



Review

Estrogen Replacement Therapy and asthma



Carlo Ticconi*, Adalgisa Pietropoli, Emilio Piccione

Academic Department of Biomedicine and Prevention, Section of Gynecology and Obstetrics, University Tor Vergata, Rome, Italy

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ABSTRACT

A growing body of clinical and experimental evidence indicates that female sex hormones, particularly estrogen, have significant effects on normal airway function as well as on respiratory disorders, such as asthma. These effects are very complex and are exerted at several levels, directly on airway reactivity or indirectly through regulation of the immune and inflammatory responses in the lung. They can have relevant clinical implications not only according to the phases of the reproductive life in women, but also in relation to the therapeutical administration of estrogen, as in the case of menopausal hormone therapy. Clinical evidence suggests that administration of estrogen to menopausal women is associated with increased rates of newly diagnosed asthma. Conversely, functional studies show that estrogen can improve objective indexes of respiratory functionality.

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1. Introduction

Asthma is a major health problem which involves approximately 300 million people worldwide [1]. It has been estimated that only in the United States over 24 million people [2] suffer from asthma. It has become clear that asthma is a chronic disease of the airways characterized by intermittent airflow obstruction in response to specific and/or non-specific stimuli that leads to bronchial obstruction of largely variable gravity and to several respiratory symptoms: chest tightness, wheezing, dyspnea, cough. Extensive research in the field has revealed that asthma is characterized not only by an exaggerated airway narrowing as a consequence of an excessive contractile response of the airway smooth muscle (ASM), called airway hyperresponsiveness (AHR), but also by many other changes in the airways [3] which concur to generate the clinical picture: a) *structural changes (remodeling)* [4]: increased ASM mass - due to cell hyperplasia and hypertrophy [5], basement membrane thickening [6], mucus gland hyperplasia [3], epithelial mucous hyperplasia [7]; b) *functional changes*: AHR, impaired relaxation of the airway, increased mucus production, bronchial edema; c) *inflammatory changes*: infiltration of the airway by several different inflammatory types of activated inflammatory cells including monocytes, neutrophils, eosinophils, mast cells and lymphocytes [8,9] which, in turn, produce - together with ASM cells - a large

array of molecules involved in the regulation of multiple inflammatory and immune responses. Interleukins 1 β , -4, -5, -6, -8, -9, -11, -13, GM-CSF, TNF- α , LIF, RANTES, complement fragments (C3a and C5a), leukotrienes and nitric oxide are only a part of the continuously growing number of the above molecules and substances found to be involved as local mediators in asthma [7–11].

Estrogen Replacement Therapy (ERT) has been used for decades and currently is still being used by millions of women worldwide to relief from menopausal symptoms; in fact, it has been clearly demonstrated that ERT has proven benefits on vasomotor and vaginal symptoms as well as on sexual function, urinary tract health and osteoporosis [12]. The wide diffusion of ERT prompted a large body of basic and clinical research to investigate, in addition to the above mentioned benefits, also several potentially relevant drawbacks or harmful effects of ERT. Therefore, a considerable number of studies have been carried out to explore the impact of ERT on several body systems and on many diseases and disorders. In this context, interest has been focused mainly on the possible effects of ERT on the cardiovascular system - with specific application to coronary heart disease, stroke and venous thromboembolism - [13–16], on the possible relationships between ERT, alone or in combination with progesterone/progestins and several major gynecologic cancers (breast, ovary, endometrium) [17–20] and on the impact of ERT on relevant metabolic disorders such as diabetes mellitus [21]. On the other hand, relatively little attention has been given to the impact of ERT on respiratory disorders, with the exception of lung cancer [22,23]. In recent years, however, interest on the possible effect of ERT on asthma has been raised, on the basis of several observations suggesting the existence of: a) an effect of estrogens on airway functionality; b) gender differences in the

* Corresponding author. Academic Department of Biomedicine and Prevention, Section of Gynecology and Obstetrics, Policlinico Tor Vergata University Hospital, Viale Oxford 81, 00133 Rome, Italy. Tel.: +39 3 383435184; fax: +39 6 20902921.

E-mail addresses: ticconi@med.uniroma2.it, ticconicarlo@tiscali.it (C. Ticconi).

clinical characteristics of asthma; c) possible variations in asthma severity in relation to the menstrual phase and to the menopausal transition. These issues will be treated in the present article, which is focused to examine current evidence on ERT and asthma.

2. Asthma and the female sex

Although asthma is a multifactorial disorder which affects people of all ages, there is clear evidence that there are significant age dependency and sex-related differences in the clinical manifestations of the disease. In fact, it is well known for a long time that in the prepubertal age the prevalence of asthma is much higher in boys than in girls, but when puberty is reached the prevalence of asthma becomes and remains higher in women than in men [24–27]. Therefore, it is clear that a puberty-related gender shift in the prevalence of asthma occurs and persists throughout the entire lifespan. Even though the magnitude of this sex-related difference is likely modest, its impact on the overall population is potentially highly relevant, given the very large number of people involved [28]. Interestingly, several clinical studies suggest an association between early menarche and higher risk of asthma and asthma symptoms [29,30] as well as of lower lung function [30]. Moreover, asthma morbidity, evaluated in terms of risk of hospital admission, in the female has been also reported to be more severe than in the male [31,32]. All these observations are consistent with the concept that female sex hormone, particularly estrogens, influence the clinical course and manifestations of asthma.

