

ASTHMA IN PREGNANCY

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ABSTRACT

Asthma is a common disease among pregnant women. Uncontrolled asthma may increase the risk of maternal and foetal complications, thus optimal asthma management is elemental during pregnancy. Therapy must aim to control the disease; asthmatic women with controlled asthma should continue taking their medications during pregnancy, and maintenance therapy should be increased if asthma is not controlled. Most of the asthma medications have no effects on foetal growth. Although oral corticosteroids may confer an increased risk of lower birth weight and congenital malformations, benefit-risk considerations still favour their use in patients with asthma exacerbations during pregnancy. This review summarises immunological changes characterising asthmatic pregnancy and the clinical implications of asthma management during pregnancy.

Keywords: Asthma, clinical implications, immunology, management, pregnancy.

INTRODUCTION

Asthma is one of the most common chronic diseases complicating pregnancy, affecting 3.7–13.9% of all pregnancies.^{1,2} Asthma influences the outcome of pregnancy, posing a risk for several maternal and foetal complications,^{3–8} and pregnancy also affects the natural course of asthma, causing deterioration of symptoms in one third of patients. Fortunately, both maternal and neonatal risks decrease with maintenance of optimal asthma control during pregnancy,^{9,10} thus appropriate asthma management is essential in these patients.

IMMUNOLOGICAL CHANGES IN HEALTHY PREGNANCY

In healthy pregnancies, the semi-allograft foetus is protected from maternal immune responses by physiological immune tolerance (Figure 1).¹¹ A trimester-dependent increase in regulatory T (CD4+CD25 high+; Treg) cell number has a key role in this process;¹² moreover, this increase is associated with physiological growth of the foetus.¹³ These cells inhibit the activation of effector T lymphocytes and natural killer (NK) cells, as well

as the differentiation of antigen-presenting cells.¹⁴ Diminished numbers of Tregs in pregnancy were associated with immunological rejection of the foetus, low foetal birth weight or preeclampsia.¹⁵ Of note, the inhibitory effect of proliferating Treg cells on NK cells¹⁶ contributes to increased susceptibility to viral infections during pregnancy, as observed in the H1N1 influenza pandemic in 2009.¹⁷ Healthy pregnancy is characterised by a subtle shift in T lymphocyte balance towards T helper (Th)2 phenotype, as a predominance of the Th1 cytokines causes spontaneous abortion.^{18,19} The circulating number of the proinflammatory Th17 cells was shown to be unaffected by healthy pregnancy,²⁰ but increased in pregnancies with adverse outcomes such as preterm labour²¹ and recurrent spontaneous abortion.²² Alterations of immune state during pregnancy may cause changes in the course of autoimmune diseases, e.g. systemic lupus erythematosus or rheumatoid arthritis.²³

IMMUNOLOGICAL CHANGES IN ASTHMATIC PREGNANCY

In the background of the usually transient and reoccurring symptoms, there is a persistent

