Asthma in Pregnancy

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ABSTRACT

Asthma is the most common chronic condition affecting pregnancy. Management of asthma during pregnancy is important to avoid asthma exacerbations. The influence of pregnancy on the onset of asthma attacks in each patient is not the same, even in an asthmatic patient, the attacks are not the same in the first pregnancy and subsequent pregnancies. Usually attacks will occur from 24 weeks of gestation to 36 weeks, and will subside at the end of pregnancy. Asthma exacerbations are associated with an increased risk of low birth weight and preterm delivery, so management of asthma during pregnancy is important to avoid asthma exacerbations.

Keywords: Pregnancy, Asthma, Lung Function

I. INTRODUCTION

Asthma is a chronic inflammatory disease of the respiratory tract, characterized by occasional episodes of wheezing and coughing that often worsens at night resulting from inflammation and structural changes in the airways in response to antigenic stimuli. This causes airway hyper-responsiveness and airflow obstruction which can lead to the presenting symptom. Patients may develop an exacerbation of the condition either in response to an acute infection, which is usually of viral origin, or because of poor control of their airway inflammation [1].

Asthma is the most common chronic condition that can cause complications in pregnancy worldwide, with the prevalence of asthma in pregnancy 8%-13% [2]. In the United States, 5-8% of pregnant women suffer from asthma and the prevalence is increasing. Asthma affects 2-13% of pregnancies [3]. Pregnancy can affect asthma control and conversely asthma can affect pregnancy [1] [4].

Asthma exacerbations are common in pregnancies accompanied by asthma, affecting 35% to 55% of pregnancies. This event is associated with an increased risk of low birth weight and preterm delivery, so management of asthma during pregnancy is important to avoid asthma exacerbations [2]. Poor asthma control has adverse effects on both mother and fetus [1].

II. LITERATURE REVIEW

Pathophysiology of Asthma

One of the consequences of inflammation is epithelial damage that varies from mild to severe. These structural changes will increase the penetration of allergens, inflammatory mediators and increase the irritation of autonomic nerve endings so that they are easily aroused. The bronchial epithelial cells themselves actually contain mediators that can act as bronchodilators. Damage to bronchial epithelial cells will cause bronchoconstriction to occur more easily. In asthmatic patients there is an increase in parasympathetic nervous response. Although not a major factor, airway obstruction is thought to play a role in airway hyperactivity [5].

The theory of inflammation in asthma was derived from morphological evaluation of endobronchial biopsy specimens in asthmatic patients: Hyperplasia and hypertrophy of the epithelial cell lining of the airways are present in asthmatic patients and cause airway wall thickening. Within the epithelial layer there is an increased number of surface secretory cells and mucus glands. In addition, the airway walls of asthmatics are infiltrated by T lymphocytes. These cells can produce a number of cytokines including interleukins IL-3, IL-4, and IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Through a complex process, when released or stimulated, these factors increase the synthesis of Immunoglobulin E (IgE) [6].

Airway obstruction in asthma is a combination of bronchial muscle spasm, mucus plugging, edema and inflammation of the bronchial walls. Obstruction gets worse during expiration because physiologically the airway narrows in this phase. This results in air distally, where the obstruction is trapped and cannot be expelled. Furthermore, there is an increase in residual volume and residual functional capacity, where the patient will breathe at a high volume that is close to the volume of the total lung breathing capacity. This hyperinflation state aims to
keep the airways open and gas exchange to run smoothly. To maintain this hyperinflation required respiratory muscles [5].

The mechanisms of external stimuli (eg allergens), airway inflammation, and asthma physiology have been studied more extensively. One theory suggests that after exposure to an allergen, there is an accumulation of T lymphocytes in the airway epithelium. Cytokines are released from T lymphocytes and mast cells, which promote IgE formation and result in the uptake of additional T cells, eosinophils, monocytes, and basophils. In the presence of IgE, these cells release inflammatory mediators, which include histamine, leukotrienes, lipoxins, platelet-activating factors, and various proteases, into the airway epithelium [5] [7].

These mediators are known as primary effector molecules, which have the capacity to stimulate airway smooth muscle, increase microvascular permeability, and increase mucus production from airway glands and secretory cells. Primary effector molecules can also stimulate further cytokine production, which serves to amplify and trigger asthmatic events. In addition, primary effector molecules can stimulate sensory nerve fibers in the airway, leading to the release of secondary effector molecules, which include substance P and neurokinin A. These two molecules cause airway smooth muscle contraction. The effect of these changes is airway obstruction, which is a hallmark of asthma [6].