There is a robust literature supporting the concept that significant variations in the incidence and severity of asthma occur in relation to the phases of the menstrual cycle. Briefly, the menstrual cycle is divided into two major phases: 1) follicular phase, in which occur the recruitment, selection and development of the follicle destined to ovulate. This phase is characterized by increasing levels of circulating 17- β estradiol (E2), produced by the preovulatory follicle; 2) luteal phase, in which the follicle, after ovulation, is converted into corpus luteum, which synthesizes and releases progesterone (P) in order to enhance blastocyst attachment to the endometrium. It is characterized by a drop in the circulating levels of estrogens and by a progressive increase in progesterone concentration until midluteal phase (approximately 22–24 day of an ideal cycle of 28 days). Thereafter, in the late luteal phase, also the progesterone circulating levels start to decrease until menstruation ensues. It has been reported that a substantial proportion of women suffer from premenstrual and menstrual worsening of asthma [33–35]. This proportion, calculated through questionnaire on self-reported symptoms, has been found to be 40% and has been found to be associated with reduction in respiratory function as measured by peak expiratory flow rate [36]. The premenstrual asthma (PMA) is unrelated to other premenstrual symptoms [36,37], even though this issue has been recently questioned [38], and has wide cycle-to-cycle variability [37]. Moreover, it has also been found that asthma symptoms requiring treatment in hospital emergency department were significantly more prevalent in the premenstrual phase (46%) than in any of the other phases [39].

In addition to the above findings, there is evidence that menstrual irregularities are associated with asthma. In two large studies carried out on 8588 and 1631 subjects, respectively, it has been shown that asthma symptoms and allergic asthma were more common in women with menstrual irregularities, namely oligomenorrhea, than in women with regular menstruations [40,41]. Moreover, oligomenorrhea was associated with a significant reduction of lung function, determined in terms of forced vital capacity [41]. Interestingly, it has been found that asthma symptoms increased significantly with Body Mass Index (BMI) [41],

suggesting that metabolic factors, in addition to hormonal factors, could concur in the regulation of airway function.

Asthma is one of the most common chronic diseases in pregnant women. It has been reported that about one third of pregnant women experience a worsening of asthma during pregnancy, one third has no change and one third has clinical improvement [42]. Interestingly, it has been reported that the most significant improvement in asthma severity during pregnancy occurred in women who were initially the most hyperresponsive [43] and that around 70% of women with asthma reported fewer symptoms in the last month of pregnancy [42] (in which the circulating levels of estrogen and progesterone are highest), thus suggesting that estrogen (and, possibly, also progesterone) could have a favorable impact on AHR. Nevertheless, there is clear evidence that 4–8% of pregnant women have clinical exacerbations of asthma, requiring hospitalization [44]. Pregnancy is a condition characterized by very high concentrations of circulating estrogens, mainly estradiol, as well as of progesterone produced by the placenta. Therefore, even though the risk factors for asthma exacerbations during pregnancy are still poorly understood at present [45], it is possible that female sex hormones could be involved. However, the exact role of estrogens, as well as of progesterone, remains largely undetermined. Interestingly, it has been demonstrated that functional oxytocin receptors are basally expressed – although at low levels – in human airway smooth muscle cells (HASMCS) [46], and that this expression is increased by interleukin-13 and TNF- α [46], which are important mediators of several inflammatory changes occurring in asthma. This finding suggests a potential role of oxytocin receptors in airways in the worsening of asthma during pregnancy. However, further investigation is still needed to clearly define the biological and clinical significance of oxytocin receptors in HASMCS.

3. Effects of estrogen on airway function with specific application to asthma

The effects of estrogen on airways are highly complex and still largely incompletely understood despite extensive research has been carried out in this area of interest. It is well known that estrogen exert their biological actions by binding to specific receptors in the target cells. These receptors are located in the nucleus, even though recently plasma membrane-bound receptors – that are believed to be involved in determining nongenomic cell responses – have been described [47]. Two specific estrogen receptors (ER- α and ER- β), as well as two specific progesterone receptors (PR-A and PR-B) have been described [48]. Both ER- α and ER- β have been shown to be expressed in animal [49,50] and human [51] lung and have been found in the nucleus, cytoplasm and mitochondria [52]. Both ER- α and ER- β are involved in the formation and function of normal alveolar units in the female, even though their specific roles appear to be different: ER- α regulates the formation of alveoli of appropriate size and number, whereas ER- β controls the composition of the extracellular matrix which, in turn, is responsible for alveolar elasticity [53,54]. Moreover, there is evidence supporting the concept that ER- α is also an important regulator of airway responsiveness [55].

Estrogen have multiple potential effects on inflammation, metabolism and immunity [56], as well as on airway hyper-responsiveness (AHR) [28], that can have a relevant impact on asthma. These effects can be exerted: 1) directly on airways; 2) indirectly by influencing the function of several immune cells recruited in the airways physiologically or in response to several stimuli and by modulating the release, from the above cells, of a large array of molecules involved in the regulation of immune response and inflammation; 3) indirectly by modulating general metabolic changes which can have relevance in the airway

functionality (i.e., body composition, BMI, fat distribution, insulin resistance) (Fig. 1).

A major biomolecular mechanism by which estrogen modulate airway responsiveness is believed to be exerted through the regulation of nitric oxide (NO) synthesis and release. It has been demonstrated that estrogen can enhance NO production by several cell types in the airways: a) lung vascular endothelial cells and pulmonary epithelial cells – through activation of the endothelial nitric oxide synthase (eNOS) enzyme – [57,58], b) smooth muscle cells through phosphorylation of neuronal nitric oxide synthase (nNOS) [59]. NO locally generated has a relaxant effect on smooth muscle cells, which is believed to be exerted through the increased production of cGMP leading, in turn, to the opening of large conductance voltage- and calcium-dependent K⁺ channels [60]. Therefore, the estrogen-induced enhanced production of NO has a vasodilatory action and a relaxing effect on airway smooth muscle. Interestingly, these actions, particularly those on airway responsiveness, appear to be impaired in tissues from asthmatic subjects or treated with serum from asthmatic subjects [61], thus suggesting that asthma can be associated to a reduction in the pathway responsible for the above reported effect of estrogen, which involve the soluble isoform of guanyl cyclase and the heat shock protein 90 (hsp90) [61]. Additionally, estrogen has been shown to enhance airway smooth muscle relaxation by a non-genomic, cAMP-mediated reduction of intracellular calcium concentration ([Ca⁺⁺]_i) [62]. It is possible that estrogen act also through other cellular pathways, such as the activation of mitogen-activated protein kinase (MAPK) [63] or by inhibiting the 11 β -hydroxysteroid dehydrogenase 1 [64], which leads to a reduced production of tissue specific cortisol production. However, further investigation is needed to ascertain whether these effects are actually operative in the airways. Recently, it has been shown that allergic airway inflammation is associated with a significant reduction in both glucocorticoid receptors (GR) and ER- β in the mitochondria of lung epithelial cells, possibly leading to an impairment in the expression

