

# ASTHMA IN PREGNANCY – DON'T LOSE CONTROL

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## ABSTRACT

Asthma is the most common chronic medical condition encountered in pregnancy. The clinical course of asthma may change during pregnancy and severe asthma carries the risk of acute exacerbation. Uncontrolled asthma is associated with adverse pregnancy outcomes and can be avoided by timeously adjusting treatment according to current guidelines. Asthma control should be reassessed throughout pregnancy. Treatment should not be limited to pharmacotherapy, but also include patient education and treatment of comorbid conditions.

## INTRODUCTION

Asthma is the most common chronic disease in pregnancy. In general, a favourable outcome may be anticipated. Severe or uncontrolled asthma, however, has been associated with adverse pregnancy outcomes. Optimal medical management can limit the risk for exacerbations and improve fetal outcomes.

## DEFINITION

Asthma is a chronic inflammatory disease of the airways, characterised by increased airway responsive-

ness to multiple stimuli. It is accompanied by episodic disease with paroxysms of dyspnoea, cough or wheezing, associated with airflow limitation that is usually reversible with treatment or resolves spontaneously. This airflow limitation is sometimes only partially reversed and airway remodelling is thought to occur in those with long-standing uncontrolled inflammation. Asthma is divided into allergic and idiosyncratic types.

## Assessment of severity

During pregnancy, it is of the utmost importance to monitor asthma control and adjust treatment accordingly. Level of asthma control is classified in Table I.<sup>1</sup>

## EPIDEMIOLOGY

Asthma is a worldwide health problem, with an increasing prevalence, occurring in 3.4-8.4% of pregnant women.<sup>2-4</sup> Australia has the highest international rate of asthma, with 12.4% of pregnant women found to have asthma.<sup>5</sup> The risk of atopic disease in a child is about 10% if the mother has asthma, increasing to 30% if both parents are affected. Breastfeeding and delay of the introduction of cow's milk protein may reduce this risk.

## EFFECT OF PREGNANCY ON ASTHMA

Monitoring of asthma is necessary during pregnancy, as the clinical status of the patient may change. Traditionally, it has been reported that asthma remains stable in a third of patients, improves in a third, and deteriorates in a third. While women with mild disease are unlikely to experience problems, a prospective study by Murphy *et al.*<sup>6</sup> clearly demonstrated that exacerbations occur with increasing frequency depending on the severity of asthma. Sixty-five per cent of women with severe asthma had an exacerbation during pregnancy. These results correlated with an earlier report of 1 739 pregnancies, where 51.9% of patients with severe asthma had severe exacerbations.<sup>7</sup>

**Table I. Level of asthma control**

CHARACTERISTIC	CONTROLLED (All of the following)	PARTIALLY CONTROLLED (Any measure present in any week)	UNCONTROLLED
Daytime symptoms	≤ 2/week	>2/week	
Limitation of activities	None	Any	
Nocturnal symptoms/ awakening	None	Any	3 or more features of partly controlled asthma in any week
Need for reliever/rescue treatment	≤ 2/week	>2/ week	
Lung function (PEF/FEV <sub>1</sub> )	Normal	<80 % predicted or personal best (if known)	
Exacerbations	None	1 or more/year *	1 in any week †

\*Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate  
†By definition, an exacerbation in any week makes that an uncontrolled asthma week  
PEF/FEV<sub>1</sub> – peak expiratory flow/forced expiratory volume in 1 second  
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### **Proposed mechanisms for the effect of pregnancy on asthma**

A number of factors related to pregnancy may influence the clinical course of asthma, but it is also recognised that coexisting conditions, especially allergic rhinitis, as well as patient adherence and triggers, play an important role in determining the risk of developing an acute exacerbation. Women whose symptoms improve during late pregnancy may experience deterioration during the puerperium. Researchers have proposed a few mechanisms for the effect of pregnancy on asthma:

- Corticotropin-releasing hormone is secreted by the placenta causing a rise in serum cortisol,<sup>8</sup> which might improve asthma through its downstream anti-inflammatory properties.<sup>9</sup>
- Oestrogen and progesterone levels rise in the first trimester and remain elevated until delivery.<sup>10</sup> Progesterone might improve asthma through its smooth-muscle relaxant properties.<sup>11</sup> Progesterone also causes increased sensitivity of the medulla to carbon dioxide<sup>12</sup> (although a direct stimulatory effect cannot be excluded), resulting in an increased tidal volume and relative hyperventilation. The respiratory rate remains unchanged. A compensated respiratory alkalosis develops, with higher pO<sub>2</sub> (100-106 mmHg) and lower pCO<sub>2</sub> (28-30 mmHg) values than in the nonpregnant state. This is of clinical relevance, since normalisation of the pH or pCO<sub>2</sub> in the setting of an acute asthma exacerbation might indicate serious respiratory compromise and should not be overlooked.
- Bronchoconstriction may be mediated through substances such as prostaglandin F<sub>2α</sub>.<sup>3</sup>
- A female fetus is associated with worsening of asthma.<sup>13,14</sup>
- During pregnancy, the maternal immune response is modulated away from cell-mediated immunity towards humoral immunity, but the clinical relevance in infection and inflammation remains unproven.<sup>15</sup>
- As a result of increased endogenous corticosteroids, acute asthma during labour is unlikely.

### **EFFECT OF ASTHMA ON PREGNANCY**

For most women there are no adverse effects of asthma on the pregnancy outcome. Historical cohort studies have produced conflicting results on the effects of asthma on pregnancy, but they have often been flawed by using different classification systems or not taking all factors (e.g. smoking or medication use) into account. Murphy *et al.*<sup>14</sup> reviewed more than 30 of these studies, as well as 2 case control studies, cross-sectional surveys, case series and prospective cohort studies. They concluded that:

- Asthma in pregnancy is associated with pre-eclampsia and low birth weight.
- Fetal sex may be a confounding factor and should be taken into consideration in statistical analysis.
- The use of oral steroids and theophylline, or respiratory complications during pregnancy is associated with preterm labour or delivery.
- An asthma attack in the preceding 12 months is a risk factor for preterm delivery.

### **Proposed mechanisms of the effect of asthma on pregnancy**

- Hypoxia might occur during an acute exacerbation. Hypoxia is also believed to cause low birth weight and pre-eclampsia.

- Placental blood flow may be reduced in moderate to severe asthmatics.<sup>16</sup>
- Exposure of the female fetus to an excess of maternal corticosteroids may lead to a low birth weight. The 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) enzyme protects the fetus against excess maternal glucocorticosteroids. In female fetuses of asthmatics who did not use inhaled corticosteroids (ICS), a reduction in 11β-HSD2 enzyme activity was demonstrated and was associated with low birth weight. In addition, cord blood oestriol levels were reduced, indicating suppressed adrenal function due to exposure to an excess of maternal cortisol.<sup>17,18</sup>
- Chronic inflammation may be a factor in low birth weight. Patients who did not qualify for ICS therapy had babies with lower birth weights, compared to other patients with more severe asthma requiring ICS. It is therefore thought that the underlying chronic inflammation plays an important role. Other chronic auto-immune diseases, such as inflammatory polyarthritis<sup>19</sup> and inflammatory bowel disease<sup>20</sup> are also associated with low birth weight and preterm delivery. It is important in these series, however, to differentiate the effect of disease activity from corticosteroid use. Chronic inflammation is associated with altered placental function and may be an explanation for growth restriction.
- Lung function correlates with low birth weight. Lung function reflects the degree of inflammation and poor function increases the risk for exacerbations, hypoxia and maternal mortality.<sup>21</sup>
- Oral steroid use and theophylline is associated with preterm delivery.<sup>22</sup>

The abovementioned mechanisms imply that addressing chronic inflammation by first using ICS, restricting the use of systemic corticosteroids and optimising therapy to avoid exacerbations may improve pregnancy outcomes. Exacerbations of asthma during pregnancy represent a significant clinical problem and may be related to poor pregnancy outcomes.<sup>23,24</sup>

### **DIFFERENTIAL DIAGNOSIS OF DYSPNOEA IN PREGNANCY**

**Benign dyspnoea or breathlessness of pregnancy.** Up to 70% of women experience dyspnoea during uncomplicated pregnancy. Benign dyspnoea of pregnancy should be differentiated from other pathology by thorough clinical examination.

**Chronic obstructive pulmonary disease (COPD).** Smoking and tuberculosis are the most common causes of COPD seen in South Africa. The diagnosis should be confirmed with pulmonary function testing and chest radiography.

**Pulmonary embolism.** Thrombo-embolism or amniotic fluid embolism should be considered especially post partum and in those patients presenting with an acute onset of dyspnoea or pleuritic chest pain.

**Pulmonary oedema.** Because of the cardiovascular changes in pregnancy, patients with underlying valve lesions, especially mitral stenosis, may deteriorate during pregnancy and develop pulmonary venous hypertension. Other causes to be considered include pre-eclampsia/hypertension and peripartum cardiomyopathy.

**Pulmonary infections.** Infective causes, including tuberculosis, should be excluded (especially in a situation of high HIV prevalence).