Airway obstruction can be assessed objectively by the Forced Expiratory Volume in one second (VEP1) or Peak Expiratory Flow (APE) while the Forced Vital Capacity (KVP) describes the degree of lung hyperinflation. Airway narrowing can occur in both large, medium and small airways. Symptoms of wheezing indicate there is narrowing in the large airways, whereas in small airways the symptoms of coughing and shortness of breath are more dominant than wheezing [5].

Hormonal, immunological, and physiological changes in pregnancy affect the symptoms and severity of asthma. However, no changes were seen in FEP1, the ratio of VEP1 to KVP or APE in asthmatic patients with pregnancy [8]. Elevated estrogen levels increase mucosal edema and hypervascularity in the upper airway [9] [10] [11].

Oxygen consumption and metabolic rate increase by 15-20% during pregnancy. Elevated estrogen concentrations result in hyperemia, hypersecretion, and edema of the upper airway mucosa, which usually peak in the third trimester and can cause nasal congestion and inflammation in up to 30% of pregnant women, regardless of their atopic history. By the end of the first trimester, progesterone can increase 40-50% minute ventilation volume. This is mainly due to a 30 to 50% increase in tidal volume (VT). Forced Vital Capacity (FVC) and Peak Expiratory Flow (APE) remain unchanged, and any decrease in these parameters during pregnancy may indicate an underlying disease [12].

As the uterus expands, the diaphragm is raised by about 4–5 cm, and there is a reduction of about 18% (approximately 1.1–1.35 L) of KVP due to a progressive decrease in expiratory reserve volume. Pregnancy also results in a 20% increase in oxygen consumption to compensate for the increased maternal metabolism. To compensate for the increased demand during pregnancy, minute ventilation is increased by 40% to 50%. This relative hyperventilation is not due to an increase in respiratory rate, but from an increase in tidal volume. These changes are a result of progesterone-mediated stimulation of the respiratory center to the point set to receive a lower partial pressure of carbon dioxide (Table 1) [9].

This natural hyperventilation of pregnancy causes arterial blood gases to produce a respiratory alkalosis that is compensated for by metabolic acidosis. In general, blood gases have a pH of 7.4-7.45 and a PCO2 of 28-32mmHg. There was an increase in PO2 from 106 to 110 mmHg. The increase in pH is compensated by increased renal
bicarbonate excretion (which causes polyuria in early pregnancy). The PO2 in the umbilical vein is lower than in the placental vein; thus, maternal hypoxemia will rapidly result in a decrease in the oxygen content supplied to the fetus. Chronic hypoxaemia can cause intrauterine growth restriction and low birth weight. Low PCO2 is essential for fetal acid-base balance, and elevated maternal PCO2 will affect the ability of the fetus to excrete acid and cause fetal acidosis. When interpreting blood gas analyzes of pregnant patients, a seemingly normal PCO2 actually reflects the level of carbon dioxide retention and the likelihood of impending respiratory failure [9] [10] [11].

Table 1. Description of Lung Volume and Changes During Pregnancy [9]

<table>
<thead>
<tr>
<th>Lung Capacity Measurement</th>
<th>Description</th>
<th>Physiologic Change in Pregnancy</th>
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</thead>
<tbody>
<tr>
<td>Functional residual capacity</td>
<td>Volume of air left in the lungs after a tidal breath out. The amount of air that stays in the lungs during normal breathing</td>
<td>17%–20%</td>
</tr>
<tr>
<td>Residual volume</td>
<td>Amount of air left in the lungs after maximum exhalation</td>
<td>20%–25%</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>Normal volume of air displaced between normal inhalation and exhalation with no extra effort</td>
<td>30%–50%</td>
</tr>
<tr>
<td>Expiratory reserve volume</td>
<td>Amount of additional air that can be pushed out after the end expiratory level of normal breathing</td>
<td>5%–15%</td>
</tr>
<tr>
<td>FEV1</td>
<td>Volume of air exhaled during the first second of a forced expiratory maneuver</td>
<td>Unchanged</td>
</tr>
<tr>
<td>PEFR</td>
<td>Maximal flow (or speed) achieved during maximally forced expiration initiated at full inspiration; measured in L/s</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Minute volume/ventilation</td>
<td>Volume of air that can be inhaled or exhaled in 1 min</td>
<td>30%–50%</td>
</tr>
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</table>

Abreviation FEV1, forced expiratory volume dalam satu detik; PEFR, peak expiratory flow rate.

