

The role of female sex hormones in the development and severity of allergic and non-allergic asthma

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Summary

Allergic asthma is usually diagnosed by the presence of variable airway obstruction, bronchial hyperresponsiveness, and allergy. However, a significant proportion of adult asthma patients (up to 40%) are non-allergic. Patients with non-allergic asthma often have a later disease onset and greater disease severity, as reflected by more severe airway obstruction and bronchial hyperresponsiveness. Furthermore, females have a higher risk of developing non-allergic asthma. The latter suggests that hormone-related events play an important role in the development and severity of adult-onset non-allergic asthma. This paper describes the associations between asthma and hormonal changes throughout the female life-span, such as those associated with the monthly cycle of menstruation and menopausal hormonal changes.

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Allergic asthma is usually diagnosed by the presence of variable airway obstruction, bronchial hyperresponsiveness, and allergy. However, a significant proportion of adult asthma patients (up to 40%) are non-allergic [1, 2]. There are many similarities between allergic and non-allergic (intrinsic) asthma. For example, the type of mucosal inflammation is comparable, i.e. increased numbers of eosinophils and mast cells, and increased levels of their mediators, e.g. IL-5 and also the two B cell IgE-switching cytokines IL-4 and IL-13 [3]. The latter may also explain the findings of increased total serum IgE levels in patients with non-allergic asthma [4]. Interestingly, Beeh et al. have shown that higher levels of serum total IgE are associated with more severe airway obstruction in patients with non-allergic asthma [4]. This had led some authors to question the existence of non-allergic asthma as a separate disease entity, thus suggesting that all asthma patients may have an atopic component and that the increased production of IgE is directed towards a yet unidentified allergen. An alternative explanation for the relation between elevated total IgE levels and more severe asthma can be derived from the findings of Kalesnikoff et al. in murine mast cells [5]. They observed that IgE

binding to its high-affinity receptor (FcεRI) was able to induce intracellular signalling pathways, resulting in the production of cytokines (e.g. IL-4, IL-6, IL-13, TNF-α), and to enhance mast cell survival on its own, without cross-linking by allergens [5]. In addition, IgE may directly bind and activate receptors present on eosinophils, neutrophils, and monocytes [6].

There are also several differences between allergic and non-allergic asthma. Patients with non-allergic asthma often have a later disease onset and more severe disease as reflected by more severe airway obstruction and bronchial hyperresponsiveness [7]. Furthermore, several studies have demonstrated that females have a higher risk of developing non-allergic asthma [7, 8]. Here, we propose that hormone-related events play an important role in the development and severity of adult-onset asthma in women independent of the presence of allergy (see Fig. 1).

The role of female sex hormones in the development and severity of asthma

A large number of studies have focused on the associations between asthma and hormonal changes throughout the

