

Gender-Specific Asthma Treatment

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Because genetic characteristics vary among subjects, the therapeutic effects of a certain drug differ among patients with the same disease. For this reason, special interest has focused on tailored treatments. Although it is well known that sex is genetically determined, little attention has been paid to sex differences in the clinical features and treatment of asthma. Females are more likely to suffer allergic asthma, to have difficulty controlling asthma symptoms, and to show adverse effects to drugs. As asthma symptoms show cyclic changes depending on female hormone levels in many women of child-bearing age, the use of contraceptives may specifically help to treat female patients with asthma such as those with perimenstrual asthma and severe asthma. Generally, testosterone seems to suppress asthma, and dehydroepiandrosterone (DHEA), a less virilizing androgen, may be effective for treating asthma. Evidence exists for a therapeutic and steroid-sparing effect of DHEA. However, further studies on the optimal dose and route of DHEA for each sex are needed. Monitoring of the serum DHEA-S level is necessary for patients with asthma on inhaled steroid treatment, and at minimum, replacement therapy for patients with a low level of DHEA may be helpful for treating their asthma.

Key Words: Asthma; dehydroepiandrosterone; sex; perimenstrual; treatment

INTRODUCTION

Asthma is defined by characteristic features such as airway hyper-responsiveness (AHR), reversible airflow obstruction, and paroxysmal cough, dyspnea, and wheezing, which are associated with airway inflammation.¹ Therefore, it is not a disease entity, but a syndrome caused by a variety of etiologic agents. Because the clinical features of asthma and responses to anti-asthma drugs are similar regardless of cause, most patients are treated with the same drugs under the same diagnostic name of asthma. However, etiology-based specific treatments have long been given, such as avoidance of offending allergens and allergen-specific immunotherapy when specific allergens have been identified. Moreover, with advances in genetics, the association of HLA-DPB*0301 or cysteinyl leukotriene receptor 1 promotor-634C>T and the necessity for leukotriene receptor antagonists has been identified in patients with aspirin-intolerant asthma.² Thus, treatments tailored for individuals have gained the attention of clinicians. Although it is premature to apply such tailored gene-analysis treatments in general practice, differential treatment according to sex can be easily introduced because genetically determined sex can be identified without the need for a gene analysis. In 2003, Osman³ mentioned sex-specific treatments in patients with asthma. However, few systematic reviews of studies on this issue have been reported so far.

SEX DIFFERENCES IN ASTHMA PREVALENCE

The prevalence of asthma is higher in males than in females before adolescence, but this trend is reversed after adolescence.³⁻⁵ In 1977, Wormald⁶ reported that the incidence of asthma with a positive response to skin prick tests using house dust mite allergens was three times higher in males before the age of 10 years, but it changed to 1.5 times and 1.6 times higher in females in their third and fourth decades (child bearing years), respectively, and was higher again in males in their fifth decade (Figure). A cross-sectional analysis of the data of the European Community Respiratory Health Survey by de Marco et al.⁷, conducted in 2000 with more than 18,000 subjects in 16 countries, found that the incidence of asthma was 0.56 times lower in females at the age of 5-10 years but increased in females after adolescence, and it was 5.91 times higher in females after their fourth decade; furthermore, this trend was observed in all 16 countries. Osman et al.⁸ also reported in 2007 an analysis of more

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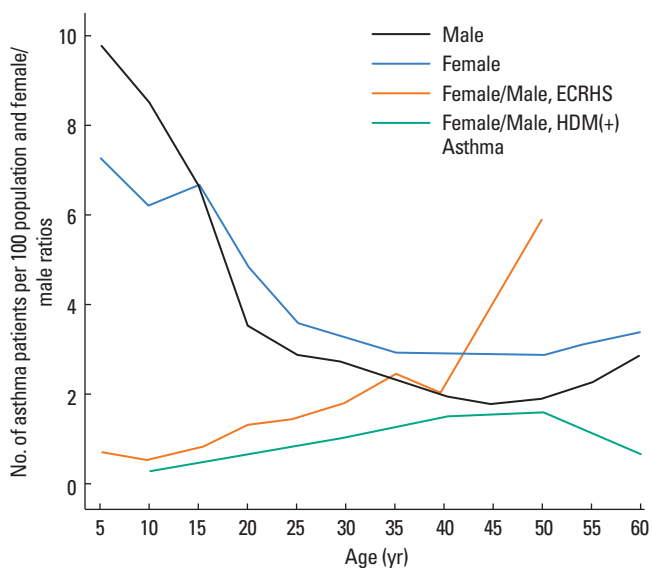