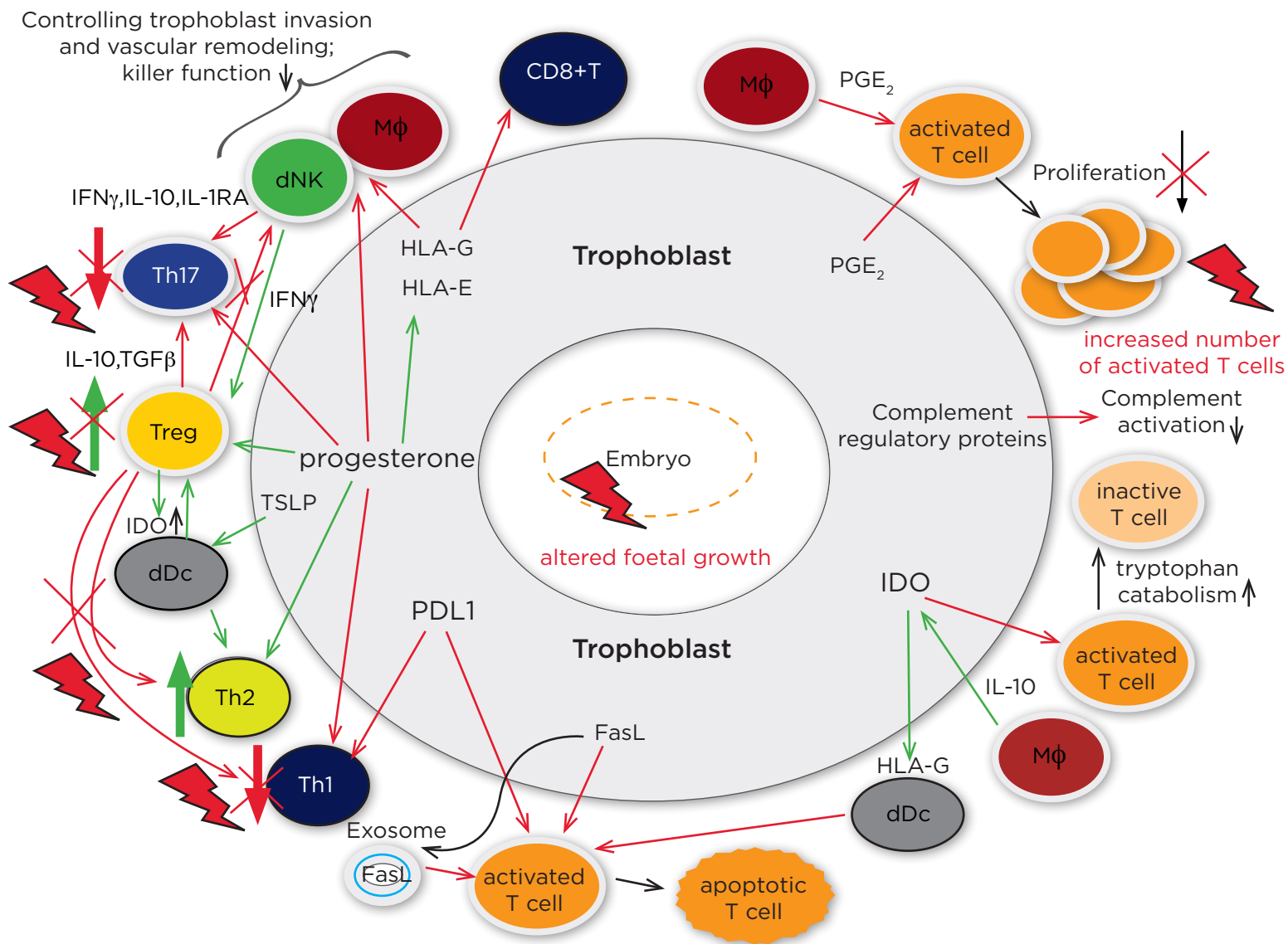


Figure 1. Alterations in the cellular mechanisms of maternal-foetal immune tolerance in asthmatic pregnancy.

(Th - T helper; Treg - regulatory T; dNK - decidual natural killer cell; Mφ - macrophage; dDC - decidual dendritic cell; CD - cluster of differentiation; PGE₂ - prostaglandin E₂; HLA - human leukocyte antigen; IL - interleukin; IDO - indoleamine 2,3-dioxygenase; FasL - Fas ligand; PDL1 - programmed cell death 1 ligand 1; TSLP - thymic stromal lymphopoietin; TGFβ - transforming growth factor β; IFNγ - interferon gamma; → stimulation/increase; → inhibition/decrease).

chronic inflammation in asthma,²⁴ in which Th2 type inflammation is elemental. Also abnormal Th17 immunity contributes to disease pathology, primarily in uncontrolled moderate to severe patients.²⁵ Expansion of these cells is accompanied by decrease in circulating Treg cell prevalence,^{26,27} which promotes airway eosinophilia, mucous hypersecretion, and airway hyperresponsiveness.²⁸

