, Westerdahl H, Hasselquist D. Sex differences in immune responses: hormonal effects, antagonistic selection, and evolutionary consequences. *Horm Behav*. 2017;88:95-105.
10. Warren KJ, Sweeter JM, Pavlik JA, Nelson AJ, Devasure JM, Dickinson JD, et al. Sex differences in activation of lung-related type 2 innate lymphoid cells in experimental asthma. *Ann Allergy Asthma Immunol*. 2017;118(2):233-4.
11. Laffont S, Seillet C, Guery JC. Estrogen receptor-dependent regulation of dendritic cell development and function. *Front Immunol*. 2017;8:108.
12. Laffont S, Blanquart E, Savignac M, Cénac C, Laverny G, Metzger D, et al. Androgen signaling negatively controls group 2 innate lymphoid cells. *J Exp Med*. 2017;214(6):1581-92.
13. Ortona E, Delunardo F, Maselli A, Pierdominici M, Malorni W. Sex hormones and gender disparity in immunity and autoimmunity. *Ital J Gender-Specific Med*. 2015;1(2):45-50.
14. Li JN, Li XL, He J, Wang JX, Zhao M, Liang XB, et al. Sex and afferent-specific differences in histamine receptor expression in vagal afferents of rats: a potential mechanism for sexual dimorphism in prevalence and severity of asthma. *Neuroscience*. 2015;303:166-77.
15. Hunninghake GM, Soto-Quirós ME, Avila L, Kim HP, Lasky-Su J, Rafaels N, et al. TSLP polymorphisms are associated with asthma in a sex-specific fashion. *Allergy*. 2010;65(12):1566-75.
16. Idolazzi L, Ridolo E, Fassio A, Gatti D, Montagni M, Caminati M, et al. Periostin: the bone and beyond. *Eur J Intern Med*. 2017;38:12-16.
17. Jia G, Erickson RW, Choy DE, Mosesova S, Wu LC, Solberg OD, et al. Bronchoscopic Exploratory Research Study of Biomarkers in Corticosteroid-refractory Asthma (BOBCAT) Study Group Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. *J Allergy Clin Immunol*. 2012;130(3):647-54.
18. Ivancsó I, Bohács A, Szalay B, Toldi G, Szilasi ME, Müller V, et al. Circulating periostin level in asthmatic pregnancy. *J Asthma*. 2016;53(9):900-6.
19. Balmes JR, Cisternas M, Quinlan PJ, Trupin L, Lurmann FW, Katz PP, et al. Annual average ambient particulate matter exposure estimates, measured home particulate matter, and hair nicotine are associated with respiratory outcomes in adults with asthma. *Environ Res*. 2014;129:1-10.
20. Hafkamp-de Groen E, Sonnenschein-van der Voort AM, Mackenbach JP, Duijts L, Jaddoe V, Moll HA, et al. Socioeconomic and sociodemographic factors associated with asthma related outcomes in early childhood: the Generation R Study. *PLoS One*. 2013;8(11):e78266.
21. Wang D, Qian Z, Wang J, Yang M, Lee Y, Liu F, et al. Gender-specific differences in associations of overweight and obesity with asthma and asthma-related symptoms in 30056 children: result from 25 districts of Northeastern China. *J Asthma*. 2014;51(5):508-14.
22. Willeboordse M, van den Bersselaar D, van de Kant K, Murris J, van Schayck, Dompeling E. Sex differences in the relationship between asthma and overweight in Dutch children: a survey study. *PLoS One*. 2013;8(10):e77574.
23. Almqvist C, Worm M, Leynaert B, working group of GALEN-WPG (2008). Impact of gender on asthma in childhood and adolescence: a GA2LEN review. *Allergy*. 63(1):47-57.
24. European Network for Understanding Mechanisms of Severe Asthma. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Respir J*. 2003;22(3):470-7.
25. Leynaert B, Sunyer J, Garcia-Esteban R, Svanes C, Jarvis D, Cerveri I, et al. Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma: a population-based cohort. *Thorax*. 2012;67(7):625-31.
26. Schatz M, Camargo CA Jr. The relationship of sex to asthma prevalence, health care utilization, and medications in a large managed care organization. *Ann Allergy Asthma Immunol*. 2003;91(6):553-8.
27. Sears MR, Greene J, Willan AR, Wiecek EM, Taylor R, Flannery E, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med*. 2003;349(15):1414-22.

