

# Evaluation of asthma course in pregnancy

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## ABSTRACT

The prevalence of asthma has been rising in recent decades. It is the most common disease among pregnant women and affects ca. 12% of this population. The course of asthma in pregnancy may change. In 1/3 of patients, it worsens; in 1/3 of patients, the symptoms are milder; in 1/3 of patients, it remains unchanged. Well-controlled asthma decreases the risk of pregnancy complications. Uncontrolled and severe asthma increases the risk of congenital malformations and obstetrical complications for both mother and baby. Exacerbations may also contribute to poor pregnancy outcomes. These occur mostly either in the first or in the second trimester. The most common triggers are viral infections and treatment non-compliance. The key to maintaining and gaining control of asthma is active treatment of asthma and its exacerbations.

**Key words:** asthma; pregnancy; asthma exacerbations; asthma treatment; asthma diagnosis

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## INTRODUCTION

The prevalence of allergic diseases and asthma has been rising in recent decades, reaching 5% of the adult, and 10% of the child and teenage population in Poland. Asthma is the most common disease complicating pregnancy, which affects 12% of pregnant women [1], and may lead to poor maternal and neonatal outcomes, especially in severe, uncontrolled, or inappropriately managed cases [2]. Likewise, pregnancy, by leading to multiple changes in the organism, influences the course of asthma. It is believed that the course of asthma during pregnancy improves in approximately one third of patients, in one third the course of the disease remains stable, and in one third it worsens. Worsening usually affects patients with uncontrolled and severe asthma, however it can also occur in patients with well-controlled symptoms [3]. Pregnant women with asthma need multidisciplinary and careful management.

The aim of this study is to summarize current knowledge on the bilateral relationship between asthma and pregnancy, and to sum up any recommendations concerning the management of asthma in pregnancy, as this remains a challenge in many aspects.

### The possible influence of physiological pregnancy changes on the course of asthma

Developing pregnancy triggers many adaptive changes in the organism. Changes in the anatomical, hormonal, and

immune system are particularly important for the control of asthma.

Anatomical changes in physiological pregnancy include: edema, increased vascularity in the upper respiratory tract, mucosa, and bronchodilation. The diaphragm is displaced, leading to changes in breathing, from a respiratory to abdominal pattern. Tidal volume (TV) and inspiratory capacity (IC) increase, while functional residual capacity (FCR), total lung capacity (TLC) and vital capacity (VC) decrease during the course of pregnancy. Forced expiratory volume in one second (FEV1), peak expiratory flow (PEF) and airway resistance remain unchanged [4, 5].

Other changes in the respiratory tract include an increase in the respiratory rate and oxygen consumption (for approximately 20%). Eventually, PaO<sub>2</sub> (partial pressure of oxygen) increases to the values 100–105 mm Hg, PCO<sub>2</sub> (partial pressure of carbon dioxide) decreases to the values 27–32 mm Hg. The resulting alkalosis leads to renal loss of bicarbonates and to a decrease of bicarbonates blood concentrations to the values between 18–21 mEq/L (Tab. 1). Even a small rise in pCO<sub>2</sub> concentrations (above 35 mm Hg) may indicate respiratory failure and may lead to fetal acidosis. A decrease in PaO<sub>2</sub> concentration below 70 mm Hg, indicates maternal hypoxemia and may also lead to fetal hypoxemia [4, 5].

Pregnancy leads to intensive hormonal changes. The blood concentration of many hormones rises. A two-fold change is observed in cortisol, a nine-fold change in pro-

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**Table 1. Reference ranges for arterial blood gases in pregnancy [5]**

Investigations	Pregnant
pH	7.40–7.45
pCO <sub>2</sub> <sup>2</sup> mmHg	27–32
pO <sub>2</sub> <sup>1</sup> mmHg	100–105
Base excess	No change
Bicarbonate (mmol/l)	18–21
Saturation	95–98%

<sup>1</sup> Pa O<sub>2</sub> partial pressure of oxygen; <sup>2</sup> PaCO<sub>2</sub> partial pressure of carbon dioxide

gesterone, and a 100–1,000 fold in estrogens serum concentration. The increase in cortisol and progesterone should potentially lead to bronchodilatation; however, due to the competitive affinity of the above-mentioned hormones to the glucocorticoids receptor, the effect may be limited [5, 6].