Both progesterone and estrogen can potentiate β-adrenergic bronchodilation [6]. The pregnancy-related increase in free cortisol may contribute to the worsening of asthma during pregnancy, as cortisol has anti-inflammatory properties. In addition, the concentrations of estradiol and progesterone increase significantly during pregnancy. Progesterone is known to contribute to an increase in minute ventilation during normal pregnancy and so may contribute to an increase in asthma during pregnancy. Changes in β2-adrenoreceptor responsiveness and airway inflammation as a result of circulating progesterone may contribute to worsening of asthma during pregnancy [13] [14].

The binding of progesterone, aldosterone, and deoxycorticosterone to glucocorticoid receptors may decrease anti-inflammatory effects, which have both endogenous and exogenous effects on glucocorticoids. Increased prostaglandin F2α can increase bronchoconstriction. Elevated progesterone levels cause hyperventilation and manifest as 'pregnancy dyspnea', or increased shortness of breath in the patient. Smoking can increase the frequency of exacerbations. Pregnant women often worry about the effects of their asthma medication, so they stop their medication inappropriately. The complex interaction of all of the above factors in each patient determines whether asthma will improve, worsen, or remain stable during pregnancy [8].

Studies by Murphy have investigated the possible association between maternal asthma, placental function and fetal development. Placental 11β-HSD2 activity is significantly reduced, which allows more maternally derived cortisol to reach the fetus. Altered placental cortisol metabolism contributes to changes in the fetus, slows growth in late gestation, and depresses fetal hypothalamic-pituitary-adrenal axis function, as demonstrated by a significant decrease in estriol concentrations in female umbilical cord blood as shown in Figure 2 [13].
Asthma Relationship with Pregnancy

Asthma is the most common chronic condition affecting pregnancy. Several studies have identified asthma as a risk factor for poor maternal and fetal outcomes [10].

The standout data comes from a large meta-analysis covering 40 studies over several decades and over 1.5 million subjects. This study shows that asthma in pregnancy is associated with the risk of low birth weight infants, intrauterine growth retardation, preterm delivery, and preeclampsia. Women with daily symptoms also had higher rates of pre-eclampsia [15]. Low birth weight was associated with measures of poor asthma control such as persistent daily symptoms or poor lung function, also in women not taking inhaled steroids. Recent evidence suggests that airway hyper-responsiveness, a hallmark of asthma, can be a predictor of pre-eclampsia and suggests a common pathway of mast cell–smooth muscle cell interactions in the airway [1].

In one study, the risk of intrauterine growth retardation increased in direct proportion to the severity of asthma based on guidelines issued by the Global Initiative for Asthma. Women who are not diagnosed with asthma but have symptoms consistent with asthma are at high risk for delivering a baby with intrauterine growth retardation. Most studies have shown that with appropriate drug administration and avoidance of exacerbations, fetal outcome in patients with severe asthma is better [15] [16].

Asthma exacerbation is a clinical problem of concern during pregnancy [17]. The rate of asthma exacerbations is higher during pregnancy, especially for patients with a history of severe asthma. In a study of 1,739 patients, 52% of those with severe asthma had an exacerbation during pregnancy, compared with moderate asthma having an exacerbation rate of 26% and 13% for mild asthma. Pregnant women with asthma are particularly susceptible to viral upper respiratory tract infections, which often lead to poor asthma control or exacerbations. Viral infections are a frequent trigger of asthma exacerbations in adults, including during pregnancy [3] [11] [17]. A prospective cohort study of 101 pregnant women with asthma and 77 women without asthma found that women with asthma were more likely to have an upper respiratory tract infection or urinary tract infection during pregnancy (35%) than pregnant women without asthma (5%), and that severe asthma associated with more infections than mild asthma. Prevention of this viral infection will improve asthma control and reduce the incidence of asthma exacerbations during pregnancy. Improved asthma control during pregnancy can reduce the chances of viral infections of the upper respiratory tract [13].

Approximately 45% of pregnant women with asthma have moderate-to-severe exacerbations that require medical intervention during pregnancy. Exacerbations and severe asthma are associated with preterm delivery, which may occur because of maternal hypoxia, the effect of inflammation on the mother, and/or changes in uterine smooth muscle function. In addition, women with asthma exacerbations were three times more likely to have a low birth weight baby than women with asthma without exacerbations [18] [11].

By pooling a total of 2,186 patients to evaluate the effect of pregnancy on asthma control, it was found that approximately 30% improved, 40% worsened, and 30% experienced symptom change. Schatz and colleagues also noted that 30% of patients initially classified as having mild asthma were classified as moderate or severe, while 23% of patients with severe or moderate asthma were later categorized as having mild asthma at the time of pregnancy [10].