**Underlying pulmonary conditions.** Patients may present with other respiratory conditions, such as interstitial lung disease, during pregnancy, or because of the clinical course may become symptomatic.

**Systemic conditions.** Anaemia is a common problem in pregnancy, and may manifest with dyspnoea.

**Psychological conditions.** Panic attacks are common in the general population and patients often present with dyspnoea.

## TREATMENT

### Patient education

Undertreatment, as a result of poor patient compliance during pregnancy, remains one of the main reasons for exacerbations.<sup>6,25</sup> Many patients (and health care per-

<b>Table II. Summary of pharmacotherapy</b>				
<b>Drug</b>	<b>Mechanism of action</b>	<b>US FDA category</b>	<b>Side-effects</b>	<b>Use and comments</b>
<b>RELIEVERS</b>				
<b>Short-acting <math>\beta_2</math>-receptor agonist</b> Salbutamol Fenoterol Terbutaline	Bronchodilator via stimulation of $\beta_2$ -adrenoreceptor in smooth muscle  Inhibits mediator release from mast cells  Inhibits tumour necrosis factor alpha from monocytes  Increases mucus clearance through action on cilia <sup>29</sup>	C	Palpitations, tachycardia, tremor, headache, irritability	Use as needed for quick relief of symptoms in all severity categories. Most data available in human pregnancies during use of salbutamol
<b>Anti-cholinergic</b> Ipratropium bromide	Inhibits vagally mediated bronchoconstriction (muscarinic receptor antagonist)	B		Use as needed for quick relief of symptoms in patients who cannot tolerate short-acting $\beta_2$ -agonists or as add-on treatment
<b>CONTROLLERS</b>				
<b>Inhaled corticosteroids (ICS)</b> Beclomethasone Fluticasone Ciclesonide	Modify airway remodelling Decrease airway hyper-responsiveness Reduce airway inflammation Decrease cytokine formation Inhibit generation of vasodilators prostaglandin E2 and I2 Inhibit influx of eosinophils into the lung Up-regulate $\beta_2$ -adrenoreceptors Decrease microvascular permeability	C	Dysphonia Oropharyngeal candidiasis	Use as first-line therapy for all classes of chronic persistent asthma. Adjust dose according to severity
Budesonide		B	Classification based on Swedish Medical Birth Registry <sup>30</sup>	Budesonide is supported by the largest database, but it is recommended to continue the ICS that controlled asthma before pregnancy.
<b>Long-acting <math>\beta_2</math>-receptor agonist (LABA)</b> Salmeterol Formoterol	Sustained bronchodilator effect due to stimulation of $\beta_2$ -adrenoreceptor in smooth muscle  Inhibits mediator release from mast cells  Inhibits tumour necrosis factor alpha from monocytes  Increases mucus clearance through action on cilia	C	Tremor Palpitations Increased mortality when used as monotherapy	Add on to ICS Preferable to use add-on therapy to increasing dose of ICS Never use as monotherapy Formoterol has a much more rapid onset of action compared with salmeterol <i>cont/...</i>

**Table II. Summary of pharmacotherapy (cont)**

Drug	Mechanism of action	US FDA category	Side-effects	Use and comments
<b>CONTROLLERS</b>				
<b>Sustained-release theophylline preparations</b>	Cause bronchodilation Potentiate exogenous catecholamines and stimulate endogenous catecholamine release Stimulate diaphragmatic muscular relaxation	C	Narrow therapeutic range Nausea and vomiting Abdominal discomfort Gastro-oesophageal reflux Palpitations Insomnia Lower seizure threshold Irritability May inhibit uterine contractions Increase risk of preterm delivery and pre-eclampsia	Add-on therapy when moderate dose ICS required. Do not use as monotherapy. Monitor levels in pregnancy, as decreased albumin binding results in an increase in free drug proportions. The free drug is metabolised, leading to a fall in total theophylline concentration. It is recommended that the target levels in pregnancy should be 8-12 µg/ml. <sup>31</sup> Theophylline clearance is reduced in the third trimester, which may require a lower maintenance dose. <sup>32</sup>
<b>Systemic corticosteroids</b> Prednisone Prednisolone Methylprednisone Methylprednisolone	Decrease inflammation Reverse increased capillary permeability Suppress polymorphonuclear neutrophil activity	C	Skin bruising Osteoporosis Cataracts Diabetes Hypertension Pre-eclampsia Cleft palate risk slightly increased in first trimester <sup>33</sup> Preterm delivery and low birth weight <sup>22,34,35</sup>	Use only when uncontrolled on high dose ICS, LABA, leukotriene modifier and theophylline combination. Prednisone is the drug of choice, since 90% is inactivated by the placenta, limiting the exposure to the fetus.
<b>Leukotriene modifiers</b> Montelukast Zafirlukast	Prevent acute attacks by anti-inflammatory action: competitively antagonise cysteinyl leukotrienes at CysLT1 receptors <sup>36</sup>	B	Headache Reports of Churg Strauss syndrome no longer substantiated <sup>37</sup> No birth defects or adverse outcomes reported in 96 women in a prospective, controlled study <sup>38</sup> Montelukast has not been associated with adverse outcomes according to the Merck Pregnancy Registry in 337 patients exposed during pregnancy.	Not recommended as monotherapy. NAEPP did not recommend discontinuation if patient was stable on therapy prior to pregnancy.
US FDA – United States Food and Drug Administration, NAEPP – National Asthma Education and Prevention Program				