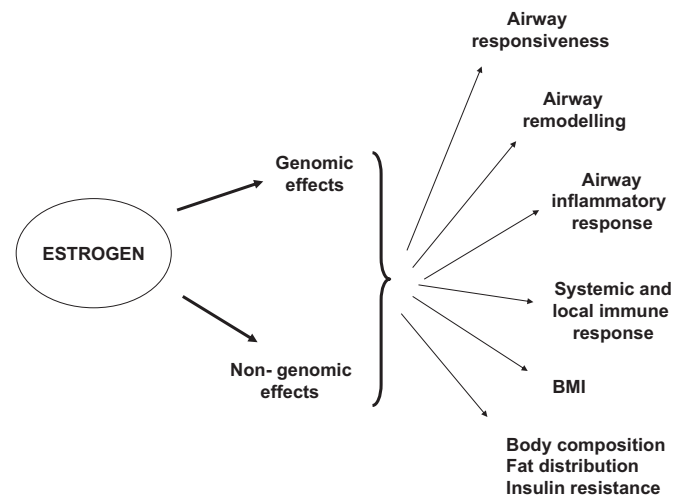


Fig. 1. Schematic representation of several mechanisms by which estrogen can influence lung and airway function with specific application to asthma.

of some enzymes involved in the mitochondrial oxidative phosphorylation (OXPHOS), so leading to an increased reactive oxygen species (ROS) production [65]. This could contribute to increase the degree of oxidative stress in the airways.

The effects of estrogen on immune system cells and on inflammatory mediators are highly complex. Some of these effects potentially relevant for asthma are summarized in Fig. 2. Collectively considered, the immunologic effects of estrogen appear to be directed towards an enhancement of the inflammatory response in the airways [70], particularly in the presence of allergens [54]. This finding is in contrast with the relaxant effects of estrogens on airway responsiveness and suggests a dichotomous effect of estrogens on asthma [28]. It can also give a key to explain the

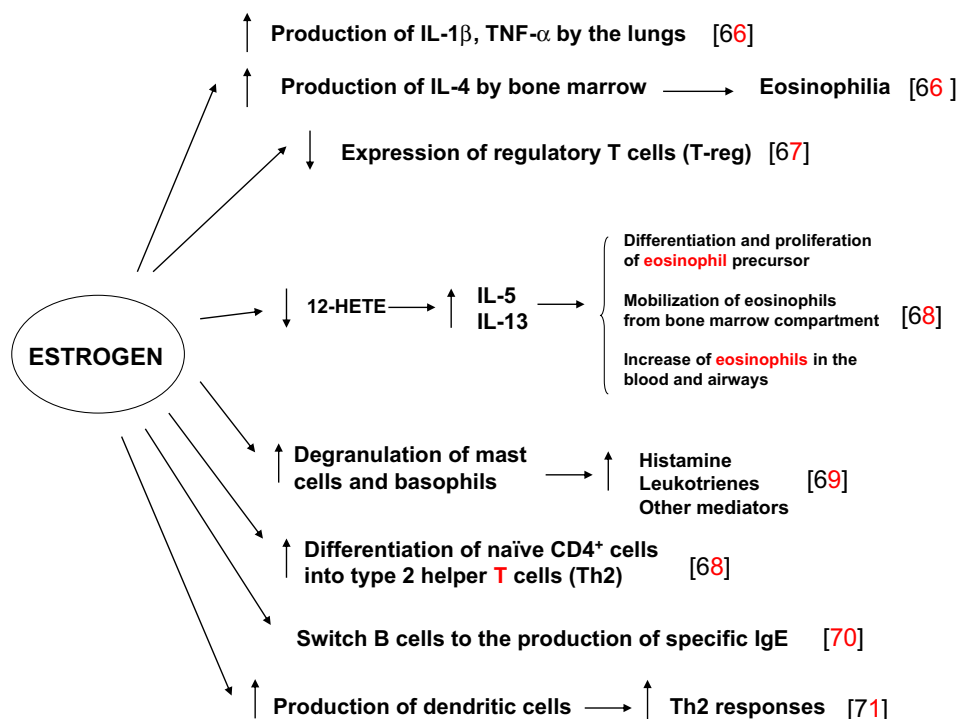


Fig. 2. Schematic representation of some of the major known effects of estrogen on immune cells and molecules of potential interest to asthma pathogenesis. References are indicated in square brackets.

Table 1

Major changes occurring throughout the menopausal transition.