Approximately 26% of women with asthma in early pregnancy worsened, and 7% required hospitalization. Among women with a history of severe asthma before pregnancy, 52-65% will experience worsening asthma symptoms, with 27% requiring hospitalization [8] [20].

Table 2 describes the physiological factors that influence asthma during pregnancy. In severe disease, asthma control is more likely to worsen (~60%) than in mild disease (~10%). Exacerbations are most common between 24 and 36 weeks of gestation. Respiratory viral infections are the most common. Frequent triggers of exacerbations (34%), followed by low adherence to inhaled steroid therapy (29%) [1].
Table 2. Physiological factors affecting asthma in pregnancy [1]

<table>
<thead>
<tr>
<th>Physiological factors that influence asthma in pregnancy</th>
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<tbody>
<tr>
<td>• Increased levels of free cortisol may protect against inflammatory triggers.</td>
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<tr>
<td>• An increase in bronchodilating substances (such as progesterone) can increase airway responsiveness.</td>
</tr>
<tr>
<td>• An increase in bronchoconstrictive substances (such as prostaglandin F₂α) can increase airway constriction.</td>
</tr>
<tr>
<td>• Placental-decreasing activity of 11β-hydroxysteroid dehydrogenase type 2 is associated with increased placental cortisol concentrations and low birth weight.</td>
</tr>
<tr>
<td>• Expression of placental inflammatory cytokine genes can increase low birth weight.</td>
</tr>
<tr>
<td>• Modifications of cell-mediated immunity may influence maternal responses to infection and inflammation.</td>
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### Asthma Diagnosis

Clinically, the common symptoms found in asthma are wheezing, shortness of breath and coughing. These symptoms may vary depending on the individual, and may change spontaneously or with age, change of season, and medication history. Symptoms may become worse at night, and episodes of waking at night are an indicator of uncontrolled asthma. The severity of asthma symptoms, and the need for treatment with systemic steroids, hospitalization, and intensive care, are important to ascertain [21].

Symptoms of an acute asthma exacerbation include diaphoresis in an upright or sitting position, inability to speak a full voice without taking additional breaths. Somnolence, assuming a recumbent position, and cyanosis, accompanied by a "silent chest" on auscultation suggest imminent breathing. The resulting respiratory alkalosis causes uterine artery vasoconstriction and reduces the blood supply to the fetus [9].

Physicians should monitor pulmonary function of patients with asthma on a regular basis subjectively and objectively. Spirometry, peak expiratory flow rate (PEFR), and standardized questionnaires are good parameters for assessing asthma control [23].

The Peak Expiratory Flow Rate in pregnancy is 380 to 550 L/min. The patient should be informed that 80% or more of the Peak Expiratory Flow Rate is considered good control. Pregnant women should be explained that if the Peak Expiratory Flow Rate is in the range of 50% to 80%, she should consult her doctor or get advice about a change in medication, if the value is less than 50%, she should be hospitalized immediately or visit the emergency department if necessary [21].

Pemeriksaan Radiologi biasanya didapatkan hasil normal. Pada pasien dengan akut eksaserbasi dapat juga ditemukan gambaran pneumothorax. CT scan bukan merupakan pemeriksaan yang rutin dilakukan pada asma [21].

### Asthma Treatment in Pregnancy

The long-term goals of asthma management are to reduce risk and control symptoms. The goal is to reduce the burden on the patient and to reduce the risk of death from asthma, exacerbations, airway compromise, and medication side effects [22]. The primary goal of asthma therapy in pregnancy is to prevent hypoxic episodes to
maintain continued fetal oxygenation; Improved maternal and perinatal outcomes are achieved with optimal asthma control. There are 4 important aspects of asthma treatment to ensure optimal control: close monitoring, patient education, avoidance of asthma triggers, and pharmacological therapy [9].

The recommendations for the management of asthma during pregnancy are the same as for the treatment of other adult asthmatic patients as described in the adult asthma treatment strategy based on the 2021 Global Initiative National for Asthma Guideline. The guidelines recommend the use of short-acting β-Agonist as lozenges and the use of inhaled steroids for women with persistent asthma. There is much convincing data on the safety of using inhaled steroids in pregnancy, especially for budesonide, which has the best safety rating during pregnancy. It is recommended to continue the use of inhaled steroids that respond to control asthma before pregnancy [3] [16] [24].