Figure. Sex differences in asthma prevalence. The ratios of female to male patients with asthma and a positive response to skin prick tests using house dust mites (HDM) (redrawn from Wormald⁶) and in patients who were reported to have asthma in the European Community Respiratory Health Survey (ECRHS) (redrawn from de Marco et al.⁷), and the number of asthma patients per 100 population for each sex in the General Practice Research Database (redrawn from Osman et al.⁸).

than 260,000 asthmatic patients retrieved from the General Practice Research Database which showed that the prevalence of asthma per 100 population was 9.8 for males and 7.3 for females at the age of 5 years, 6.7 and 6.7 at 15 years, 2.9 and 3.6 at 25 years, 2.3 and 3.0 at 35 years, 1.8 and 2.9 at 45 years, and 2.3 and 3.2 at 55 years, respectively, suggesting that the sex ratio reverses after adolescence. They also reported a similar trend in patients with allergic rhinitis. Similarly, Poulos et al.⁹ reported in 2007 that the hospital admission rates for urticaria, angioedema, and anaphylaxis were higher in boys than in girls among children aged less than 15 years, whereas those rates were higher in females than in males among those aged 15 years and older.

This reversal in sex ratio after puberty is not caused by increased loss of established asthma in boys, but by late incidence of asthma among girls.^{4,10} The sex difference in the prevalence of asthma is reflected in the sex difference in the hospitalization rate and asthma severity.⁴ The reasons for the higher prevalence of asthma in boys may be that their airways develop relatively slowly compared with lung volume (dysanapsis)^{3,4} and are easily sensitized to indoor allergens such as house dust mites and cat dander,¹¹ whereas girls and young women tend to be treated after their asthma becomes aggravated (Yentl syndrome).^{3,4} Actually, the sex difference begins during gestation; the lung matures more slowly and surfactant is produced later in the male than in the female fetus.¹² Consequently, male neonates tend to have lower specific airway conductance than do female neonates.

In adults, because the airway caliber and lung function of males are greater than those of females, a smaller airway caliber in females may contribute to the reversal of the sex ratio for asthma prevalence after puberty.⁷ Because airway resistance is inversely proportionate to the fourth power of airway diameter, airway resistance easily increases when airway caliber is small, and CO₂ retention in blood may occur in females due to the small airway caliber even when the degree of airflow obstruction is not as severe although frank ventilatory failure generally occurs when forced expiratory volume in 1 second (FEV₁) is $\leq 25\%$ during an asthma attack.¹³ Some genetic polymorphisms are associated with asthma in females and not in males, such as cytotoxic T lymphocyte-associated 4 receptor (+49 A/G), cyclooxygenase-2 (-165 G/C), defensin β -1, toll-like receptor 4, and estrogen receptor α .¹² In addition to these genetic, anatomical, and physiological differences, apparent immunological differences must exist between the sexes because not only allergic asthma,⁶ but also other allergic diseases,^{8,9} occur more frequently in females after puberty, as mentioned above. Moreover, females are more sensitive to environmental factors such as smoking, cooking gas, ozone, and pets, and body mass index (BMI) is closely related to asthma and atopy in women.⁴ Sex hormones may play an important role in this sex difference.

SEX HORMONES AND ASTHMA

The immunological system interacts with the endocrine system. In general, female sex hormones aggravate asthma and other allergic diseases, whereas male sex hormones suppress such diseases.³ Females seem to be born with a Th2 bias, as humans naturally tend to shift to Th2 to prevent mothers from rejecting their fetuses during pregnancy, and immunity becomes mature in a Th2-suppressing manner following exposure to infections after birth (the so-called hygiene hypothesis).