Immunological changes in lymphocyte proportions during pregnancy, described as Th<sub>2</sub> domination, may predispose to asthma exacerbations [5, 7]. Moreover, to prevent a maternal response to fetal antigens, the concentration of Th regulatory cells increases. This state results in decreased activation of effector lymphocytes T and natural killers (NK), which, in turn, leads to immunosuppression [7]. This increases susceptibility to viral infections and elevates the risk of possible complications if infection occurs [6]. One of the studies confirmed that the co-existence of asthma and pregnancy may predispose respiratory and urinary tract infections [8].

### The influence of asthma on the course of pregnancy

Correspondingly, asthma may influence the course of pregnancy in numerous ways.

An association between asthma and gestational diabetes, perinatal hemorrhage, placental defects [2], pre-eclampsia [9], and congenital defects including cleft palate and gastroschisis [10], have been confirmed in several meta-analyses. Some studies indicated a risk of cesarean section [2], preterm birth [11], low birth weight, longer hospitalization of the newborn and even newborn death [12]. Possible mechanism of mentioned complications include hypoxia, maternal inflammation, changed uterine smooth muscle relaxation, reduction of placental 11 beta hydroxysteroid dehydrogenase enzyme and drug (mainly betamimetics) influence [10, 11], and is mostly linked with exacerbations [11]. Many authors and guidelines suggest that the complications may be prevented if appropriate effective treatment is used [11, 13]. The latter was confirmed in research from recent years, in which women with diagnosed asthma were enrolled in the programme before 18 week of gestation and obtained active management. This consisted of monthly visits with objective assessment, including spirometry, fractional exhaled nitric oxide (FENO) and

the adjustment of medication. A reduction in the prevalence of uncontrolled asthma of 80% was observed. Achieving good asthma control prevented most of the previously mentioned complications. However, the study confirmed that a small, but significantly higher, risk of pre-eclampsia and small for gestational age (SGA) is associated with asthma, despite good control [3]. The risk of SGA increases with increased asthma severity.

### Diagnostic tests in pregnancy

Proper diagnosis and evaluation of asthma control is crucial, particularly during pregnancy. General approach to asthma diagnose in pregnancy is the same as in non-pregnant patients. Tests generating a risk of pregnancy complications (provocation tests and skin prick tests) are contraindicated during the whole course of pregnancy [4]. Acceptable tests are shown in a Table 2. Lung function tests are considered to be safe during pregnancy. Interpretation may be difficult, especially during the third trimester of pregnancy [14], due to associated physiological changes. One recent study demonstrated moderate changes in the pulmonary function. FEV1 declined significantly in second semester (mean 139 mL), then improved significantly in the last weeks of gestation (mean 51 mL higher to baseline). FVC and FEV6 changed insignificantly. Authors suggest that FEV6 may be used in asthma monitoring during pregnancy as it correlated positively with FVC. Nevertheless, changes in pulmonary function were not significantly associated with changes in asthma control [15]. PEF remains a valuable test during pregnancy. It should range between 380–550 L/min, but each asthmatic individual needs to establish his or her best effort. Maintaining levels > 90% of personal best value is considered optimal control [4]. Contraindications

**Table 2. Diagnostic tools in pregnancy**

Diagnostic tools in pregnancy	Remarks	Contraindications
PEF	useful/no changes, normal values described in the text	pre-eclampsia, cervix insufficiency
Spirometry	useful, problematic evaluation in advanced pregnancy,	pre-eclampsia, cervix insufficiency
FENO	useful	no contraindications
Blood gases	changes in normal values	no contraindications
Oximetry	changes in normal values	no contraindications
Provocation tests	–	generally contraindicated
SPT, ICT	–	generally contraindicated

**Table 3. Main points for good asthma management in pregnancy on the basis of a GINA report [13]**





ICS — inhaled glucocorticosteroids; GCS — glucocorticosteroids;  
SABA — short acting betamimetics

for lung function testing include cervix insufficiency and pre-eclampsia [14].