28. Sekerel BE, 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(7): 869-77.
29. Kjellman B, Gustafsson PM. Asthma from childhood to adulthood: asthma severity, allergies, sensitization, living conditions, gender influence and social consequences. *Respir Med*. 2000;94(5):454-65.
30. Vink NM, Postma DS, Schouten JP, Rosmalen JG, Boezen HM. 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(3):498-504.
31. Arshad S, Raza A, Lau L, Bawakid K, Karmaus W, Zhang H, et al. Pathophysiological characterization of asthma transitions across adolescence. *Respir Res*. 2014;15(1):153.
32. 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(2):e435-42.
33. Tantisira KG, Colvin R, Tonascia J, Strunk RC, Weiss ST, Fuhlbrigge AL, Childhood Asthma Management Program Research Group. Airway responsiveness in mild to moderate childhood asthma: sex influences on the natural history. *Am J Respir Crit Care Med*. 2008;178:325-31.
34. Tan KS, McFarlane LC, Lipworth BJ. Loss of normal cyclical beta 2 adrenoceptor regulation and increased premenstrual responsiveness to adenosine monophosphate in stable female asthmatic patients. *Thorax*. 1997;52(7):608-11.
35. Wheeldon NM, Newnham DM, Coutie WJ, Peters JA, McDewitt DG, Lipworth BJ. Influence of sex-steroid hormones on the regulation of lymphocyte beta 2-adrenoceptors during the menstrual cycle. *Br J Clin Pharmacol*. 1994; 37(6):583-8.
36. Tan KS, McFarlane LC, Coutie WJ, Lipworth BJ. Effects of exogenous female sex-steroid hormones on lymphocyte beta 2-adrenoceptors in normal females. *Br J Clin Pharmacol*. 1996;41(5):414-6.
37. Lieberman D, Kopemic G, Porath A, Levitas E, Lazer S, Heimer D. Influence of estrogen replacement therapy on airway reactivity. *Respiration*. 1995;62(4):205-8.
38. Laufer N, Navot D, Schenker JG. The pattern of luteal phase plasma progesterone and estradiol in fertile cycles. *Am J Obstet Gynecol*. 1982;143(7):808-13.
39. Owen JA Jr. Physiology of the menstrual cycle. *Am J Clin Nutr*. 1975;28(4):333-8.
40. O'Connor KA, Ferrell R, Brindle E, Shofer J, Holman DJ, Miller RC. Total and unopposed estrogen exposure across stages of the transition to menopause. *Cancer Epidemiol Biomarkers Prev*. 2009;18(3):828-36.
41. Jain R, Ray JM, Pan JH, Brody SL. Sex hormone-dependent regulation of cilia beat frequency in airway epithelium. *Am J Respir Cell Mol Biol*. 2012;46(4):446-53.
42. Rao CK, Moore CG, Bleecker E, Busse WW, Calhoun W, Castro M. Characteristics of perimenstrual asthma and its relation to asthma severity and control: data from the Severe Asthma Research Program. *Chest*. 2013;143(4):984-92.
43. Tan KS, McFarlane LC, Lipworth BJ. Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill. *Am J Respir Crit Care Med*. 1997;155(4):1273-7.
44. Jenkins MA, Dharmage SC, Flander LB, Douglass JA, Ugoni AM, Carlin JB, et al. Parity and decreased use of oral contraceptives as predictors of asthma in young women. *Clin Exp Allergy*. 2006;36(5):609-13.
45. Schatz M, Harden K, Forsythe A, Chilingar L, Hoffman C, Sperling W, et al. The course of asthma during pregnancy, post partum, and with successive pregnancies: a prospective analysis. *J Allergy Clin Immunol*. 1988;81(3):509-17.
46. Schatz M, Dombrowski MP, Wise R, Thom EA, Landon M, Mabie W, et al. Asthma morbidity during pregnancy can be predicted by severity classification. *J Allergy Clin Immunol*. 2003;112(2):283-8.
47. Gluck JC. The change of asthma course during pregnancy. *Clin Rev Allergy Immunol*. 2004;26(3):171-80.
48. Beecroft N, Cochrane GM, Milburn HJ. Effect of sex of fetus on asthma during pregnancy: blind prospective study. *BMJ*. 1998;317(7162):856-7.
49. Kwon HL, Belanger K, Holford TR, Bracken MB. Effect of fetal sex on airway lability in pregnant women with asthma. *Am J Epidemiol*. 2006;163(3):217-21.
50. Firoozi F, Ducharme FM, Lemièrre C, Beauchesne MF, Perreault S, Forget A, et al. Effect of fetal gender on maternal asthma exacerbations in pregnant asthmatic women. *Respir Med*. 2009;103(1):144-51.
51. Osei-Kumah A, Smith R, Jurisica I, Caniggia I, Clifton VL. Sex-specific differences in placental global gene expression in pregnancies complicated by asthma. *Placenta*. 2011;32(8):570-8.
52. Triebner K, Matulonga B, Johannessen A, Suske S, Benediksdóttir B, Demoly P, et al. Menopause is associated with accelerated lung function decline. *Am Rev Respir Crit Care Med*. 2017;195(8):1058-65.
53. Takeda M, Tanabe M, Ito W, Ueki S, Konno Y, Chihara M, et al. Gender difference in allergic airway remodelling and immunoglobulin production in mouse model of asthma. *Respirology*. 2013;18(5):797-806.
54. Shah R, Newcomb DC. Sex bias in asthma prevalence and pathogenesis. *Front Immunol*. 2018;9:2997.

Acknowledgments

Dr Cilloniz is the recipient of a Postdoctoral Grant (Strategic plan for research and innovation in health - PERIS 2016-2020) and SEPAR fellowship.

Conflict of interest statement: the Authors declare no conflicts of interest.

Correspondence to:

Antonello Nicolini
Respiratory Diseases Unit, General Hospital
via Terzi 43, 16039 Sestri Levante
tel +390185329145
email antonellonicolini@gmail.com