<i>Changes within the ovary</i>
- Reduction of ovarian mass
- Reduction in the number of ovarian follicles until total disappearance
- Reduction in the number of granulosa cells
<i>Functional changes in the physiology of the reproductive system</i>
- Slight reduction of cyclic activity of the hypothalamus
- Increase in the frequency and amplitude of GnRH pulses
- Progressive loss of ovarian response to gonadotropins
- Ovulatory cycles less frequent
- Menstrual irregularities (Oligomenorrhea/Transient amenorrhea/Menorrhagia)
- Shift in estrogen production sites from the ovaries to peripheral tissues (fat, muscle)
- Changes in the type of estrogen produced from estradiol to estrone
<i>Changes in circulating levels of reproductive hormones</i>
- Decrease of inhibin
- Marked decrease of antimüllerian hormone (AMH)
- Increase of FSH
- Progressive increase of LH (less marked than FSH)
- Increase of estradiol concentrations followed by marked decrease
- Progressive increase of estrone (relative to estradiol)
- Decrease of progesterone
- Slight decrease of androstenedione
- Testosterone unchanged
- Decrease of sex hormone binding globulin (SHBG)
<i>Metabolic changes</i>
- Increase in BMI
- Increase in insulin resistance
<i>Changes in other endocrine systems</i>
- Slight decrease in thyroid function
- Slight decrease in adrenal function

conflicting and unequivocal results of clinical studies on asthma and the menopausal transition as well as on the effects of exogenously administered estrogens, which will be treated in the following sections.

4. Asthma and the menopausal transition

The menopausal transition is the time period in which the reproductive function declines until menopause is reached. It starts with the beginning of the menstrual irregularities (around 47 years) and ends with the last menstruation. Usually it has a mean duration of 4 years (range: 2–8 years) and is characterized by a series of complex hormonal and metabolic changes, the most relevant of which are reported in Table 1. It is also characterized by a series of symptoms – of variable severity in the individual woman – which are the consequence of the above described changes, particularly of the estrogen deprivation secondary to follicle reduction (until complete disappearance), and/or to follicle dysfunction. These symptoms are reported in Table 2. They occur in the menopausal transition and usually worsen during the menopause (defined retrospectively as the lack of menstrual cycle for one year) and the postmenopause (defined as the period starting after the menopause until death), with the only possible exception of vasomotor symptoms; their treatment is currently the major indication for ERT, that is associated with their disappearance or substantial improvement in the vast majority of cases.

Since a relationship between changes in circulating female hormones and asthma has been detected and described, it is reasonable to hypothesize that menopausal transition and menopause could be associated with significant variations in asthma incidence and/or severity. However, there are only few reliable studies that investigated this issue. In the US Nurses' Health Study (NHS), a large prospective follow-up study carried out on 582,135 person-years, a statistically significant reduction of 35% in asthma

Table 2

Major menopause-related symptoms and problems.

<i>Vasomotor symptoms</i>
- Hot flushes
- Nocturnal sweating
- Sleep disturbances
<i>Menstrual symptoms</i>
- Transient amenorrhea
- Long-lasting amenorrhea
- Oligomenorrhea
- Menorrhagia
- Abnormal uterine bleeding
<i>Urinary and genital symptoms</i>
- Urinary incontinence
- Sexual dysfunction
- Vaginal dryness
- Changes in the libido (usually reduction)
- Dyspareunia
<i>Psychological symptoms</i>
- Irritability
- Depression
- Increased anxiety
- Reduced concentration and memory
<i>Long-lasting metabolic problems</i>
- Osteopenia, osteoporosis and bone fractures
- Cardiovascular diseases
- Insulin resistance
- Increased BMI/obesity

incidence was observed in 12,630 postmenopausal women not taking hormone replacement therapy (HRT) compared to premenopausal women (age-adjusted R.R.: 0.65; 95% C.I. = 0.46–0.92) [72]. This finding is in contrast with the results of other more recent studies. In the RHINE (Respiratory Health in Northern Europe) study – stage I of the European Community Respiratory Health Survey in Northern Europe (ECRHS I) – a questionnaire-based cross-sectional analysis carried out on 1103 premenopausal and 424 postmenopausal women not using HRT, a statistically significant association between menopause and self-reported asthma, wheeze, asthma symptoms and hay fever was not found [73]. In a successive cross-sectional study of the ECRHS II international survey, carried out on women in the menopausal transition, it has been found that women who had amenorrhea for more than 6 months had more respiratory symptoms – associated or no with allergy – and reduced lung function – measured as FEV1 and forced vital capacity (FVC) – than women who were still regularly menstruating [74]. Moreover, it has been reported that asthma starting at menopause is more severe and less responsive to treatment [75]. A systematic review and meta-analysis carried out very recently on this issue found no significant association between asthma prevalence or incidence and spontaneous menopause in women who did not take any HRT [76]. However, these conclusions are based on the results of the few studies considered eligible for and included in the analysis; therefore, additional investigation is still needed to fully elucidate the impact of spontaneous menopause on asthma. Recently, a new biological phenotype of menopausal asthma has been described [77]. It is characterized by a neutrophilic rather than eosinophilic pattern of airway inflammation and by elevated levels of urinary and exhaled leukotriene E4 as well as of exhaled IL-6. The clinical correlate of this phenotype is characterized by severe asthma with poor symptom control and scarce response to corticosteroid therapy [77].

The issue of asthma and surgical menopause has been addressed in a cross-sectional English study in which surgical cessation of menstruation has been found to be associated with a significantly increased reporting of asthma-like symptoms, particularly wheeze, in women who did not take HRT (O.R.: 1.55; 95% C.I. = 1.09–2.20) [78].

Collectively considered, the currently available data suggest that menopausal transition is associated with some impairment of lung function and respiratory symptoms; the possible association with asthma, albeit suggested by several evidences, is still debated and needs additional investigation to be fully determined. In this context, it is difficult to fully understand the specific contribution of other factors that can have a significant impact on incidence and severity of asthma in the menopause and menopausal transition. Among these factors there are genetic factors, smoking – that has an anti-estrogen effect [79] – and smoking cessation, BMI and increased insulin resistance as well as the degree of estrogen production by non-ovarian sources, such as the fat tissue.