Furthermore, the FENO test was found to be a useful diagnostic tool, and was proven to help in gaining asthma control, if used with monthly control [16]. Moreover, multi-disciplinary management [14] and asthma control test were also proven to be useful during pregnancy. The latter test correlates well with actual asthma control.

### Asthma treatment in pregnancy, peripartum and lactation

#### Pregnancy

Despite constant concern about medication safety in pregnancy, asthma treatment is generally consid-

**Table 4. Treatment of asthma in pregnancy [1, 13]**

Step 1	<b>ICS (small dose)*</b> or none
Step 2	<b>ICS (small dose)*</b> or LTRA* or theophylline
Step 3	<b>ICS (small dose) + LABA*</b> or <b>ICS (medium dose)*</b> or <b>ICS (high dose)*</b> or <b>ICS small dose + LTRA*</b> or ICS small dose + theophylline
Step 4	<b>ICS (medium or high dose) + LABA*</b> <b>ICS high dose + LTRA*</b> ICS high dose + theophylline add tiotropium
Step 5	<b>Higher level care*</b> <b>oral glucocorticost eroids*</b> add tiotropium

\*Emboldened text suggests more suitable therapeutic option in pregnancy

ered safe. Principals are adequate to those concerning non-pregnant patients (Tab. 3, Tab. 4). The authors agree that the treatment must be intensified if asthma control is insufficient, as complications of undertreated asthma markedly exceed the possible, but not fully proven, side effects of the treatment (Tab. 5). The basis of treatment are inhaled glucocorticoids (ICS). Other drugs including ipratropium, leukotriene receptor antagonists (LTRA), short and long acting betamimetics (SABA, LABA), systemic glucocorticosteroids and omalizumab are also accepted in treatment, particularly in partly and uncontrolled asthma. Theophylline is not recommended to be used in pregnancy due to possible side effects. There is no

**Table 5. Treatment in pregnancy**

Treatment in pregnancy	Former FDA class	Possible side effects	Studies confirming occurrence of malformations	Remarks	Studies confirming safety of drugs
<b>Betamimetics</b>	C	Cleft lip and palate, omphalocele	Garne [10]	Meta-analysis of Eltonsy indicates defects both in studies concluding on safety and those asserting side effects of the treatment [17]	Eltonsy [18]
<b>Inhaled Glucocorticosteroids</b>	B/C	Musculoskeletal and heart defect for large doses	Blais [19]	Defects confirmed only for large doses of inhaled GCS	Garne [10]
<b>Systemic glucocorticosteroids</b>	C	Preterm birth, low birth weight, pre-eclampsia	Gregersen [20]	Mentioned findings should be balanced against severe asthma control	–
<b>Antileukotriens</b>	B	No connection	–	Short observation period	Bakhireva [21]
<b>Antimuscarinic agents</b>	B (ipratropium)	–	–	–	–
<b>Omalizumab</b>	B	No connection	–	Short observation period	Namazy [22]
<b>Mepolizumab</b>	–	–	–	–	–

ISC — inhaled glucocorticosteroids; LABA — long acting betamimetics; LTRA — acting betamimetics

sufficient data concerning tiotropium and mepolizumab in pregnancy.

Although guidelines on asthma treatment are easily accessible, most studies confirm a tendency to reduce treatment in pregnant women.

