4

Respiratory diseases in pregnancy: asthma

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During pregnancy, hormonal, immunological and physiological adaptations alter the course of many respiratory diseases. In addition, many respiratory illnesses produce significant negative effects on maternal and fetal outcomes.

Among pregnant women, the most common respiratory disease by far is asthma, with a prevalence ranging from 3.8 to 8%[1–5]. This illness is becoming an increasing concern, as its prevalence has increased among all women over the past decade[2,6,7]. Because of this, this chapter focuses on the diagnosis and management of asthma and its effect on pregnancy.

PREVALENCE, EPIDEMIOLOGY AND PATHOPHYSIOLOGY

In the United States alone, an estimated 14–15 million people have been diagnosed with asthma[2,6,7]. During childhood, the ratio of males to females is 2 : 1, whereas by adulthood the gender difference is no longer present. Regardless of gender or patient age, the health consequences of asthma are profound. Each year, complications of asthma account for 5000 deaths in the US. According to the Center for Disease Control and Prevention, patients with asthma collectively account for a total of 100 million days of restricted activity and 470,000 annual hospital admissions. Of particular note, adverse outcomes are not equally distributed, with disproportionate effects in African-Americans who have the greatest rates of hospital admission and asthma-related deaths among those aged 15–24[2,6,8].

Symptoms of asthma result from a combination of inflammation, edema and bronchospasm. Certain individuals appear to have a genetic predisposition that results in IgE production in response to various stimuli. IgE antibodies bind to mast cells and basophils, leading to the release of mediators including histamine, leukotrienes and cytokines, which in turn stimulate smooth muscle contraction, leading to narrowing of airway passages. Activation of cytokines promotes tissue inflammation, which both narrows bronchial airways and increases airway hyperresponsiveness[9].

Histologically, examination of the airways reveals denuded epithelium, edema and collagen deposition beneath basement membranes that leads to sub-basement fibrosis. Also seen is inflammatory cell infiltration with eosinophils, neutrophils and type 2 lymphocytes[9].

DIAGNOSIS

The signs and symptoms of asthma differ from patient to patient, and their severity may also vary in any given patient at different times. The following components are required for the diagnosis of asthma:

- Episodic symptoms of airflow obstruction
- Airflow obstruction that is at least partially reversible

- Absence of alternative diagnoses to explain symptoms.

Asthma symptoms may remit spontaneously or may require medical therapy. Common symptoms include coughing, wheezing, shortness of breath and chest tightness. In general, symptoms are worse at night and during early morning and improve during the day.

To make a diagnosis of asthma, a detailed history and physical examination should be performed to identify the following signs and symptoms:

- Hyperexpansion of the thorax
- Expiratory wheezing
- Severe rhinitis
- Nasal polyps
- Atopic dermatitis or eczema.

In addition, patients with newly diagnosed asthma should undergo spirometric evaluations or pulmonary function tests (PFTs) before and after inhaling β2 agonists in order to demonstrate reversible airway obstruction. Hand-held peak flow assessments should be used to monitor asthma symptoms, but should not be used to make the initial diagnosis[9,10].

Asthma is categorized according to the frequency and severity of symptoms and the results of PFTs[6,7,11]. Assignment of a diagnostic category is important because it helps predict prognosis, both prior to and during pregnancy, and guides initial selection of pharmacotherapy[8,9,12–16].

Mild intermittent asthma is characterized by fewer than two daytime exacerbations per week, and two or fewer night-time exacerbations per month. Exacerbations tend to be brief, lasting from a few hours to a few days. On formal PFTs, the forced expiratory volume in 1 second (FEV1) should be greater than or equal to 80% of expected value. There should be less than 20% variability of peak expiratory flow rate.

Mild persistent asthma is characterized by two or more daytime exacerbations per week, but less than one exacerbation per day, and two or more night-time exacerbations per month, but less than one exacerbation per week. Exacerbations may affect a person's level of activity. On PFTs, the FEV1 is still greater than or equal to 80% of expected value, but there is 20–30% variability of peak expiratory flow rate.

Moderate persistent asthma is characterized by daily daytime symptoms and at least one night-time exacerbation per week. These exacerbations are generally longer in duration, often lasting days, and may affect a person's level of activity. PFTs reveal an FEV1 60–80% of expected value, and greater than 30% variability of peak expiratory flow rate.