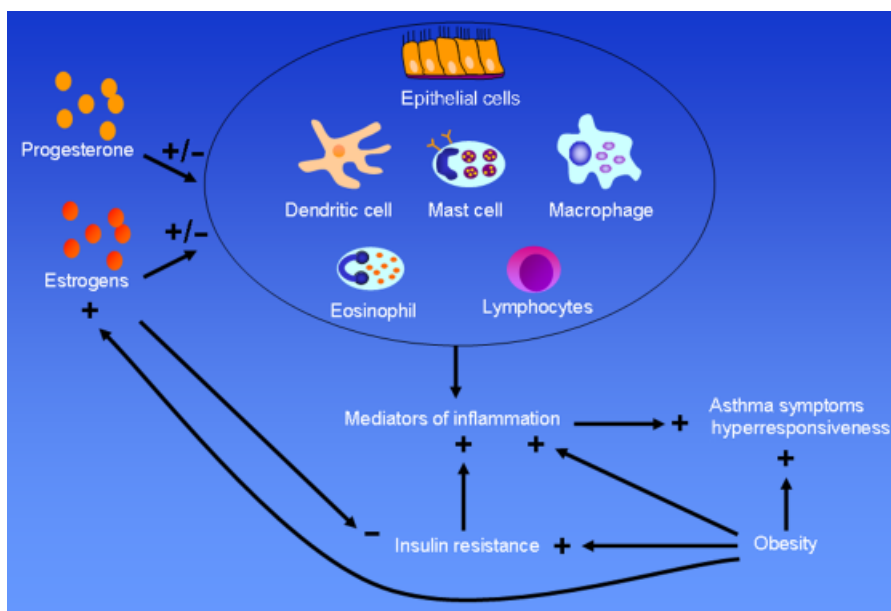


Fig. 1. Influence of female sex hormones on asthmatic inflammation and asthma symptoms. Possible interactions with obesity and insulin resistance.

female life-span, such as those associated with the monthly cycle of menstruation and menopausal hormonal changes.

Changes in asthma during the menstrual cycle

Perimenstrual aggravation of asthma (PMA) with an increase in symptoms and a significant decline in peak flow (> 20%) has been reported in 30–40% of women [9]. Importantly, Siroux *et al.* reported PMA to be independent of the presence or absence of allergy [10]. Only five small studies have measured the level of bronchial hyperresponsiveness during the menstrual cycle in women with PMA. No cyclical variations were found in PC₂₀ methacholine or PC₂₀ histamine [9, 11–13]. However, Tan *et al.* found a 2.5-fold increase in the premenstrual level of PC₂₀ AMP [14]. This indicates an effect of female sex hormones on airway inflammation during the menstrual cycle, because changes in AMP closely reflect changes in eosinophilic airway inflammation [15, 16].

A relationship between hormonal swings and asthma worsening could theoretically be due to increases or decreases of hormone levels or a change in their ratio. Several sex hormones have been implicated to play a role in perimenstrual worsening of asthma, of which oestrogens and progesterone (or both) seem to be the most important. Thus far, few studies have investigated the contribution of sex hormones to asthmatic airway inflammation. Results have been conflicting, and both pro- and anti-inflammatory effects of oestrogens and progesterone have been described. For example, oestrogens can augment the release of histamine and serotonin from rat mast cells [17]. In addition, oestrogens significantly enhance eosinophil adhesion to human mucosal endothelial cells and a combina-

tion of oestrogens and progesterone induces eosinophil degranulation [18]. Finally, oestrogens inhibit the production of cortisol, which may contribute to more severe asthma as well [19]. However, the anti-inflammatory effects of oestrogens have also been described. Oestrogens inhibit the oxidative burst in human blood leucocytes and may suppress airway inflammation by increasing the number of FoxP3+ regulatory T cells [20]. Furthermore, it has been shown in knock-out mice that the absence of oestrogen receptors leads to an increase in airway hyperresponsiveness, and polymorphisms in the oestrogen receptor have been implicated in the development of hyperresponsiveness, as well as accelerated lung function decline particularly in female asthma [21, 22]. Little is known about the effects of progesterone on inflammation and asthma. Progesterone has been shown to enhance bronchial hyperresponsiveness and eosinophilic airway inflammation in an allergic mouse model of asthma [23]. However, progesterone may also exert anti-inflammatory effects. For example, progesterone enhances the effects of corticosteroids in mouse fibroblasts [24] and inhibits the release of inflammatory mediators from human blood basophils [25].

Many clinical studies have been performed to assess whether hormonal therapy with different combinations of oestrogens and/or progesterone may improve symptoms in women with PMA. Most studies have reported favourable effects, with an improvement in perimenstrual symptoms and peakflow values and a reduction in the number of asthma exacerbations. However, firm evidence is lacking so far, as no randomized-controlled clinical trials have been performed. Furthermore, it is unclear which combination of oestrogens and/or progesterone would be the most effective to treat PMA.