5. ERT and asthma

Current clinical evidence concerning the effects of menopausal ERT on asthma suggests that estrogen use is associated to an increased risk of asthma incidence and symptoms severity. In their prospective study carried out on a large cohort of women, Troisi et al. [72] found a moderate age-adjusted increased risk of asthma in both past (R.R.: 1.52, 95% C.I. = 1.08–2.13) and current (R.R. = 1.50, 95% C.I.: 0.98–2.30) postmenopausal users of hormone replacement therapy (HRT) than in postmenopausal women who never used this therapy. In this study, conjugated equine estrogen (CEE) – which were the most common ERT used in U.S. at the time of the study – were used. The authors also found that the age-adjusted increased relative risk for asthma was positively dose-related (p for trend = 0.007) [72]. This finding is in accordance with the results of an other contemporary study showing a reduction in the measured peak expiratory flow and an increased consumption of bronchodilators by inhalation in 15 postmenopausal women during ERT [80]. The potential detrimental effects of ERT on asthma in menopausal and postmenopausal women has been reported in a series of successive studies. Barr et al. [81] found that current use of estrogen alone resulted associated with an increased rate of newly physician-diagnosed asthma (R.R. = 2.29, 95% C.I.: 1.59–3.29). In a cross-sectional studies carried out on 2206 perimenopausal women, 884 of which were taking HRT, Gomez Real et al. found that the therapy was associated with an increased risk for asthma (OR = 1.57, 95% C.I.: 1.07–2.30), wheeze and hay fever [73]. Interestingly, these authors found that the risk for asthma increased with increasing BMI in perimenopausal women not taking HRT, whereas this association could not be detectable in women taking HRT. This finding suggests the existence of a possible relevant relationship between asthma, menopausal status, HRT and metabolic factors. In another cross-sectional study, Jarvis et al. found that the use of HRT was associated with an increase in wheeze in women who underwent surgical menopause [78]. Intriguingly, this effect was observed particularly in lean women (BMI < 25, O.R. = 1.90; 95% C.I.: 1.17–3.05; BMI > 25, O.R. = 1.02; 95% C.I.: 0.69–1.51) [78]. More recently, in a prospective study carried out on a large cohort of 57,664 postmenopausal women in which a follow-up of 495,448 person-years was accomplished, Romieu et al. [82] found that a significantly increased rate of newly diagnosed asthma was associated with estrogen use (hazard ratio, HR = 1.54, 95% C.I.: 1.13–2.09), whereas no increased risk was observed in women who used estrogen and progestagen. The risk was particularly evident in never smoker women (H.R. = 1.80, 95% C.I.: 1.15–2.80).

The results of the above reported clinical studies, usually carried out on large populations of women by using questionnaires and long-lasting follow-up times, are in contrast with the findings of other studies carried out by using objective measurements of lung function indexes in women taking ERT. In 2001, Hepburn et al. [83] found that in postmenopausal asthmatic women ERT had no effect on forced expiratory volume at 1 s (FEV1), an objective measure of

airway obstruction. Interestingly, the majority of women included this study (15 out of 20) underwent hysterectomy and, therefore, were taking estrogen alone at study entry. Therefore, the effects of estrogen were observed independently of progesterone or progestin, that are usually administered in combination with estrogen in women in which the uterus is conserved, in order to reduce the risk of endometrial estrogen-related hyperplasia or cancer. This finding is in accordance with those of several other studies, all of which demonstrated that HRT was associated with a significant increase in FEV1 [84–86] and in FVC [85,86] in postmenopausal women.

6. Unanswered questions and clinical implications

Current knowledge concerning menopausal ERT and asthma provide evidence that estrogen have multiple actions that are, at least in part, conflicting. In fact, on the one hand estrogen have a relaxant effect on airway smooth muscle and increase pulmonary function, so supporting a potential benefit of their use in menopausal ERT. On the other hand, it has been shown that estrogen have an inflammatory action on airways, which is in agreement with the clinical observations suggesting an increase in new asthma rate associated with ERT and support the concept that estrogen can have a potential harmful effect on asthma. There are several potential explanations for these conflicting findings, which can be also in some way confusing, at least to some extent.

Differences in the methodology of the studies carried out on asthma and menopause – particularly in study design, patient and control selection, definition of normal and disease – as well as differences in outcomes of interest, can explain different results obtained in several studies.

Another potential explanation for these finding is that the biological effects of estrogen on airways can not be simply applied to the overall clinical setting, since there are many potential factors that can be involved in the respiratory function in menopausal women undergoing ERT. These factors include smoking, smoking cessation, BMI, metabolic changes occurring at menopause, hormonal status at menopause, physical activity and lifestyle of women, age at menopause, spontaneous or surgical menopause, specific type of drugs used for ERT, way of administration of ERT (vaginal, oral, transdermal), regimen of estrogen administration, concurrent administration of progesterone or progestin, concurring respiratory problems other than asthma, genetic factors. It is actually hard to exactly separate the specific effect or contribution of each of these factors in determining asthma risk of ERT in an individual menopausal woman. This will be a major task for future research in the field.

An important, still unresolved issue is whether respiratory function should be fully investigated before starting ERT. At present, there is no clear indication for an in-depth study of lung function before starting ERT; however, the data from literature suggest that clinicians should be aware of the possibility of an impairment in lung health, and particularly of asthma, in women taking ERT and should discuss this possibility with patients before starting ERT. Another issue of interest is whether women who are taking ERT should undergo extensive investigation of the respiratory function while they are in therapy.

7. Conclusion

The issue of the impact of ERT on asthma is still partly unresolved, despite extensive basic and clinical research has been carried out in the last two decades. The available data show that female sex hormone, particularly estrogen, have a substantial impact on airway function and health. However, they are in part contradictory and

potentially confusing. For this reason, it is difficult to conclude this review with a clear take-home message on ERT and asthma. We believe that, in a time in which much attention is given to limit problems that are potentially created by ERT, the potential impact of ERT on asthma and on overall lung health should be carefully considered by clinicians who prescribe ERT, and that this impact should be taken into account when making a balance between advantages and drawbacks of ERT. Future studies, that are without doubt needed, will help to better understand the effects of estrogen as well as of the other female hormones on normal airways and on respiratory disturbances including asthma.