If the disease is well controlled, the physiological maternal immune suppression may attenuate the

allergic response in asthmatic pregnant women, but not in patients with uncontrolled asthma. 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 with non-pregnant healthy controls). However, in the mostly well controlled pregnant asthmatics, no further lymphocyte activation was observed, suggesting that the immunosuppressive effect of uncomplicated pregnancy may blunt the

lymphocyte activation that characterises asthma.²⁹ In contrast with this, in mostly uncontrolled asthmatic pregnant women, a substantial number of peripheral interferon (IFN)- γ and IL-4 producing T cells were detected, and a negative correlation was revealed between the numbers of these cells and birth weight of newborns, suggesting that foetal growth restriction (intrauterine growth restriction - IUGR) may be related to active, asthma-associated maternal immune reactions.³⁰ Similarly, circulating levels of heat shock protein Hsp70, which is an inflammatory marker, were higher in asthmatic than in healthy pregnant women, and foetal birth weight was lower in pregnancies complicated with asthma.³¹ Again in uncontrolled, symptomatic asthmatic women the Th1/Th2 cell ratio increased during pregnancy compared to healthy pregnant women, but remained unaltered in gestations of mostly well or partially controlled patients.²⁰ The physiologic elevation of peripheral Treg numbers was blunted during gestation of either symptomatic or asymptomatic asthmatic women; furthermore, the positive correlation between Treg numbers and birth weight of newborns was absent.¹³ In asthmatic pregnant women, an abnormal asthma-dependent Th17 elevation was also detected²⁰ (Figure 1, Table 1). In a recent *in vitro* study, a reduction in adaptive antiviral immunity was found in pregnant women with well controlled asthma, which may be related to the susceptibility to respiratory virus infections.³²

In healthy pregnancies, the normally increased oxidative stress is counterbalanced by increased antioxidant mechanisms;³³ however, in placentae of asthmatic women, more increased protein oxidation and lipid peroxidation were found together with more increased antioxidant capacity.³⁴ Also, circulating levels of antioxidants were elevated in moderate/severe asthmatic pregnant patients, suggesting a response to the high oxidative load induced by asthma during pregnancy.³⁵ Offset of this sensitive balance potentially contributes to the altered placental function and reduced foetal growth.

THE EFFECT OF MATERNAL ASTHMA ON PREGNANCY OUTCOMES

Due to the immunological and clinical changes, the risk of several maternal and foetal complications is higher in asthmatic pregnancy compared to healthy pregnancy; thus pregnancies in women with asthma need to be considered as high-risk

pregnancies.³⁶ Perinatal mortality increases by 35% according to a database cohort of 13,100 pregnant asthmatics,⁵ and prematurity and/or low birth weight seem to be the major contributing factors, which are associated with uncontrolled asthma, maternal obesity, or smoking.⁶ However, optimal asthma management may prevent the adverse events.⁶ The incidence of preterm delivery was higher among patients with inadequate asthma symptom control during the first part of pregnancy compared with patients with adequate asthma control, and it was higher among patients who were hospitalised for asthma during pregnancy compared with asthmatic women without a history of hospitalisation.⁹ Severe and moderate asthmatic pregnant women have a higher risk for small gestational age babies than those with mild asthma, according to a population-based cohort of 13,007 pregnancies in asthmatic women.³⁷ Maternal asthma was also associated with a higher risk of spontaneous abortion, and uncontrolled asthma increased the risk by 26%.³⁸ A recent meta-analysis of 40 publications (involving 1,637,180 subjects) found an increased risk of low birth weight, small for gestational age, preterm delivery, and preeclampsia associated with maternal asthma, however, active asthma management reduced the relative risk of preterm delivery.³⁹

Maternal asthma may increase the risk of congenital malformations in the nervous, respiratory and digestive systems;^{40,41} however, there are also population-based data that did not detect any teratogenic effect of maternal asthma.^{42,43} Finally, a multicentre, prospective, observational cohort study found that asthma also affects newborns' morphometry, as asthma severity was associated with an increased head circumference/birth weight ratio.⁴⁴ Asthma exacerbations during pregnancy are a particularly unfavourable issue because an exacerbation itself raises the risk of low birth weight⁴⁵ and congenital malformations.⁴¹ Maternal asthma also has long-term consequences for offspring health. In a recent cohort study, asthma was associated with an increased risk of infectious and parasitic diseases, diseases of the nervous system, ear, respiratory system and skin, and potentially (not confirmed in secondary analyses) of endocrine and metabolic disorders, diseases of the digestive system, and malformations in the offspring during childhood.⁴⁶

Table 1. The already established immunological changes in asthmatic pregnancy.