Women who reached menarche before the age of 12 years have a 2.08-fold higher risk of asthma after puberty compared with those who reached menarche after the age 12 years.¹⁴ During the menstrual cycle, skin-test responses to allergens,^{15,16} adenosine-AHR,¹⁷ and exhaled nitric oxide level¹⁶ vary according to the levels of sex hormones, and these responses are abolished by the use of oral contraceptives.^{16,17} Progesterone¹⁸ and estrogen,^{19,20} the representative female sex hormones, increase the secretion of interleukin (IL)-4 and the total IgE level, respectively. However, progesterone inhibits histamine release from mast cells,²¹ and estrogen induces FoxP3⁺ regulatory T (Treg) cells^{22,23}; thus, these hormones do not simply work in one direction. Nevertheless, generally speaking, when the luteal phase, with its increased blood levels of progesterone and estrogen, is suppressed by the use of oral contraceptives, associated cyclic changes in AHR are inhibited.¹⁷ The risk of asthma decreases by 7% per year during oral contraceptive pill use in young women²⁴ and increases 2.29 times with hormone replacement therapy in postmeno-

pausal women.²⁵

Male mice have higher numbers of CD4⁺/CD25⁺ T cells, so it is difficult to establish an asthma model using male mice; ovalbumin sensitization and challenge in male mice increases the levels of ovalbumin-specific IgE, IL-4, and IL-13 and the numbers of CD4⁺ T cells, B cells, and eosinophils less remarkably than in female mice.²⁶ During a transient medical castration in men, not only serum testosterone, but also CD4⁺/CD25⁺ T cell numbers and CD8⁺ T cell interferon (IFN)- γ expression decreases, and this is prevented by testosterone replacement.²⁷ Androgen inhibits leukotriene synthesis by controlling the activity of extracellular signal-regulated kinases.²⁸ Dehydroepiandrosterone (DHEA), a weak androgen, which is produced in the adrenal gland, has similar activity, so there is a significant relationship between the serum level of DHEA sulfate ester (DHEA-S), a precursor of DHEA, and the number of IFN- γ -secreting cells.²⁹ Because the serum DHEA-S level is relatively low in patients with asthma³⁰ or atopic dermatitis,³¹ and because it decreases in a dose-dependent manner with the use of inhaled corticosteroids,³² screening tests for serum DHEA-S level may be useful for examining adrenal function and for determining DHEA replacement therapy in patients with asthma who are receiving inhaled steroid treatment. Testosterone replacement therapy in male patients with rheumatoid arthritis and low testosterone levels increases CD8⁺ T cells and decreases IgM rheumatoid factor and medication requirements.³

SEX, OBESITY, AND ASTHMA

Although women are usually under stress to be lean, and their greatest concern is eating habits, obesity develops more frequently in women. When obesity is defined as a BMI ≥ 30 kg/m², the prevalence of obesity is 24.1% in men and 24.9% in women in the United Kingdom, and 28.6% in men and 34.2% in women in the United States.³³ Although women must store excess fat for reproduction and lactation, the exact mechanism underlying the need for excess body weight in women is not well understood; however, lower energy expenditure due to shorter stature and less fat-free body mass in women must play an important role.³⁴ Estrogen rather decreases appetite and body weight. This hormone decreases abdominal and visceral fat, which is associated with metabolic syndrome, but it distributes fat to the gluteo-femoral area, and this fat is used through lipolysis by lipoprotein lipase activity during lactation.

Recently, the prevalence of asthma and obesity have simultaneously increased, so it is presumed that obesity may be one of the causes of asthma.³⁵ Camargo et al.³⁶ reported in 1999 that the risk for developing asthma was 2.7 times higher in obese women and 2.5 times higher when body weight had increased by 25 kg at the 4-year follow-up after the age of 18 years. The mechanisms by which obesity affects asthma include 1) mechanical factors such as lower lung volume and compliance and smaller

diameter of the peripheral airways, 2) comorbidities such as gastroesophageal reflux disease (GERD), 3) systemic inflammation caused by fat-cell-secreting adipokines including IL-6, tumor necrosis factor (TNF)- α and eotaxin, 4) a decrease in adiponectin, an obesity hormone with an anti-inflammatory effect, 5) an increase in AHR by leptin, which has a similar structure as IL-6, and 6) increased oxidative stress.^{37,38} Unlike patients with Th2-mediated asthma, obese asthmatics show unremarkable airway inflammation, suggesting a distinct asthma phenotype.³⁸ Thus, these patients may have relative resistance to conventional corticosteroid therapy,^{38,39} and special attention should be paid to frequently comorbid GERD.³⁸ However, Yoo et al.⁴⁰ have reported that the prevalence of atopy is higher in obese Korean male adolescents. Jeon et al.⁴¹ have documented that the FEV1/forced vital capacity (FVC) ratio is significantly lower in obese women or during the menstrual period, but unfortunately, they did not observe whether obese patients with asthma showed a decreased FEV1/FVC ratio during the menstrual period.