References

- [1] WHO. GINA Report, Global Strategy for asthma Management and Prevention. Geneva, Switzerland: World Health Organization; 2010.
- [2] Al-Mushen S, Johnson JR, Hamid Q. Remodeling in asthma. *J Allergy Clin Immunol* 2011;128:451–64.
- [3] Doege DC, Sowa J. Airway smooth muscle in the pathophysiology and treatment of asthma. *J Appl Physiol* 2013;114:834–43.
- [4] West AR, Syong HT, Siddiqui S, Pascoe CD, Murphy TM, Maarsingh H, et al. Airway contractility and remodeling: link to asthma symptoms. *Pulm Pharmacol Ther* 2013;26:3–12.
- [5] James AL, Elliott JG, Jones RL, Carroll ML, Mauad T, Bai TR, et al. Airway smooth muscle hypertrophy and hyperplasia in asthma. *Am J Respir Crit Care Med* 2012;185:1058–64.
- [6] James AL, Maxwell PS, Pearce-Pinto G, Elliot JG, Carroll NG. The relationship of reticular basement membrane thickness to airway wall remodeling in asthma. *Am J Respir Crit Care Med* 2002;166:1590–5.
- [7] Holgate ST. A brief history of asthma and its mechanisms to modern concepts of disease pathogenesis. *Allergy Asthma Immunol Res* 2010;2:165–71.
- [8] Khan MA. Inflammation signals airway smooth muscle cell proliferation in asthma pathogenesis. *Multidisciplinary Respir Med* 2013;8:1–5.
- [9] Tulic MK, Christodoulou P, Hamid Q. Small airway inflammation in asthma. *Respir Res* 2001;2:333–9.
- [10] Howarth PH, Babu KDS, Arshad HS, Lau L, Buckley M, McConnell W, et al. Tumour necrosis factor (TNF α) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;60:1012–8.
- [11] Szefer SJ, Dakhama A. New insights into asthma pathogenesis and treatment. *Curr Opin Immunology* 2011;23:801–7.
- [12] Schmidt P. The 2012 hormone therapy position statement of the North American menopause Society. *Menopause* 2012;19:257–71.
- [13] Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;297:1465–77.
- [14] Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, et al. for the WHI Investigators. Effect of estrogen plus progestin on stroke in postmenopausal women. The women's Health Initiative: a randomized trial. *JAMA* 2003;289:2673–84.
- [15] Prentice RL, Manson JE, Langer RD, Anderson GL, Pettinger M, Jackson RD, et al. Benefits and risks of postmenopausal hormone therapy when it is initiated soon after the menopause. *Am J Epidemiol* 2009;170:12–23.
- [16] Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007;115:840–5.
- [17] Beral V., Million Women Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet* 2003;362:419–27.
- [18] Chlebowski RT, Anderson GL. Changing concepts: menopausal hormone therapy and breast cancer. *J Natl Cancer Inst* 2012;104:517–27.
- [19] Zhou B, Sun Q, Cong R, Gu H, Tang N, Yang L, et al. Hormone replacement therapy and ovarian cancer risk: a meta-analysis. *Gynecol Oncol* 2008;108:641–51.
- [20] Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. *Obstet Gynecol* 1995;85:304–13.
- [21] Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women; results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004;47:1175–87.
- [22] Slatore CG, Chien JW, Au DH, Satia JA, White E. Lung cancer and hormone replacement therapy: association in the vitamins and lifestyle study. *J Clin Oncol* 2010;28:1540–6.
- [23] Oh SW, Myung SK, Park JY, Lym YL, Ju W. Hormone therapy and risk of lung cancer: a meta-analysis. *J Women Health* 2010;19:279–88.
- [24] Skobeloff EM, Spivey WH, St. Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA* 1992;268:3437–40.
- [25] Strachan DP, Butland BK, Andersin HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ* 1996;312:1195–9.
- [26] Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax* 1999;54:1119–38.
- [27] De Marco R, Locatelli F, Sunyer J, Burney P. Differences in incidence of reported asthma related to age in men and women. A retrospective analysis of the data of the European Respiratory Health Survey. *Am J Respir Crit Care Med* 2000;162:68–74.
- [28] Lim RH, Kobzik L. Sexual tension in the airways. The puzzling duality of estrogen in asthma. *Editorial Am J Respir Cell Mol Biol* 2008;38:499–500.
- [29] Salam MT, Wenten M, Gilliland FD. Endogenous and exogenous sex steroid hormones and asthma and wheeze in young women. *J Allergy Clin Immunol* 2006;117:1001–7.
- [30] Macsali F, Real FG, Plana E, Sunyer J, Anto J, Dratva J, et al. Early age at menarche, lung function, and adult asthma. *Am J Respir Crit Care Med* 2011;183:8–14.