Asthma and menopause

Menopause can coincide with the clinical expression of asthma. In agreement with this, Bonner et al. found a peak in the prevalence of adult-onset asthma in women around the age of 50 years, the mean age of the onset of menopause [26]. When asthma starts during menopause, it is frequently associated with an absence of allergy and with higher asthma severity and frequent exacerbations [27]. It has been suggested that the increase in asthma severity and incidence may be due to the decrease in oestrogens during menopause [28]. In agreement with this, Kos-Kudla et al. showed that the level of serum oestrogens was lower in postmenopausal asthmatic women than in postmenopausal healthy women [29]. In addition, they showed that hormone replacement therapy (HRT) with oestrogens and medroxyprogesterone acetate improved asthma symptoms. In agreement with this, a higher level of FEV₁ was observed in elderly postmenopausal women with the use of HRT [30]. However, there is controversy in this area, as the Nurses Health Study and the Copenhagen City Heart study showed that postmenopausal women have a higher risk of developing asthma when they use HRT, either with oestrogens alone or with oestrogens and progesterone combined [28, 31]. A possible explanation for these discrepant findings could be that the effects of HRT differ in subgroups of women. For instance, Lange et al. found that the association of HRT with asthma was weaker in a subgroup of women who were smokers, which was attributed to the anti-oestrogen effects of smoking [31]. Further, Gomez Real et al. showed that the risk of developing postmenopausal asthma (both allergic and non-allergic asthma) was greater in lean women than in obese women when they used HRT [32].

Asthma, menopause, and insulin resistance

The finding that lean postmenopausal women who use HRT have a higher risk of developing asthma is surprising, as many studies have shown obesity to be associated with a higher risk of developing asthma [33]. In addition, several authors have demonstrated that asthmatics with a higher body mass index are less sensitive to the beneficial effects of corticosteroids [34–36]. A possible explanation for the relation between obesity and asthma may be the presence of a low-grade systemic inflammation with increased levels of pro-inflammatory cytokines and mediators such as TNF- α , IL-1 β , IL-6, and leptin [37]. In addition, the systemic inflammation that is present in obesity may cause insulin resistance [38]. In this context, the findings of Thuesen et al. are of special interest. They showed that insulin resistance is an even stronger predictor for the development of adult-onset asthma than the presence of obesity [39]. It is unclear whether insulin resistance itself contributes to the development of asthma

or whether the association between insulin resistance and asthma is caused by an increased level of pro-inflammatory mediators leading to both insulin resistance and asthma. This remains to be elucidated in future studies.

With respect to the possible effects of insulin, studies have observed that treatment with insulin has anti-inflammatory effects that may also be relevant to asthma. For example, it has been shown that an insulin infusion decreases the levels of nuclear factor kappa B, monocyte chemo-attractant protein-1, and the production of the reactive oxygen species in peripheral blood mononuclear cells derived from obese non-diabetic subjects [40]. In addition, it has been demonstrated that treatment with insulin increases the number of FoxP3+ regulatory T cells in patients with type 1 diabetes [41]. Thus, it could be speculated that resistance to the anti-inflammatory effects of insulin may contribute to the development or severity of asthma. However, there is controversy in this area, as other authors have demonstrated that insulin increases the contractility of airway smooth muscle cells, which may contribute to bronchial hyperresponsiveness [42]. Taken together, the role of insulin and insulin resistance in asthma is presently unclear, but warrants further attention in future studies.

Interestingly, oestrogens have been shown to protect against insulin resistance and menopause is accompanied by an increased insulin resistance due to a decline in oestrogen levels [43]. This might also explain the increase in asthma incidence and severity during this period in life. In addition, it could provide an explanation for the differential effects of HRT between lean and obese women, as suggested by Gomez Real et al. [32]. In lean women without insulin resistance, the pro-inflammatory effects of oestrogens (as described above) may predominate. However, in overweight and more insulin-resistant women, the pro-inflammatory effects of oestrogens may be counterbalanced by a reduced insulin resistance.

In conclusion, a large proportion of patients with adult-onset asthma are non-allergic and female. In these patients, we propose an important role for female sex hormones such as oestrogens and progesterone in conjunction with a relative insulin resistance.

