

# Asthma in pregnancy – from immunology to clinical management

## Asma in gravidanza – dall'immunologia alla gestione clinica

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### ABSTRACT

Asthma is one of the most common chronic medical conditions that may complicate pregnancy. Asthma influences the outcome of pregnancy and, vice versa, pregnancy affects asthma severity, but the underlying immunological mechanisms of this interaction are not fully understood. As a sign of pregnancy-induced immunotolerance, attenuation of allergic responses can be detected in controlled asthmatic pregnant patients; however non controlled asthmatic pregnant women show significant asthma-associated immune reactions that may, beside other factors, influence fetal growth. Generally, although uncontrolled asthma may increase the risk of adverse perinatal outcomes, women with well-controlled and adequately treated disease during pregnancy do not develop maternal or fetal complications.

**Keywords:** Asthma, clinical management, immunological interactions, inflammation, pregnancy.

### RIASSUNTO

L'asma è una delle patologie croniche più comuni che possono complicare la gravidanza. L'asma influenza il decorso della gravidanza e, a sua volta, la gravidanza influenza la gravità dell'asma; tuttavia il substrato immunologico che sottende a questa interazione non è ancora completamente delucidato. A riprova dell'immunotolleranza indotta dalla gravidanza si può rilevare un'attenuazione della reazione allergica riscontrabile nelle pazienti gravide con asma controllato; al contrario pazienti gravide con asma non controllato mostrano importanti reazioni immuni associate all'asma che, oltre tutto, influenzano la crescita fetale. In generale, sebbene un asma non controllato possa aumentare il rischio di eventi avversi perinatali, le donne con asma ben controllato e che hanno ricevuto un trattamento adeguato durante la gravidanza non sviluppano complicanze materne o fetali.

**Parole chiave:** Asma, gestione clinica, gravidanza, infiammazione, interazioni immunologiche.

### INTRODUCTION

Asthma is one of the most common chronic medical conditions that may complicate pregnancy, with a prevalence of 3.7 - 8.4% of all pregnancies [1]. Pregnant women with asthma represent a special challenge for asthma specialists and allergists. Asthma influences the outcome of pregnancy and, vice versa, pregnancy affects asthma severity, but the underlying immunological mechanisms of this interaction are not fully understood. Asthma represents a risk factor for several maternal and fetal complications, such as asthma exacerbations, use of steroids, hospitalizations due to asthma attacks, preeclampsia, gestational hypertension, preterm delivery, cesarean delivery, low birth weight, intrauterine growth restriction, and fetal death [2-7], posing a need for careful decision making and optimal training of physicians treating these patients. Adequate management of asthma and maintenance of optimal asthma control during pregnancy decrease perinatal risk [8,9].

### The effect of asthma on pregnancy

Pregnancy is characterized by immunological tolerance (physiological immunosuppression) that blunts maternal immune response against paternal antigens expressed by the fetus [10]. Physiological pregnancy has been described as a Th2-dominated state, and current studies show that proliferating regulatory T cells (Tregs) may have a key role in the maintenance of peripheral tolerance to paternal antigens during pregnancy [11]. Treg cells, however, exert an inhibitory effect on natural killer lymphocytes responsible for protection against viruses [12] that may contribute to increased susceptibility to viral

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Data di arrivo del testo: 15/2/2010 – Accettato dopo revisione: 30/03/2010