- [31] Prescott E, Lange P, Vestbo J. Effect of gender on hospital admission for asthma and prevalence of self-reported asthma: a prospective study based on a sample of the general population. Copenhagen city heart study group. *Thorax* 1997;53:387–9.
- [32] Chen Y, Stewart P, Johansen H, McRae L, Taylor G. Sex difference in hospitalization due to asthma in relation to age. *J Clin Epidemiol* 2003;56:180–7.
- [33] Rees L. An aetiological study of premenstrual asthma. *J Psychosom Res* 1963;7:191–7.
- [34] Hanley SP. Asthma variation with menstruation. *Br J Dis Chest* 1981;75:306–8.
- [35] Chandler MHH, Schuldheisz S, Phillips BA, Muse KN. Premenstrual asthma: the effect of estrogen on symptoms, pulmonary function, and beta-2 receptors. *Pharmacotherapy* 1997;17:224–34.
- [36] Gibbs CJ, Coutts II, Lock R, Finnegan OC, White RJ. Premenstrual exacerbation of asthma. *Thorax* 1984;39:833–6.
- [37] Murphy VE, Gibson PG. Premenstrual asthma: prevalence, cycle-to-cycle variability, and relationship to oral contraceptive use and menstrual symptoms. *J Asthma* 2008;45:696–704.
- [38] Pereira-Vega A, Sanchez JL, Gil FL, Maldonado JA, Bravo JM, Ignacio JM, et al. Premenstrual asthma and symptoms related to premenstrual syndrome. *J Asthma* 2010;47:835–40.
- [39] Skobeloff EM, Spivey WH, Silverman RA, Eskin BA, Harchelroad FP, Alessi TV. The effect of the menstrual cycle on asthma presentations in the emergency department. *Arch Intern Med* 1996;156:1837–40.
- [40] Svanes C, Real FG, Gislason T, Jansson C, Jogi R, Norman E, et al. Association of asthma and hay fever with irregular menstruation. *Thorax* 2005;60:445–50.
- [41] Gomez Real F, Svanes C, Reidar Omenaas E, Antò JM, Plana E, Jansson C, et al. Menstrual irregularity and lung function. *J Allergy Clin Immunol* 2007;120:557–64.
- [42] Schatz M, Harden K, Firsytte 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;81:509–17.
- [43] Juniper EF, Daniel EE, Roberts RS, Kline PA, Hargreave FE, Newhouse MT. Improvement in airway responsiveness and asthma severity during pregnancy: a prospective study. *Am Rev Respir Dis* 1989;140:924–31.
- [44] Kwon HL, Triche EW, Belanger K, Bracken MB. The epidemiology of asthma during pregnancy: prevalence, diagnosis, and symptoms. *Immunol Allergy Clin North Am* 2006;26:29–62.
- [45] Ali Z, Ulrik CS. Incidence and risk factors for exacerbations of asthma during pregnancy. *J Asthma Clinical Allergy* 2013;6:53–60.
- [46] Amrani Y, Syed F, Huang C, Li K, Liu V, Jain D, et al. Expression and activation of the oxytocin receptor in airway smooth muscle cells: regulation by TNF- α and IL-13. *Respir Res* 2010;11:104.
- [47] Levin ER. Minireview: extranuclear steroid receptors: roles in modulation of cell functions. *Mol Endocrinol* 2011;25:377–84.
- [48] Ellmann S, Sticht H, Thiel F, Beckmann MW, Strick R, Strissel PL. Estrogen and progesterone receptors: from molecular structures to clinical targets. *Cell Mol Life Sci* 2009;66:2405–26.
- [49] Giannopoulos G, Smith SK. Androgen receptors in fetal rabbit lung and the effect of fetal sex on the levels of circulating hormones and pulmonary hormone receptors. *J Steroid Biochem* 1982;17:461–5.
- [50] Couse JF, Lindzey J, Grandien K, Gustafsson JA, Korach KS. Tissue distribution and quantitative analysis of estrogen receptor- α (ER α) and estrogen receptor- β (ER β) messenger ribonucleic acid in the wild-type and ER α -knockout mouse. *Endocrinology* 1997;138:4613–21.
- [51] Townsend EA, Meuchel LW, Thompson MA, Pabelik CM, Prakash YS. Estrogen increases nitric-oxide production in human bronchial epithelium. *J Pharmacol Exp Ther* 2011;339:815–24.
- [52] Ivanova MM, Mazhawidza W, Dougherty SM, Minna JD, Klinge CM. Activity and intracellular location of estrogen receptors α and β in human bronchial epithelial cells. *Mol Cell Endocrinol* 2009;305:12–21.
- [53] Massaro D, Massaro GD. Estrogen receptor regulation of pulmonary alveolar dimensions: alveolar sex dimorphism in mice. *Am J Physiol Lung Cell Mol Physiol* 2006;290:L866–70.
- [54] Tam A, Morrish D, Wadsworth S, Dorscheid D, Man SFP, Sin DD. The role of female hormones on lung function in chronic lung diseases. *BMC Women's Health* 2011;11(24):1–29.
- [55] Carey MA, Card JW, Bradbury JA, Moorman MP, Haykal-Coates N, Gavett SH, et al. Spontaneous airway hyperresponsiveness in estrogen receptor- α -deficient mice. *Am J Respir Crit Care Med* 2007;175:126–35.
- [56] Gomez Real F, Svanes C, Macsali F, Omenaas R. Hormonal factors and respiratory health in women – a review. *Clin Respir J* 2008;2:111–9.