Insulin resistance is associated with obesity; diacylglycerol accumulates in the skeletal muscle and liver and triggers protein kinase C activation, with subsequent impairments in insulin signalling.⁴² Insulin has an anti-inflammatory effect by inhibiting nuclear factor κ B and inducing FoxP3⁺Treg cells, so insulin may affect asthma.²³ Despite the observation that sex hormone replacement therapy increases the risk of developing postmenopausal asthma in lean women without insulin resistance, it may improve asthma in obese postmenopausal women with insulin resistance by decreasing body weight and insulin resistance.

FEMALE-SPECIFIC ASTHMA

Perimenstrual (catamenial) asthma

As mentioned above, asthma and allergy markers vary during the menstrual cycle according to sex hormone levels,¹⁵⁻¹⁷ and perimenstrual asthma occurs in 30–40% of female asthmatics during the child-bearing years, regardless of allergy.²³ Recently, in a study monitoring daily respiratory symptoms of fertile asthmatic females during two consecutive menstrual cycles, Pereira Vega et al.⁴³ reported that 59.6% of patients showed premenstrual exacerbation of symptoms in at least one of the two cycles, but only 22.3% in both cycles. Autoantibodies against sex hormones are also able to induce perimenstrual asthma and miscarriage.⁴⁴ Since perimenstrual asthma was first described by Frank et al.⁴⁵ in 1931, numerous studies have reported on this type of asthma. During the perimenstrual period, not only adenosine-AHR,¹⁷ but also methacholine-AHR⁴⁶ is aggravated, and the use of oral contraceptives can prevent such aggravation^{17,46} and improve clinical symptoms.²³

Asthma-related menstrual irregularity

As asthmatics show changes in sex hormones such as a decrease in serum DHEA-S level regardless of drug therapy, they

can also have associated menstrual irregularities. In a study at seven institutions with approximately 8,000 women of child-bearing age, Svanes et al.⁴⁷ found that the prevalence of menstrual irregularity was 1.54 times higher in patients with asthma and 1.29 times higher in those with allergic rhinitis regardless of the use of antiasthmatic medications, and this difference was similar at all seven institutions. They suggested that insulin resistance may correlate with both asthma and menstrual irregularity.

Pregnancy

Pregnancy affects asthma and vice versa, including mechanical changes in lung function. The purpose of asthma treatment during pregnancy is delivery of a healthy baby, which is an important goal in addition to those for general asthma. Since the considerable number of congenital malformation cases due to thalidomide in the 1960s, careful administration of drugs during pregnancy has become common sense. Details about this issue can be found elsewhere.⁴⁸

SEX DIFFERENCES IN THE EFFECTIVENESS OF AND ADVERSE REACTIONS TO ASTHMA TREATMENT

Treatment effectiveness

Because a sex difference exists in the prevalence of asthma and allergic diseases and sex hormones affect allergic diseases, it is postulated that responses to anti-asthmatic drugs differ between the sexes; however, few investigations have examined this issue. Montelukast, but not fluticasone, increases FEV1 in females more than in males among patients aged 6–17 years with asthma.⁴⁹ Johnston et al.⁵⁰ reported that montelukast prevents asthma's worsening in younger boys aged 2–5 years (odds ratio [OR], 0.03; $P < 0.001$) or 6–9 years (OR, 0.27; $P = 0.028$) and in older girls aged 10–14 years (OR, 0.17; $P = 0.001$). Such sex differences in treatment effectiveness may be mainly attributable to dysanaptic lung growth in boys^{3,4,51} and female sex hormone after menarche, which are associated with more active asthma.⁵¹ BCG and DHEA are more effective in female mice than in male mice.⁵² Male mice have a high IFN- γ /IL-5 ratio and low allergen-specific IgE level, but they develop asthma despite this and may require treatment to help overcome these conditions. Furthermore, male children have higher theophylline clearance⁵³ and lower drug adherence during asthma exacerbation,⁵⁴ but controlling their asthma is relatively easier.⁵⁵