References

- 1 Wuthrich B, Schindler C, Leuenberger P, Ackermann-Lieblich U. Prevalence of atopy and pollinosis in the adult population of Switzerland (SAPALDIA study). Swiss Study on Air Pollution and Lung Diseases in Adults. *Int Arch Allergy Immunol* 1995; 106:149–56.
- 2 Charpin D, Ramadour M, Lanteaume A, Vervloet D. Triggers in intrinsic asthma in the EGEA study. *J Asthma* 2003; 40:87–91.
- 3 Humbert M, Durham SR, Kimmitt P *et al.* Elevated expression of messenger ribonucleic acid encoding IL-13 in the bronchial mucosa of atopic and nonatopic subjects with asthma. *J Allergy Clin Immunol* 1997; 99:657–65.

- 4 Beeh KM, Ksoll M, Buhl R. Elevation of total serum immunoglobulin E is associated with asthma in nonallergic individuals. *Eur Respir J* 2000; **16**:609–14.
- 5 Kalesnikoff J, Huber M, Lam V *et al*. Monomeric IgE stimulates signaling pathways in mast cells that lead to cytokine production and cell survival. *Immunity* 2001; **14**:801–11.
- 6 Bjerke T, Hoffmann HJ, Christensen EI, Poulsen LK, Skjold T, Dahl R. Regulation of FcεpsilonRI synthesis in human eosinophils. *Int Arch Allergy Immunol* 1999; **118**:440–2.
- 7 Nieves A, Magnan A, Boniface S *et al*. Phenotypes of asthma revisited upon the presence of atopy. *Respir Med* 2005; **99**:347–54.
- 8 Accordini S, Corsico A, Cerveri I *et al*. The socio-economic burden of asthma is substantial in Europe. *Allergy* 2008; **63**:116–24.
- 9 Shames RS, Heilbron DC, Janson SL, Kishiyama JL, Au DS, Adelman DC. Clinical differences among women with and without self-reported perimenstrual asthma. *Ann Allergy Asthma Immunol* 1998; **81**:65–72.
- 10 Siroux V, Curt F, Oryszczyn MP, Maccario J, Kauffmann F. Role of gender and hormone-related events on IgE, atopy, and eosinophils in the Epidemiological Study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy. *J Allergy Clin Immunol* 2004; **114**:491–8.
- 11 Juniper EF, Kline PA, Roberts RS, Hargreave FE, Daniel EE. Airway responsiveness to methacholine during the natural menstrual cycle and the effect of oral contraceptives. *Am Rev Respir Dis* 1987; **135**:1039–42.
- 12 Weinmann GG, Zacur H, Fish JE. Absence of changes in airway responsiveness during the menstrual cycle. *J Allergy Clin Immunol* 1987; **79**:634–8.
- 13 Pauli BD, Reid RL, Munt PW, Wigle RD, Forkert L. Influence of the menstrual cycle on airway function in asthmatic and normal subjects. *Am Rev Respir Dis* 1989; **140**:358–62.
- 14 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**:608–11.
- 15 Van den Berge M, Kerstjens HAM, Postma DS. Provocation with adenosine 5'-monophosphate as a marker of inflammation in asthma, allergic rhinitis and chronic obstructive pulmonary disease. *Clin Exp Allergy* 2002; **32**:824–30.
- 16 Van den Berge M, Kerstjens HAM, Meijer RJ *et al*. Corticosteroid-induced improvement in the PC20 of adenosine monophosphate is more closely associated with reduction in airway inflammation than improvement in the PC20 of methacholine. *Am J Respir Crit Care Med* 2001; **164**:1127–32.
- 17 Vliagoftis H, Dimitriadou V, Boucher W *et al*. Estradiol augments while tamoxifen inhibits rat mast cell secretion. *Int Arch Allergy Immunol* 1992; **98**:398–409.
- 18 Hamano N, Terada N, Maesako K, Numata T, Konno A. Effect of sex hormones on eosinophilic inflammation in nasal mucosa. *Allergy Asthma Proc* 1998; **19**:263–9.
- 19 Jamieson PM, Nyirenda MJ, Walker BR, Chapman KE, Seckl JR. Interactions between oestradiol and glucocorticoid regulatory effects on liver-specific glucocorticoid-inducible genes: possible evidence for a role of hepatic 11beta-hydroxysteroid dehydrogenase type 1. *J Endocrinol* 1999; **160**:103–9.