- [57] Hisamoto K, Ohmichi M, Kurachi H, Hayakawa J, Kanda Y, Nishio Y, et al. Estrogen induces the Akt-dependent activation of endothelial nitric-oxide synthase in vascular endothelial cells. *J Biol Chem* 2001;276:3459–67.
- [58] Shaul PW. Rapid activation of endothelial nitric oxide synthase by estrogen. *Steroids* 1999;64:28–34.
- [59] Dimitropoulou C, Drakopanagiotakis F, Catravas D. Estrogens as a new therapeutic target for asthma and chronic obstructive pulmonary disease. *Drug News Perspect* 2007;20:241–52.
- [60] Dimitropoulou C, White RE, Ownby DR, Catravas JD. Estrogen reduces carbachol-induced constriction of asthmatic airways by stimulating large-conductance voltage and calcium-dependent potassium channels. *Am J Respir Cell Mol Biol* 2005;32:239–47.
- [61] Intapad S, Dimitropoulou C, Snead C, Piyachaturawat P, Catravas JD. Regulation of asthmatic airway relaxation by estrogen and heat shock protein 90. *J Cell Physiol* 2012;227:3036–43.
- [62] Townsend EA, Satish V, Thompson MA, Pabelik CM, Prakash YS. Estrogen effects on human airway smooth muscle involve cAMP and protein kinase A. *Am J Physiol Lung Cell Mol Physiol* 2012;303:L923–8.
- [63] Russel KS, Haynes MP, Sunha D, Clerisme E, Bender JR. Human vascular endothelial cells contain membrane binding sites for estradiol, which mediate rapid intracellular signalling. *Proc Natl Acad Sci USA* 2000;97:5930–5.
- [64] Cohen PG. Estradiol induces inhibition of 11 β -hydroxysteroid dehydrogenase 1: an explanation for the postmenopausal hormone replacement therapy effects. *Med Hypotheses* 2005;64:989–91.
- [65] Simoes DC, Psarra A-MG, Mauad T, Pantou I, Roussos C, Sekeris C, et al. Glucocorticoid and estrogen receptors are reduced in mitochondria of lung epithelial cells in asthma. *PLoS ONE* 2012;7:1–12.
- [66] Ligeiro de Oliveira AP, Domingos HV, Cavriani G, Damazo AS, dos Santos Franco AL, Oliani SM, et al. Cellular recruitment and cytokine generation in a rat model of allergic lung inflammation are differently modulated by progesterone and estradiol. *Am J Physiol Cell Physiol* 2007;293:C1120–8.
- [67] Melgert BN, Postma DS, Kuipers I, Geerlings M, Luinge MA, van der Strate BW, et al. Female mice are more susceptible to the development of allergic airway inflammation than male mice. *Clin Exp Allergy* 2005;35:1496–503.
- [68] Cai Y, Webb DC. Estrogen stimulates Th2 cytokine production and regulates the compartmentalisation of eosinophils during allergic challenge in a mouse model of asthma. *Int Arch Allergy Immunol* 2012;158:252–60.
- [69] Zierau O, Zenclussen AC, Jensen F. Role of female sex hormones, estradiol and progesterone, in mast cell behavior. *Front Immunol* 2012;3:156. <http://dx.doi.org/10.3389/fimmu.2012.00169>.
- [70] Bonds RS, Midoro-Horiuti T. Estrogen effects in allergy and asthma. *Curr Opin Allergy Clin Immunol* 2013;13:92–9.
- [71] Uemura Y, Liu TY, Narita Y, Suzuki M, Matsushita S. Beta-estradiol (E2) plus tumor necrosis factor- α induces a distorted maturation of human monocyte derived dendritic cells and promotes their capacity to initiate T-helper 2 responses. *Hum Immunol* 2008;69:149–57.
- [72] Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. *Am J Respir Crit Care Med* 1995;152:1183–8.
- [73] Gomez Real F, Björnsson EH, Franklín K, Gislason D, Gislason T, Gulsvik A, et al. Hormone replacement therapy, body mass index and asthma in perimenopausal women: a cross sectional survey. *Thorax* 2006;61:34–40.
- [74] Gomez Real F, Svanes C, Omenaas ER, Antò JM, Plana E, Jarvis D, et al. Lung function, respiratory symptoms, and the menopausal transition. *J Allergy Clin Immunol* 2008;121:72–80.
- [75] Balzano G, Fuschillo S, De Angelis E, Gaudiosi C, Mancini A, Caputi M. Persistent airway inflammation and high exacerbation rate in asthma that starts at menopause. *Monaldi Arch Chest Dis* 2007;67:135–41.
- [76] Zemp E, Schikowski T, Dratava J, Schindler C, Probst-Hensch N. Asthma and the menopause: a systematic review and meta-analysis. *Maturitas* 2012;73:212–7.
- [77] Foschino Barbaro MP, Costa VR, Resta O, Prato R, Spanevello A, Palladino GP, et al. Menopausal asthma: a new biological phenotype? *Allergy* 2010;65:1306–12.
- [78] Jarvis D, Leynaert B. The association of asthma, atopy and lung function with hormone replacement therapy and surgical cessation of menstruation in a population-based sample of English women. *Allergy* 2008;63:95–102.
- [79] Key TJ, Pike MC, Brown JB, Hermon C, Allen DS, Wang DY. Cigarette smoking and urinary oestrogen excretion in premenopausal and postmenopausal women. *Br J Cancer* 1996;74:1313–6.
- [80] Lieberman D, Kopernik G, Porath A, Lazer S, Heimer D. Sub-clinical worsening of bronchial asthma during estrogen replacement therapy in asthmatic postmenopausal women. *Maturitas* 1995;21:153–7.
- [81] Barr RG, Wentowski CC, Grodstein F, Somers SC, Stampfer MJ, Schwartz J, et al. Prospective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. *Arch Intern Med* 2004;164:379–86.
- [82] Romieu I, Fabre A, Fournier A, Kauffmann F, Varraso R, Mesrine S, et al. Postmenopausal hormone therapy and asthma onset in the E3N cohort. *Thorax* 2009;65:292–7.
- [83] Hepburn MC, Dooley DP, Morris MJ. The effects of estrogen replacement therapy on airway function in postmenopausal, asthmatic women. *Arch Intern Med* 2011;161:2717–20.
- [84] Carlson CL, Cushman M, Enright PL, Cauley JA, Newman AB. Hormone replacement therapy is associated with higher FEV1 in elderly women. *Am J Respir Crit Care Med* 2001;163:423–8.
- [85] Pata Ö. The effects of hormone replacement therapy type on pulmonary function in postmenopausal women. *Maturitas* 2003;213–8.
- [86] Cevrioglu AS, Fidan F, Unlu M, Yilmazer M, Oman A, Fenkci IV, et al. The effects of hormone therapy on pulmonary function tests in postmenopausal women. *Maturitas* 2004;49:221–7.