Multidisciplinary Respiratory Medicine 2010; 5(4): 259-263

infections (e.g. influenza), as observed with H1N1 influenza in pregnant women [13]. Diminished numbers of Treg cells in pregnancy were associated with immunological rejection of the fetus as well as preeclampsia and low fetal birth weight [14]. Asthma is traditionally considered as an allergic T helper cell 2 (Th2) type inflammation that leads to bronchial hyperresponsiveness, airway obstruction and – in some cases – tissue remodeling [15]. Immunological changes in asthmatic pregnancy are not well established. In a recent study we found signs of pregnancy-induced attenuation of allergic responses. Activated pools within CD4 and CD8 T cells were larger, and the number of natural killer T (NKT) cells was increased both in non-pregnant asthmatic and in healthy pregnant subjects (compared to non-pregnant healthy controls), but in (mostly well controlled) pregnant asthmatics no further lymphocyte activation was observed suggesting that the immunosuppressive effect of uncomplicated pregnancy may blunt the lymphocyte activation which characterizes asthma [16]. On the other hand, in our earlier study a significant amount of interferon (IFN)- $\gamma$  producing cells was detected in peripheral blood obtained from not well controlled asthmatic pregnant women and a significant negative correlation was revealed between the number of IFN- $\gamma$  positive T-cells and birth weight of newborns, pointing at fetal growth retardation related to active, asthma-associated maternal immune reactions [17]. In addition, considering another inflammatory marker, heat shock protein (Hsp)-70, higher circulating levels were detected in pregnant asthmatic women than in healthy pregnant women. Fetal birth weight is lower in pregnancies complicated with asthma, showing a relationship between asthmatic immune responses and altered fetal growth [18]. Supporting the possible adverse effect of asthmatic inflammation on pregnancy, in a recent database cohort of 13,100 pregnant asthmatics, a 35% increased risk of perinatal mortality was observed in the pregnancies of women with asthma [4]. Major factors contributing to this increased perinatal mortality might be maternal obesity and smoking, as well as uncontrolled asthma [5]. Another recent study of pregnant women with physician-diagnosed asthma evaluated their asthma control repeatedly during pregnancy based on symptom frequency and interference with daily activities and sleep, and reported hospitalizations and unscheduled clinic visits for asthma exacerbations. According to their results, the incidence of preterm delivery is higher among patients with inadequate asthma symptom control during the first part of pregnancy compared to patients with adequate asthma control, and patients who are hospitalized for asthma during pregnancy have a higher incidence of preterm delivery compared to asthmatic women without a history of hospitalization. Thus there may be a risk for preterm delivery posed by poorly controlled maternal asthma [8]. Maternal asthma is also known as a risk factor for the development of asthma in children [19].

### **Influence of pregnancy on the course of asthma**

Pregnancy has also an effect on the course of asthma. Asthma improves during pregnancy in about one-third, remains the same in another one-third, and worsens in one-third of pregnant women. More severe asthma before pregnancy represents a higher risk of worsening during pregnancy and there is a concordance between the courses of asthma during subsequent pregnancies [20]. Asthma-specific quality of life in early pregnancy is related to subsequent asthma morbidity during pregnancy [21]. Severity of asthma symptoms during pregnancy may also be influenced by fetal gender. Worsened asthma symptoms [22] and higher incidence of intrauterine growth retardation [23] were observed in pregnant asthmatics with female fetuses. On the other hand, obesity was also associated with an increased risk of asthma exacerbations during pregnancy [3]. In addition, maternal obesity without asthma influences also pregnancy negatively by increasing the risk for adverse perinatal outcomes (preeclampsia, gestational diabetes, intrauterine fetal retardation and fetal death) [24]. However, immunological mechanisms underlying alteration of the course of asthma during pregnancy or predicting biomarkers of worsening are largely unknown.

### **Management of asthma during pregnancy**

#### ***Diagnosis and monitoring***

Due to the bilateral interactions of asthma and pregnancy and alterations of asthma severity during pregnancy, establishing optimal asthma management during gestation often represents a special challenge for the attending physician. The diagnosis of asthma is usually known already before pregnancy. However, if first symptoms occur during gestation, reduced forced expiratory volume in one second (FEV<sub>1</sub>) or ratio of FEV<sub>1</sub> to forced vital capacity (FVC), together with a 12% or greater improvement in FEV<sub>1</sub> after inhalation of rapid acting beta-agonist, confirm the diagnosis of asthma. Testing bronchial hyperresponsiveness is contraindicated during pregnancy (because of the lack of safety data); thus women with a clinical picture of new-onset asthma without spirometric confirmation of the diagnosis should be treated for asthma during pregnancy [25]. Skin prick tests are not recommended during pregnancy (risk of systemic reactions), but specific IgE antibodies to suspected allergens may be evaluated [25]. Assessment of asthma control level in pregnant asthmatics is similar to the method applied in non-pregnant patients [7]. Fractionated concentration of nitric oxide present in exhaled breath (FE<sub>NO</sub>) has been evaluated as a simple and non-invasive tool for assessing airway inflammation in asthma [26]. Our recent study provided data supporting high reproducibility of FE<sub>NO</sub> measurement in pregnant subjects. According to the results pregnancy itself does not alter FE<sub>NO</sub> levels either in healthy or in asthmatic patients and FE<sub>NO</sub> levels of pregnant asthmatic patients correlate with the level of asthma control [27]. A single-blind trial of corti-

costeroid therapy based on either FE<sub>NO</sub> measurements or current guidelines showed lower daily dose of inhaled corticosteroid in the FE<sub>NO</sub> group [28]. Since reaching asthma control by using the lowest possible required dose is critical in pregnant asthmatics, exhaled NO measurement may have importance in this patient group.