- 20 Tai P, Wang J, Jin H *et al*. Induction of regulatory T cells by physiological level estrogen. *J Cell Physiol* 2008; **214**:456–64.
- 21 Carey MA, Card JW, Bradbury JA *et al*. Spontaneous airway hyperresponsiveness in estrogen receptor-alpha-deficient mice. *Am J Respir Crit Care Med* 2007; **175**:126–35.
- 22 Dijkstra A, Howard TD, Vonk JM *et al*. Estrogen receptor 1 polymorphisms are associated with airway hyperresponsiveness and lung function decline, particularly in female subjects with asthma. *J Allergy Clin Immunol* 2006; **117**:604–11.
- 23 Mitchell VL, Gershwin LJ. Progesterone and environmental tobacco smoke act synergistically to exacerbate the development of allergic asthma in a mouse model. *Clin Exp Allergy* 2007; **37**:276–86.
- 24 Hackney JF, Holbrook NJ, Grasso RJ. Progesterone as a partial glucocorticoid agonist in L929 mouse fibroblasts: effects on cell growth, glutamine synthetase induction and glucocorticoid receptors. *J Steroid Biochem* 1981; **14**:971–7.
- 25 Mittman RJ, Bernstein DI, Steinberg DR, Enrione M, Bernstein IL. Progesterone-responsive urticaria and eosinophilia. *J Allergy Clin Immunol* 1989; **84**:304–10.
- 26 Bonner JR. The epidemiology and natural history of asthma. *Clin Chest Med* 1984; **5**:557–65.
- 27 Balzano G, Fuschillo S, De AE, 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.
- 28 Barr RG, Wentowski CC, Grodstein F *et al*. Prospective study of postmenopausal hormone use and newly diagnosed asthma and chronic obstructive pulmonary disease. *Arch Intern Med* 2004; **164**:379–86.
- 29 Kos-Kudla B, Ostrowska Z, Marek B *et al*. Hormone replacement therapy in postmenopausal asthmatic women. *J Clin Pharm Ther* 2000; **25**:461–6.
- 30 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.
- 31 Lange P, Parner J, Prescott E, Ulrik CS, Vestbo J. Exogenous female sex steroid hormones and risk of asthma and asthma-like symptoms: a cross sectional study of the general population. *Thorax* 2001; **56**:613–6.
- 32 Gomez RF, Svanes C, Bjornsson EH *et al*. Hormone replacement therapy, body mass index and asthma in perimenopausal women: a cross sectional survey. *Thorax* 2006; **61**:34–40.
- 33 Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med* 2006; **174**:112–9.
- 34 Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DY. Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med* 2008; **178**:682–7.
- 35 Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. *Eur Respir J* 2006; **27**:495–503.
- 36 Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med* 2007; **101**:2240–7.
- 37 Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005; **115**:911–9.
- 38 Mikhail N. The metabolic syndrome: insulin resistance. *Curr Hypertens Rep* 2009; **11**:156–8.
- 39 Thuesen BH, Husemoen LL, Hersoug LG, Pisinger C, Linneberg A. Insulin resistance as a predictor of incident asthma-like symptoms in adults. *Clin Exp Allergy* 2009; **39**:700–7.

- 40 Dandona P, Aljada A, Mohanty P *et al.* Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab* 2001; **86**:3257–65.
- 41 Tiittanen M, Huupponen JT, Knip M, Vaarala O. Insulin treatment in patients with type 1 diabetes induces upregulation of regulatory T-cell markers in peripheral blood mononuclear cells stimulated with insulin in vitro. *Diabetes* 2006; **55**:3446–54.
- 42 Gosens R, Nelemans SA, Hiemstra M, Grootte Bromhaar MM, Meurs H, Zaagsma J. Insulin induces a hypercontractile airway smooth muscle phenotype. *Eur J Pharmacol* 2003; **481**: 125–31.
- 43 Kanaya AM, Herrington D, Vittinghoff E *et al.* Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003; **138**:1–9.