Up to 40% of patients declared to give up treatment after getting pregnant without consultation with a doctor [6]. The declarations mentioned may be partly confirmed by a Dutch study using a large database, comprising of detailed data on prescriptions. It shows a clear tendency for a reduction in the number of prescriptions issued after a diagnosis of pregnancy, which may indicate a decline in treatment after getting pregnant. This phenomenon may partly be the result of a milder course of asthma during pregnancy [23]. In addition, the problem of under-treatment is related to medical personnel, as pregnant asthmatics were significantly less likely to be given oral steroids, either in the emergency department or on discharge from hospital, than non-pregnant women [9], regardless of recommendations and results of studies that concluded on the relative safety of systemic GCS use for asthma exacerbations [12]. In the study cited, the use of systemic GCS was not related to poor perinatal outcomes, except for an increases rate of caesarean delivery.

Proper education on the treatment and safety of both patients and physicians may play an essential role in the improvement of asthma treatment during pregnancy.

### Peripartum

Although exacerbations of asthma in peripartum period are rare, regular treatment should be maintained to avoid exacerbations. Hyperventilation [13] and drugs indicated due to obstetric and anesthetic management of labour may influence asthma and cause bronchospasm [24]. Short acting betamimetics are drugs of choice for peripartum bronchospasm [4, 13]. Neonates require blood glucose control for the subsequent 48 hours after exposure to excessive doses of mentioned drugs, to detect possible hypoglycemia [13]. Specification and safety of the most frequently used drugs in peripartum period is enclosed in Table 6.

### Breastfeeding

Although studies concerning safety of anti-asthmatic drugs are limited, most of the drug groups are considered safe in lactation. For inhaled glucocorticosteroids (budesonide, fluticasone) infant exposure is far below the therapeutic level for an infant. Available in vitro studies for ciclesonide predict undetectable exposure of infant [25]. Inhaled betamimetics are accepted during breastfeeding as their concentrations in mothers' blood remain low. [25, 26]. Antileukotrienes, anticholinergic agents and omalizumab are accepted if necessary for asthma control and the excretion into milk or bioavailability (omalizumab) is suggested to be minimal [27]. Among oral glucocorticosteroids prednisolone is preferred to avoid double peak of parent medicine and

**Table 6.** Drugs used in peripartum period [24]

Group of drugs	Drugs safe in asthma	Drugs contraindicated in asthma
<b>Induction of labour</b>	In some cases drugs may be administered with caution eg. oxytocin	generally contraindicated
<b>Analgesia</b>	opioids administered with caution (risk of bronchoconstriction)	contraindicated in actively wheezing patient and in respiratory distress
<b>Anesthesia</b>		
<b>Epidural anesthesia</b>	opioids	
	local anesthetics	avoid high and dense level of anesthesia due to possible impairment of accessory respiratory muscles
<b>General anesthesia</b>	only if regional anesthesia is contraindicated	
<b>Intravenous</b>	ketamine	
	propofol	
<b>Volatile halogenated agents</b>	isoflurane	
	sevoflurane	
<b>Miorelaxants</b>	pancuronium	atracurium
	cis-atracurium	
	rocuronium	
<b>Other treatment</b>		betablockers
		ergot alkaloids

metabolite. The amount of drug excreted in milk remains low up to dose 80 mg [25].

### Patophysiological factors influencing the course of asthma during pregnancy

#### *Exacerbations*

Exacerbations of asthma during pregnancy represent a significant problem that may lead to unfavourable pregnancy outcomes. About 5 to 20% of asthmatic pregnant women require medical intervention due to the occurrence of exacerbations of asthma during pregnancy [9]. It has been suggested that well-controlled asthma, together with no history of previous exacerbations and no prescribed controller medication, is associated with a lower risk of exacerbations during pregnancy [28]; however, these may occur in up to 37% of pregnancies complicated by well-controlled asthma, and 40% of these exacerbations may be severe [3].