Authors	Chemical	Level of asthma control	Alteration	How they affect the situation
Bohács A et al. 2010 ²⁹	CD4 and CD8 T cells, B cells, NK and NKT cells	Controlled	No further lymphocyte activation in AP compared either with ANP, or HP women.	Lower average birth weight in the AP than in the HP group.
Tamási L et al. 2005 ³⁰	IFN- γ + and IL-4+ T cells	Mostly uncontrolled	Culminating proliferation of IFN- γ + and IL-4+ T cells in AP group. Increased IFN- γ + /IL-4+ T cell ratio in AP compared with HP group.	Numbers of IFN- γ + and IL-4+ T cells correlated negatively with maternal PEF as well as birth weight. Patients on higher doses of maintenance therapy had higher numbers of IFN- γ + and IL-4+ T cells. Pregnancy-related change in asthma severity was not associated with any T cell subsets.
Tamási L et al. 2010 ³¹	Hsp-70	Satisfactory level of asthma control (mean ACT score 20.66 \pm 2.24)	Increased serum levels in AP than in HP group.	Lower average birth weight in the AP than in the HP group. ACT scores showed a trend towards an increase in Hsp70 levels with the loss of asthma control.
Toldi G et al. 2011 ²⁰	Th1, Th2, Th17, Treg, IL-17-producing CD8+ and NK cells	Well controlled in most cases (median ACT score: 22)	Lower prevalence of Th1 cells and elevated prevalence of Th2 cells in HP, ANP and AP than in HNP group. As a result, similar Th1/Th2 ratio in HP and AP groups. Higher Th17 prevalence in ANP than in HNP as well as in AP than in HP group. Higher prevalence of Treg cells in HP than in HNP or AP groups. As a result, higher Th17/Treg ratio in AP than in HP group.	Similar median birth weights in AP and HP groups. No correlation between any of the lymphocyte subsets and ACT values, FeNO levels or neonatal birth weight in any group.
Bohács A et al. 2010 ¹³	effector/memory and naive CD4+ T cells, Treg, NK, NKT and iNKT cells	Median ACT scores (quartiles): 20.5 (18-24) in AP and 19 (17-22) in ANP group	Lower prevalence of Treg and higher prevalence of iNKT cells in AP compared with HP women. Higher naive and lower NK and effector/memory T cell prevalence in AP than in ANP group.	Positive correlation between Treg prevalence and foetal birth weight in HP, but not in AP group. Only 3 newborns to healthy and 14 newborns (mostly girls) to asthmatic mothers had birth weight below 3 kg. Lower PEF, ACT scores, and birth weight in AP patients with female foetuses. In the AP group, lower prevalence of naive T cells in obese patients.
Vanders RL et al. 2013 ³²	IFN- γ , IL-10 and IL-17 from culture supernatant of PBMCs stimulated <i>in vitro</i> by PHA or a strain of the 2009 pandemic swine influenza	Well controlled	Following PHA stimulation: enhanced IL-17 response in AP, HP and ANP than in HNP group; reduced IFN- γ response in AP than in HNP group. Following infection with influenza: reduced IFN- γ and IL-10 response in AP and HP than in HNP group. Differences in IFN- γ , IL-10 and IL-17 persisted for at least 6 months post-partum.	Asthma is suggested to lead to an impaired adaptive immune response during pregnancy.

AP: asthmatic pregnant; HP: healthy pregnant; ANP: asthmatic non-pregnant; HNP: healthy, non-pregnant; CD: cluster of differentiation; Th: T helper; Treg: regulatory T; NK: natural killer; iNKT: invariant NKT; IFN γ : interferon gamma; IL: interleukin; Hsp: heat shock protein; PBMC: peripheral blood mononuclear cell; PHA: phytohemagglutinin; PEF: peak expiratory flow; ACT: Asthma Control Test; FeNO: fractional exhaled nitric oxide.