Adverse reactions

Adverse drug reactions occur more frequently in females than in males. For instance, the rate of a positive skin test to penicillin is 3.2 times higher in females than in males.⁵⁶ Additionally, as females have a lower drug clearance rate, adverse reactions due to theophylline⁵³ and hypersomnia resulting from first-generation antihistamines and cetirizine occur more frequently in

females than males.⁵⁷ Asthmatic women using fluticasone dry powder inhalers complain of hoarseness and dysphonia more frequently than men do.⁵⁸ Estrogen inhibits osteoclast proliferation and bone turnover, so deficiency in this hormone in postmenopausal women makes them prone to developing steroid-induced osteoporosis.⁵⁹ Testosterone prevents the development of osteoporosis by directly acting on osteoblasts or after being converted to estrogen by aromatase.

SEX-SPECIFIC ASTHMA TREATMENT

Females

Female-specific asthma including perimenstrual asthma may require appropriate therapy such as oral contraceptives. Considering that asthma and other allergic diseases as well as adverse reactions to drugs occur more frequently in females, it is conceivable that DHEA, an androgen with a less virilizing effect, could be used as a treatment option for female-specific asthma. DHEA reduced the steroid requirement without significant adverse reactions, other than mild acne, in patients with systemic lupus erythematosus.⁶⁰ A phase IIa clinical trial of an inhalation formulation of synthetic DHEA sulfate EPI-12323 (Naturasone) found a significant inhibition of allergen-induced late airway reactions,⁶¹ suggesting its potential use in clinical practice.

Although DHEA is the crucial precursor for converting both testosterone and estrogen, DHEA administration increases circulating androgens in women.⁶² T lymphocytes and endothelial cells have high-affinity binding sites for DHEA. A previous study demonstrated that DHEA inhibits AHR/airway eosinophilia and that its effects are related to a decrease in IL-5 concentration in mice.⁶³ DHEA inhibits cell proliferation but maintains Th1 bias⁶⁴ and may also work through IL-10 production.⁶⁵ Furthermore, the antagonistic action of DHEA against glucocorticoid-induced Th2 deviation can probably occur through peroxisome proliferator-activated receptor- α .⁶⁶ DHEA inhibits airway smooth muscle proliferation and airway remodeling by inhibiting DNA binding of activator protein (AP)-1, and it may produce a steroid-sparing effect by suppressing AP-1-induced glucocorticoid resistance.⁶⁷ Moreover, DHEA inhibits production of TNF- α ⁶⁸ and neutrophilic inflammation,⁶⁹ through which it exerts a therapeutic effect on severe asthma associated with such factors. However, the long-term systemic use of DHEA may induce chronic heart failure by deleting ubiquinone through the inhibition of glucose 6-phosphate dehydrogenase and hydroxymethylglutaryl coenzyme A reductase activities.⁷⁰ Therefore, an inhaled preparation of DHEA is desirable for patients to avoid any unexpected serious adverse reactions.

Males

Serum DHEA-S level significantly correlates with IFN- γ level,²⁹ and men have a high serum DHEA-S level. Thus, allergic diseases do not frequently develop in men. However, the therapeutic

effectiveness of DHEA may be low because an increase in the IFN- γ /IL-5 ratio by DHEA is inversely related to serum DHEA-S level.⁶⁴ In that case, men would require treatment modalities that induce Th1 cells more strongly or act through different mechanisms. However, clinicians should remember that if the dosage of DHEA is excessively high, its therapeutic effect tends to decrease.⁶³ Because the dose of inhaled steroid correlates with the degree of decrease in serum DHEA-S level,³² DHEA replacement therapy would be ideal for asthma treatment in men with a decreased DHEA-S level detected through regular monitoring.

CONCLUSIONS

Females are more prone to suffer allergic asthma, to having difficulty controlling asthma symptoms, and to showing adverse responses to drugs. As asthma symptoms show cyclic changes depending on female hormone levels in many women of child-bearing age, the use of contraceptives in women may specifically help treat such perimenstrual asthma and severe asthma as well. Generally, testosterone seems to suppress asthma, and DHEA, a less virilizing androgen, may be effective for treating asthma. Evidence exists for the therapeutic and steroid-sparing effect of DHEA. However, further studies on the optimal dose and route of DHEA for each sex are needed. Monitoring of the serum DHEA-S level is necessary for patients with asthma who are receiving inhaled steroid treatment, and at least replacement therapy for patients with a low level of DHEA may be helpful for treating their asthma.

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