In most of the studies, exacerbations occurred in the second trimester of pregnancy [9]. However, in one recent study, exacerbations were detected most frequently during the first trimester of pregnancy [3]. Moreover, Blais et al. [29] confirmed the risk of congenital malformation and its association with exacerbations in 19% in of pregnancies during the first trimester. These findings may indicate a need for the intensification of treatment and management of asthma preconceptionally.

The most important trigger of exacerbations are infections, to which pregnant women are more susceptible due to adaptive changes in the immune system. Respiratory tract infections are the most frequent of these [8]. It was also confirmed that both pregnancy and asthma raise the risk of AH1N1 influenza [30]. Furthermore, influenza vaccination in pregnant asthmatics increased the improvement of the condition by 50%, in comparison with 15% in the patients who had not been vaccinated [31].

Another important factor for exacerbations is lack of treatment compliance [9]. Further factors include inadequate prenatal care, lack of or inappropriate GCS treatment, and smoking [6].

Some authors consider obesity and excessive weight gain in pregnancy a risk factor for the exacerbation of asthma in pregnancy. Furthermore, an increased risk of gestational diabetes has been noticed in the group of patients with the co-morbidities of asthma and obesity [6].

The occurrence of severe exacerbations creates a risk of pre-term birth, small for gestational age [6] and pre-eclampsia [3, 6].

#### *Toxins and allergens exposure*

Smoking, both active and passive, is an underestimated factor influencing the course of asthma during pregnancy. About 15% of pregnant women are active smokers [32];

**Table 7. Side effect of smoking in pregnancy**

• placenta previa
• abruptio placentae
• premature rupture of the membranes,
• pre-term birth
• intrauterine growth restriction
• sudden infant death syndrome

another 30% are passively exposed to cigarette smoke [33]. Data from the United States shows that from 6 to 30% of pregnancies complicated with asthma are also complicated by active smoking [12]. Another study found more smokers among the group of pregnant women with asthma than among pregnant women without asthma [6].

Smoking causes many well recognised pregnancy complications [32] (Tab. 7); moreover, in pregnant women with asthma, it increases the risk of severe exacerbation and risk of urinary tract infection and pre-term birth [34].

A few studies examined the influence of atopy on the course of asthma in pregnancy. The research of Stenius-Aarniala, from 1988, found a more frequent occurrence of exacerbations in non-atopic asthma.

#### *Other factors*

Some minor factors may also contribute to a worsening of asthma control during pregnancy or may additionally burden pregnancy.

The influence of psychological stress on the occurrence of exacerbations during pregnancies with asthma has been investigated in many studies. Some of them indicate that anxiety, and a perception by the patient of the asthma as being uncontrolled, may influence exacerbations and be a risk factor for a cesarean section. A more frequent occurrence of depression in pregnancies complicated by asthma exacerbations was confirmed by the Tata research, cited by Murphy [6].

However, some factors are found to be questionable.

No association was found between GERD and asthma severity during pregnancy. A possible reason for this phenomenon may be related to an equal frequency in the presentation of GERD in pregnant and non-pregnant populations [35].

A few studies have suggested that fetal sex influences the course of asthma during pregnancy, with the course of asthma worsening with a female fetus. However, the data is inconsistent.

#### **Education**

Many guidelines point out the importance of education in asthma management and control [13]. This may be even more

important during pregnancy, as up to 80% of female patients attempting to conceive are concerned about the influence of therapy on the fetus, and up to 40% cease treatment without consultation with a doctor. Pre-conceptional education, with an emphasis on treatment and symptoms of uncontrolled asthma, may play an important role in asthma management [6].

### Summary

Management of asthma during pregnancy remains a challenge in everyday practice. The essentials of good asthma management include proper education and active treatment of patients. Frequent and accurate monitoring is vital to prevent, detect and treat exacerbations, and other conditions influencing the course of asthma. Gaining and maintaining good asthma control may prevent adverse perinatal outcomes for both mother and baby.

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