PREGNANCY-INDUCED CHANGES IN ASTHMA CONTROL

As a consequence of pregnancy-associated immunological and clinical changes, asthma improves in approximately one-third, remains the same in another one-third, and worsens in one-third during gravidity, but the underlying immunological mechanisms are mostly unknown and biomarkers predicting deterioration are lacking. However, there are some clinical signs that can draw the attention of the treating physician. The risk of asthma worsening during pregnancy increases with disease severity before pregnancy, and there is a concordance between the courses of asthma during consecutive pregnancies.⁴⁷ Similarly, asthma-specific quality of life in early pregnancy is related to subsequent asthma morbidity during pregnancy.⁴⁸ Asthma exacerbations are more common and more severe in pregnant women who smoke.⁴⁹ Interestingly, female foetuses also cause greater risk for worsening symptoms^{13,50} and IUGR.^{13,51} Obesity is associated both with asthma exacerbations and non-pulmonary complications during pregnancy (e.g. preeclampsia, gestational diabetes, and gestational hypertension).⁴ Lower prevalence of naive T cells observed in obese compared to non-obese asthmatic pregnant patients may be a sign of dysfunctional pregnancy-induced immune tolerance in obese patients.¹³

MANAGEMENT OF ASTHMA DURING PREGNANCY

Diagnosis and Monitoring

The diagnosis of asthma is usually known before pregnancy; however, there are a further proportion of pregnant women who possibly have asthma.² In the latter case, reduced forced expiratory volume in one second (FEV1), or ratio of FEV1 to forced vital capacity (FVC), and a 12% or greater improvement in FEV1 after inhalation of rapid acting beta-agonist confirm the diagnosis. Lacking safety data, the bronchial hyperresponsiveness test is contraindicated during pregnancy, thus women with a clinical picture of new-onset asthma without spirometric confirmation of the diagnosis should be treated for asthma during pregnancy. Skin prick tests are not recommended due to risk of systemic reactions, but blood tests for specific IgE antibodies to suspected allergens may be evaluated.⁵²

Monthly assessments are required in all asthmatic pregnant women. Beyond asthma control evaluation, physical examination and spirometry, evaluation of arterial oxygen saturation is important: at least 95% measured by pulse oximetry is recommended⁵² because, due to pregnancy, induced physiological hyperpnoea^{53,54} and even mild maternal hypoxaemia may represent respiratory compromise during pregnancy. Fractioned concentration of nitric oxide present in exhaled breath (FENO) reflects airway inflammation in asthma.⁵⁵ This method has been shown to be applicable also in asthmatic pregnant patients;⁶⁰ contrarily, a recent longitudinal study found large intrasubject variability in pregnant asthmatics, regardless of the degree of asthma control.⁵⁷ However, asthma exacerbation rate, such as neonatal hospitalisations, could be reduced by treating pregnant patients according to a FENO-based treatment algorithm.⁵⁸

Regarding obstetrical care, ultrasonographic examinations are recommended in the first trimester to confirm the accuracy of the estimated due date, anytime after recovery from a severe exacerbation and serially from the 32nd gestational week (together with nonstress testing), in case of suboptimally controlled or moderate to severe asthma, to monitor foetal growth and wellbeing.⁵⁹

Treatment

Patient education

Maintaining control of the disease is essential but many patients do not use any reliever or prophylactic medications during pregnancy, even if their asthma is poorly controlled.² Therefore, pregnant asthmatics should be better educated about their disease and possible risks regarding maternal and foetal outcomes, such as their avoidance by reducing exposure to allergens, regular visits, proper treatment, and correct use of devices; furthermore, they need to be equipped with a written self-treatment action plan.^{8,52,60}

Approximately one third of pregnant asthmatic women smoke,⁶¹ which increases exacerbations,⁴⁹ asthma symptoms, foetal growth abnormalities,⁵⁴ and neonatal asthma as well.⁶² Moreover, asthma combined with cigarette smoking increases the risk of preterm birth and urinary tract infections to a greater degree than with either exposure alone.⁶³ Thus, smoking cessation during pregnancy is indispensable.