Severe persistent asthma is characterized by continuous daytime symptoms and frequent night-time exacerbations. These patients often have a chronically limited level of activity due to frequent exacerbations. PFTs reveal an FEV1 less than 60% of expected value and greater than 30% variability of peak expiratory flow rate.

The patient's 'triggers' for exacerbation(s) should be identified as part of the diagnostic work-up. These can include environmental allergens, upper respiratory infections, occupational exposures, medications (notably aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)), exercise and emotional stress. The avoidance and control of triggers is discussed in the 'Management of asthma during pregnancy' section of this chapter.

EFFECTS OF PREGNANCY ON ASTHMA

Epidemiology

Although it is commonly stated that asthma improves during pregnancy in one-third of women, worsens in one-third of women, and remains unchanged in one-third of women, several studies have demonstrated that the

severity of asthma preconceptionally and during early pregnancy is predictive of the clinical course during the remainder of the pregnancy[3,17]. Women with mild asthma are less likely to require hospitalization, unscheduled office visits, oral steroids or experience exacerbations compared with women with moderate or severe asthma. Accordingly, among women with mild pre-pregnancy asthma, only 8–13% experience deterioration, and only 2% require hospitalization. In contrast, approximately 26% of women with moderate pre-pregnancy asthma deteriorate, and 7% require hospitalization. Among women with severe asthma prior to onset of pregnancy, 52–65% will develop a worsening of asthma symptoms, with 27% requiring hospitalization[3,8,16,18–20].

Other factors also predict which women are at greater risk of worsening of their asthma during pregnancy. Asthma symptoms tend to correlate with rhinitis symptoms, and women with more significant symptoms during pregnancy experience more asthma exacerbations as well[19]. Pregnant African-American women with asthma tend to have higher asthma-related morbidity than pregnant Caucasian women with asthma, independent of socioeconomic status[8]. Additionally, women pregnant with female fetuses experience more severe asthma symptoms than women pregnant with male fetuses[21,22]. It has been postulated that the surge in androgens at 12–16 weeks' gestation produced by male fetuses has a protective effect on maternal asthma.

With all three types, the severity of asthma symptoms reverts to pre-pregnancy levels within 3 months of delivery.

Pathophysiology

The hormonal, immunological and physiological changes of pregnancy affect the symptoms as well as the severity of asthma. Importantly, however, no pregnancy-related changes are seen in the FEV1, the ratio of FEV1 to vital capacity, or peak flow in patients with asthma; this stability means that criteria for diagnosis and monitoring of asthma do not change[9,23,24].

A number of pregnancy-related changes may act to ameliorate the course of asthma. For example, progesterone increases dramatically during pregnancy. This hormone acts as a smooth muscle relaxant, which may explain improved symptoms in some patients. Furthermore, both progesterone and estrogen potentiate β-adrenergic bronchodilation. Increased relaxin levels also promote relaxation of bronchial smooth muscle. At the same time, plasma histamine is decreased during pregnancy due to an increase in circulating histaminase. This may lead to a decrease in histamine-mediated bronchoconstriction. Further, pregnancy-related increases in circulating cortisol may produce anti-inflammatory effects, and circulating glucocorticoids may also increase β-adrenergic responsiveness, potentially improving the efficacy of some medications. Other changes that may promote bronchodilation and bronchial stabilization include increased levels of prostaglandin E2, prostaglandin I2 and atrial natriuretic factor[1,18,24–26].

At the very same time, however, competing pregnancy-related factors may exacerbate the course of asthma. Functional residual capacity (FRC) is decreased due to diaphragmatic elevation of up to 4 cm. This phenomenon may result in airway closure during tidal breathing and may alter ventilation–perfusion ratios. Competitive binding of progesterone, aldosterone and deoxycorticosterone to glucocorticoid receptors may decrease the anti-inflammatory effects of both endogenous and exogenous glucocorticoids. Increased prostaglandin F2α may promote bronchoconstriction, and placental-derived major basic protein (MBP) may increase immunologic sensitization[1,3,4,19,24–26].

In addition to these cited physiological changes, certain asthma triggers are either more common or more stimulatory in pregnancy. Some pregnant women experience

increased sensitivity to viral and bacterial respiratory tract infections. There may also be a marked increase in gastroesophageal reflux, often an asthma trigger[26–28]. Increased emotional stress can also increase the frequency of asthma exacerbations[15,29]. Finally, increased progesterone levels result in centrally mediated hyperventilation, manifested as 'dyspnea of pregnancy', or an increased patient sense of shortness of breath[18,25]. This latter circumstance may result in more patient complaints of respiratory symptoms, even in the absence of worsening asthma.