### Treatment

Asthmatic pregnant patients should be educated about their disease and its treatment (Table I), as strongly recommended in the GINA guidelines [7]. Smoking cessation is necessary for asthmatic pregnant women, due to known adverse effects of smoking on mother's disease as well as the known higher risk for neonatal asthma in asthmatic pregnant women who smoke [29]. According to data on adverse effects of asthma medications in pregnancy, most of the findings are reassuring [25]. Many observational studies have shown no increased perinatal risks associated with the use of currently available inhaled beta-agonists and corticosteroids [30-33]. The use of bronchodilators during pregnancy was associated with an increased risk of gastroschisis among infants in one study [34]. Higher risk of cardiac defects was also observed in newborns of asthmatic pregnant women in one study [35]; however, asthma exacerbation itself during pregnancy may increase the risk of congenital malformations [36].

Generally, according to currently available safety data albuterol is the reliever medication of preference. Considering inhaled corticosteroids, budesonide is the preferred choice due to reassuring data in human pregnancies [32]. Among the long-acting inhaled beta-agonists, both formoterol and salmeterol may be used as add-on therapy in pregnant patients if warranted by symptoms occurring despite regularly used inhaled corticosteroid therapy. Leukotriene-receptor antagonists montelukast and zafirlukast seemed also to be safe during gestation, but the available human data are scarce [9]. In one recent study enrolling 180 asthmatic pregnant women taking montelukast, no increase in the rate of major congenital malformations was observed [37]. Pregnant patients with well-controlled asthma should continue taking their medications. Although

**TABLE I: MAIN PATIENT EDUCATIONAL TOPICS FOR ASTHMATIC PREGNANT PATIENTS**

Main patient educational topics	Description
General information	Basic information about asthma and its relationship to pregnancy Facts regarding mother and fetus safety
Use of inhaler devices	Demonstration of correct use of devices prescribed to the patient
Adherence to treatment	Necessity of regular visits and proper controller medication during pregnancy complicated with asthma
Environmental control measures to reduce exposure to allergens and irritants	Avoidance of known allergens and smoking
Self-treatment action plan	Written schedule for maintenance therapy and doses of rescue medication for increased symptoms; education about signs of asthma exacerbation and urgent or emergency help providers

in non pregnant and permanently well-controlled asthmatics the guidelines recommend consideration of a step down in therapy [7], in pregnant well-controlled patients the maintenance of controller treatment may be decided in order to reduce the risk of control loss. Therapy should be increased by one step in patients with asthma that is not well controlled (Table II). A two-step increase, a course of oral corticosteroids, or both should be recommended for women with asthma that is very poorly controlled (Table II) [25].

Monthly asthma control assessment is recommended for women who require controller therapy during pregnancy. Optimal obstetrical care of not well controlled asthmatic pregnant patients means more frequent ultrasonographic examinations (to monitor fetal growth, which can be affected by uncontrolled asthma) and assessment of fetal well-being (nonstress

**TABLE II: STEPS OF ASTHMA MAINTENANCE THERAPY DURING PREGNANCY**

Step	Preferred controller medication	Alternative controller medication
1	none	-
2	Low-dose inhaled corticosteroid	LTRA, cromolyn, theophylline
3	Medium-dose inhaled corticosteroid	Low-dose inhaled corticosteroid + LABA or LTRA or theophylline
4	Medium-dose inhaled corticosteroid + LABA	Low-dose inhaled corticosteroid + LTRA or theophylline
5	High-dose inhaled corticosteroid + LABA	-
6	High-dose inhaled corticosteroid + LABA + oral corticosteroid	-

*Definition of abbreviations:* LTRA, leukotriene-receptor antagonist; LABA, long-acting beta-agonist. From [25] with permission.

testing from the 32<sup>nd</sup> gestational week). During labor and delivery the use of asthma medications should be continued. Women who have received systemic corticosteroids during pregnancy are recommended to receive intravenous corticosteroids during labor and for 24 hours after delivery [25].

In conclusion, asthma is probably one of the most common chronic diseases complicating pregnancy and influencing its outcome. Generally, although uncontrolled asthma may increase the risk of adverse perinatal outcomes, women with well-controlled, adequately treated disease during pregnancy do not develop maternal or fetal complications. Good and

frequent communication between obstetrics, pulmonologists, allergist and general practitioners is a vital necessity of asthma treatment during pregnancy.

**ACKNOWLEDGEMENT:** This study was supported by the Hungarian Scientific Research Foundation (OTKA K- 68758). The authors thank Professor Michael Schatz from Kaiser-Permanente Medical Center, San Diego, CA for his kind permission to use data of Table II.

**CONFLICT OF INTEREST STATEMENT:** None of the authors has any conflict of interest to declare in relation to the subject matter of this manuscript.

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