Treatment with inhaled steroids should be started as soon as possible after the diagnosis of asthma is established for better outcomes, because even mild asthmatic patients can have severe exacerbations. Low-dose inhaled steroids can reduce the incidence of hospitalization and death, are very effective in preventing severe exacerbations, reducing symptoms, improving lung function, and preventing bronchoconstriction, even in mild asthmatic patients. Initial treatment with low-dose inhaled steroids can lead to better lung function than symptoms that have existed for 2-4 years [24].

Consider starting a higher step (eg medium/high dose inhaled steroids, or low dose inhaled steroids – long acting β-Agonist if the patient is predominant with asthma symptoms or wakes up one or more times a week due to asthma. If asthmatic severe uncontrolled, or with acute exacerbations, give oral corticosteroids for a short period of time and start on controlling therapy (eg, inhaled steroids, medium-dose long-acting -agonists). Consider lowering the step if after 3 months asthma has been controlled. However, in adult and adolescent patients, inhaled steroids should not be discontinued completely [22] [25].

Inhaled steroids are preferred for the management of all stages of persistent asthma in pregnancy. Corticosteroids are the most effective treatment for airway inflammation in asthma and reduce airway hyper-responsiveness to allergens and other triggers. This drug has also been shown to reduce the incidence of exacerbations more than threefold compared to those not taking inhaled steroids. Concerns about the risk of congenital malformations with the use of inhaled steroids in the first trimester are not evidence-based; several studies have confirmed its safety in terms of dosage [9] [26] [27].

Asthma control often changes during pregnancy. For both the baby and the mother, the benefits of treating asthma far outweigh the risks that controller or lozenges can pose. Downward titration is not a priority in pregnancy. Exacerbations must be treated aggressively [22]. Theophylline is an alternative treatment for mild persistent asthma and an adjunct treatment for moderate and severe persistent asthma, but is not a recommended therapeutic option. Theophylline is useful only for chronic therapy and is not helpful in acute exacerbations. Theophylline is associated with several side effects such as insomnia, palpitations, and nausea. Theophylline has many significant drug interactions because the rate of clearance of theophylline is altered, which can result in increased theophylline levels and possible toxicity [9]. Therefore, its use during pregnancy is only recommended if other treatments are not sufficient to achieve asthma control [12].

Exacerbation of asthma in pregnant women places both mother and fetus at increased risk of severe hypoxaemia. The most important management of acute exacerbations is prevention; However, it was noted that 52% of patients with severe asthma had exacerbations during pregnancy [9]. Management of worsening asthma and exacerbations must be carried out continuously, from patient self-management, can be done by writing an Asthma Action Plan, management of more severe symptoms in primary care, emergency rooms and in hospitals. The Asthma Action Plan should cover the patient’s usual asthma treatment, when and how to increase treatment and start oral corticosteroids, how to contact primary care if symptoms have resolved [22].

Management of exacerbations in primary care is to start therapy with a short-acting -agonist, eg repeated doses of pMDI, initial corticosteroids, and oxygen if available. Check for symptoms and saturation periodically, and measure lung capacity after 1 hour. Titrate oxygen to maintain saturation around 93-95% in adults and adolescents. For severe exacerbations, add ipratropium bromide and consider administration of a short-acting nebulized β-Agonist. In emergency care facilities, intravenous administration of magnesium sulfate may be considered if unresponsive or requiring intensive therapy [28].

III. CONCLUSION

Asthma is the most common chronic condition that affects and can cause complications in pregnancy. Pregnancy can affect asthma control and conversely asthma can affect pregnancy.

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Hormonal, immunological, and physiological changes in pregnancy affect the symptoms and severity of asthma. Pregnant women with asthma are particularly susceptible to viral upper respiratory tract infections, which often lead to poor asthma control or exacerbations. Asthma exacerbations are associated with an increased risk of low birth weight and preterm delivery, so management of asthma during pregnancy is important to avoid asthma exacerbations. Appropriate drug administration and avoiding exacerbations can improve fetal outcomes in patients with severe asthma.

Non-adherence to controller drug use during pregnancy is also associated with an increased risk of acute exacerbations during pregnancy. Non-adherence to asthma control medications is most likely associated with fear of the potential teratogenic risks of treatment. Salbutamol and inhaled steroids are both recognized not to increase the teratogenic risk.

Pulmonary function monitoring and questionnaires are good parameters for assessing asthma control. The long-term goals of asthma management are to reduce risk and control symptoms. The primary goal of asthma therapy in pregnancy is to prevent hypoxic episodes to maintain continued fetal oxygenation; Improved perinatal maternal outcomes are achieved with optimal asthma control. Therefore, optimal control of asthma symptoms is very important for the health of pregnant women and their fetuses.

REFERENCES