As with non-pregnant women, cigarette smoking increases the frequency of exacerbations[12]. Interestingly, the same may be said regarding excessive weight gain[30]. Furthermore, pregnant women often worry about effects of their asthma medications, and may discontinue them inappropriately. The complex interaction of all of the above factors in each individual patient determines whether asthma will improve, worsen, or remain stable during gestation.

EFFECTS OF ASTHMA ON PREGNANCY

Older, retrospective data had suggested associations of asthma with a host of poor pregnancy outcomes including hyperemesis, gestational diabetes, hypertension/pre-eclampsia, puerperal hemorrhage, cesarean delivery, preterm birth, intrauterine growth restriction, congenital malformations, perinatal mortality and stillbirth[16]. In contrast, recent prospective studies contradict this generalization. Indeed, the more recent data suggest that most women with asthma will have an uneventful pregnancy course[31–33]. For women with well controlled asthma, pregnancy outcomes are similar to those of women without asthma[26,31–34].

This having been said, and in line with comments earlier in this chapter, women with more severe or poorly controlled asthma are prone to adverse perinatal outcomes. One study showed statistically significant increases in gestational diabetes, small for gestational age newborns and cesarean delivery for women with moderate–severe asthma, even with optimal control, when compared to controls without asthma[35]. Women with daily symptoms also had higher rates of pre-eclampsia[36]. Need for oral steroids was independently predictive of delivery prior to 37 weeks and low birth weight (less than 2500 g)[35,37]. Pulmonary function testing was also predictive of pregnancy outcomes: an FEV1 less than 80% of predicted values was associated with preterm delivery, pre-eclampsia, cesarean delivery and small for gestational age newborns[1,32,35].

Importantly, management by a physician with experience in asthma, such as a pulmonologist or perinatologist, decreases the risk of perinatal mortality, preterm birth and low birth weight in women with moderate to severe asthma[11]. Unfortunately, similar management has not been shown to be beneficial in decreasing the risk of pre-eclampsia in pregnant women with asthma. Women with acute exacerbations requiring emergency room visits or hospitalization should be managed collaboratively by the emergency physician or pulmonologist and the obstetrician[11].

MANAGEMENT OF ASTHMA DURING PREGNANCY

A detailed history and physical examination should be performed to identify signs/symptoms of asthma during the initial encounter with the patient. Optimally, this assessment should occur prior to conception in order to establish a baseline[1]. Patients who have not had a baseline status established prior to pregnancy should have it established at their first obstetric visit[34,38].

A detailed history of disease status during prior pregnancies should be elicited because asthma symptoms experienced during prior pregnancies are generally predictive

of symptoms experienced in subsequent pregnancies in any given patient[16,19,35]. Patients should be encouraged to take an active role in their disease management, paying close attention to factors which affect their disease status and the onset of exacerbations[39,40]. This includes the avoidance of potential triggers, particularly cigarette smoking and recognizing the impact of excessive weight gain during pregnancy[7,12].

Management or co-management of these patients by a physician with sufficient experience in caring for pregnant asthmatics improves outcome[34]. The following criteria should be used to guide decisions about referrals. Patients who experience a life-threatening exacerbation; fail to meet treatment goals; exhibit atypical or severe persistent symptoms or with an unclear diagnosis; present as candidates for immunotherapy; require continuous systemic corticosteroid therapy or more than one short course of corticosteroids per year; or have complicating symptoms including nasal polyps, gastroesophogeal reflux disease (GERD), severe rhinitis, or chronic obstructive pulmonary disease (COPD) all will benefit from early and/or urgent referral[7,11,39–41].

Women who experience acute asthmatic exacerbations during pregnancy should be managed similarly to women with asthma who are not pregnant. Asthma exacerbations tend to be most common between 24 and 36 weeks' gestation, at which time patients should be advised to be proactive in the management of their disease[11,23,24,32]. Mild to moderate respiratory symptoms should be recognized and treated as aggressively as if these women were not pregnant with the recognition that the evolution to a more serious condition has the potential to worsen maternal as well as fetal status. Fewer acute exacerbations are reported to occur after 37 weeks' gestation and exacerbations are also uncommon during labor. However, and most importantly, women with inadequately controlled symptoms prior to labor are more likely to have exacerbations during labor[4,24,31–34,42].