sonnel) fear side-effects from medication and are not well educated regarding their safety. The potential harm to the fetus and themselves during acute severe asthma should be pointed out. Education should also include the following:

- Indications for emergency department care and assessment.
- Correct inhaler technique.

- As in all asthma patients, triggers should be avoided, especially tobacco smoke.
- Use of a home peak flow meter. This will help to distinguish between poorly controlled asthma and benign dyspnoea of pregnancy.
- Patients should understand the mode of action and dose of medication.

- Treatment name, dose and frequency should be given as written instructions.
- Medic Alert discs should be obtained for high-risk patients (brittle asthma, drug allergies, high-dose corticosteroids).

### Treatment of exacerbating factors

#### Rhinitis and sinusitis

Asthma and allergic rhinitis can be regarded as components of a single airway disease.<sup>26</sup> Up to 80% of asthmatics also have allergic rhinitis<sup>27</sup> and a correlation was shown between asthma progression and rhinitis symptoms. Treatment of underlying rhinitis could therefore improve asthma control.<sup>28</sup> Rhinitis and sinusitis should be considered in all cases where control is difficult to achieve, even in the absence of symptoms. Intranasal corticosteroids should be used as first-line therapy.

#### Gastro-oesophageal reflux (GER)

GER is increased in pregnancy. It is well established that acid reflux may aggravate asthma and treatment of GER may improve asthma control.

#### Pharmacotherapy

Most drugs used to treat asthma are considered safe in pregnancy and lactation, based on the data available. In contrast, if asthma is undertreated, the risk to the mother and fetus cannot be sufficiently emphasised. The South African Thoracic Society published a revision of guidelines for the management of chronic asthma in adolescents and adults in 2007<sup>1</sup> (summarised in Table II). The management principles remain mostly the same during pregnancy. These guidelines are in keeping with those recommended by the Working Group on Asthma and Pregnancy of the National Asthma Education and Prevention Program (NAEPP 2007)<sup>39</sup> in North America. The effectiveness of the treatment regimen should be reassessed throughout the pregnancy. Asthma control is reached when the patient has daytime symptoms less than twice a week, has no limitation of activity or nocturnal symptoms, uses reliever medication twice a week or less, has normal lung function and no exacerbations. Treatment should be adjusted according to the level of control.

Most of the concern in asthma in the past was regarding the use of corticosteroids. A recent meta-analysis found that ICS do not increase the risk of major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension. They can therefore be considered safe in pregnancy.<sup>28,40</sup> Systemic absorption of ICS may be limited by mouth washing, combined with the use of spacer devices.<sup>1</sup> ICS should be used as first-line therapy for all classes of chronic persistent asthma.

#### Other drugs

**Antihistamines** are not effective in adult asthma. They can be used to treat allergic rhinitis.

**Nebuliser** use should not be necessary if correct inhaler technique is followed and adequate therapy is prescribed.

**Magnesium sulphate** intravenously has bronchodilator activity in acute asthma, possibly due to inhibition of calcium influx into airway smooth-muscle cells. It can be used in patients who present with severe asthma attacks and whose condition is not satisfactory after initial standard therapy.<sup>29,41</sup> Intravenous magnesium has an excellent safety profile when used correctly; however, it is contraindicated in the presence of renal

insufficiency, and hypermagnesaemia can result in muscle weakness.

### CONCLUSION

Asthma can be treated effectively in pregnancy without significant risk to the fetus. Reassessment should be done frequently during pregnancy and treatment adjusted according to current guidelines to maintain optimal control. In this way, outcomes for both mother and baby will be improved.

#### Declaration of conflict of interest

The authors declare no conflict of interest.

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