Pharmacological therapy

Because safety data of asthma medications in pregnancy are, in general, reassuring,⁵² pregnant women with well controlled asthma should continue taking their medications in order to reduce the risk of loss of control. If asthma is poorly controlled, therapy should be increased by one or more steps similarly to the treatment of non-pregnant asthmatic patients.⁵² The required doses are, in general, also similar to that of non-pregnant patients.

Based on current data in human pregnancies, albuterol is the reliever medication of choice, and budesonide is the preferred controller treatment.^{64,65} However, no increase in adverse pregnancy outcomes has been reported with beclomethasone or with fluticasone.⁶⁶ In addition, recent cohort showed no association between any dose of inhaled corticosteroid (ICS) use and perinatal mortality;⁶⁷ thus any ICS that achieved optimal control before pregnancy should be pursued during gestation.⁶⁶ Observational studies of inhaled corticosteroids and inhaled beta-agonists showed no increase in perinatal risks or congenital malformations.⁶⁸⁻⁷² Long-acting inhaled beta-agonists (formoterol and salmeterol) can be used as add-on therapy if symptoms persist in spite of the already received ICS treatment. In a large Canadian cohort of pregnant women with asthma, no increased prevalence of low birth weight, preterm birth or small for gestational age was found for LABA use and ICS doses <125 µg/day.⁷³ Leukotriene-receptor antagonists also seem to be safe during gestation; in one study enrolling 180 asthmatic pregnant women taking montelukast, no increase in the rate of major congenital malformations was observed.⁷⁴

However, there are also data about possible adverse effects of asthma medication during pregnancy. The use of bronchodilators was associated with an increased risk of gastroschisis,⁷⁵ cardiac defects,⁷⁶ oesophageal atresia and omphalocele,⁷⁷ and anti-inflammatory use was associated with anorectal atresia and omphalocele.⁷⁷ But the role of asthma itself could not be excluded; hence these findings may be a consequence of maternal asthma severity and related hypoxia rather than medication use.⁷⁷ But systemic corticosteroid use may indeed adversely affect pregnancy outcomes, as it was associated with gestational hypertension, preeclampsia, preterm birth, lower birth weight, and congenital malformations.^{72,78,79}

Acute asthma exacerbations

Acute asthma exacerbations may be prevented with optimal treatment, avoidance of trigger factors (e.g. viral infection),⁴⁵ and greater perceived control of asthma,⁸⁰ which is extremely important during pregnancy. Even so, asthma exacerbations occur in about 20% of asthmatic pregnant women primarily in the late second trimester, with approximately 6% of women needing hospitalisation.⁴⁵

Therapy of acute asthma during pregnancy is similar to that in non-pregnant state. In the first 48 hours of an exacerbation, 120-180 mg/day of oral prednisone (or equivalent) are recommended in 3 or 4 divided doses, then 60-80 mg/day until PEF reaches 70% of predicted or personal best, followed by 7-14 days of tapering. For outpatient burst, 40-60 mg/day for 3-10 days may be sufficient, followed by 7-14 days of tapering.⁵⁹ Effective, rigorous treatment is important for the health of both the mother and foetus;⁵³ however, in everyday clinical practice, pregnant asthmatics are less likely to receive appropriate treatment with corticosteroids.⁸¹ Status asthmaticus is a life-threatening disorder in obstetric patients; however, there are reports of excellent pregnancy outcomes after mechanical ventilation started due to severe respiratory acidosis in acute asthma exacerbation during pregnancy.⁸²

CONCLUSION AND SUMMARY

Asthma is one of the most common chronic diseases complicating pregnancy. Although uncontrolled asthma may increase the risk of maternal and foetal complications, women with adequately-treated and well-controlled disease during pregnancy do not appear to be at increased risk. The difference is caused by the physiological function of pregnancy-induced immune tolerance that may attenuate inflammation in controlled asthmatic pregnant patients. Thus, controlling asthma during pregnancy with appropriate therapy is essential. Effective patient consultations with treating physicians and frequent communication between obstetricians, asthma specialists, and general practitioners are important. Most of the asthma medications have no effects on foetal growth. Although taking oral corticosteroids during pregnancy may confer an increased risk of lower birth weight and congenital malformations; benefit-risk considerations still favour their use in patients with asthma exacerbations.

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