Establishing patient-centered treatment goals

In order to engage the patient in monitoring and treating her own disease, as well as to determine when therapy is inadequate and requires escalation or augmentation, it is critical to establish specific goals at the outset of treatment. Treatment goals should be geared towards the prevention of chronic symptoms, and/or exacerbations, and maintenance of normal activity level[6,7,41]. An effective medication regimen with as few side-effects as possible should be prescribed.

Treatment algorithm[7,10,11,23,31–34,37,41]:

1. Patients should be educated on how to perform accurate peak flow measurements. They should establish with their physician their personal best baseline peak flow measurement which is used to compare future values:
    a. 'Typical' peak flow in pregnancy: 380–550 l/min
    b. Green zone: >80% of personal best
    c. Yellow zone: 50–80%
    d. Red zone: <50%.
2. Follow-up evaluations of pulmonary function can be accomplished with peak-flow measurements.
3. All pregnant women with asthma should receive a written action plan describing the management of acute and chronic symptoms.
4. Patients with mild persistent disease should monitor peak flow values monthly. Patients with moderate–severe disease should be counseled to do daily peak flow evaluations. All patients should evaluate peak flow values during an exacerbation.

5. Patients should be educated on how to perform accurate peak flow measurements. They should establish with their physician their personal best baseline peak flow measurement which then can be used to compare to future values. The 'typical' peak flow in pregnancy ranges from 380 to 550 l/min. If patients find that their peak flow is between 50 and 80% of their personal best, they should follow additional steps, depending upon whether their peak flow is above or below 50% of their personal best.
6. Patient should immediately notify physicians of any red zone values and the patient should have a prescribed action plan.
7. Patients with repeated values in their yellow zone may require an escalation of therapy at their next office visit.
8. Chest radiographs should be used to evaluate patients with exacerbations to rule out infection and other disease processes.
9. Serial ultrasound surveys for growth should be performed during the third trimester for patients with poorly controlled asthma and/or baseline moderate–severe persistent disease requiring chronic oral corticosteroid therapy.
10. Additional testing (non-stress test) may be considered based on asthma severity or evidence of fetal growth restriction.

Management of labor and delivery

Scheduled asthma medications should be continued during labor and delivery. Patients on systemic steroids should receive stress dose steroids at the time of delivery and for up to 24 hours postdelivery[27,37]. Indomethacin should be used with caution in patients with NSAID-induced asthma symptoms because of its potential to cause bronchospasm[42]. Morphine and meperidine should be used with caution, given that these medications stimulate histamine release that can worsen asthma symptoms[27].

Although some prostaglandins (PG) may worsen asthma symptoms, this effect is not universal, and the individual properties of each prostaglandin should be considered when making decisions with regards to their use in patients with asthma. For example, PGE1 (misoprostol) induces airway dilation while decreasing inflammation and cellular proliferation; as such it is not contraindicated in pregnant asthmatics. PGE2 (dinoprostone) is a potent bronchodilator and also is not contraindicated in such patients. On the other hand, PGF2α (carboprost) may trigger airway constriction, inflammation and vasoconstriction and thus should be used with caution in women with asthma[9,25,43].

ASTHMA TRIGGERS AND COMORBIDITIES

The identification and avoidance of triggers is important in optimizing asthma management both during and outside of pregnancy. A number of triggers should be considered and it is important to remember that more than one may be operative in any given patient.

Infections

Respiratory infections are the most common triggers of asthma exacerbations, accounting for as many as 60% of all asthma-related hospital admissions. Colonization of the upper respiratory tract by pathogens leads to cell-mediated inflammatory processes, which in turn lead to bronchoconstriction. Individuals with asthma are more susceptible to colonization by infectious agents and experience slower rates of pathogen clearance. Effects from infection

-related exacerbations may last up to 8 weeks after the primary infection[19,28,32,43].

Viral infections are more commonly associated with asthma exacerbations than bacterial infections and should be considered in all patients experiencing exacerbations. In adults, rhinovirus is most commonly associated with exacerbations. Co-infection with influenza virus is also common in individuals experiencing exacerbations. Accordingly, all women who expect to be pregnant during the influenza season should be offered influenza vaccination[28].

Drugs

Drug-induced exacerbations most commonly are due to aspirin or cyclooxygenase-1 (COX-1)-inhibiting NSAIDs. The prevalence of NSAID-induced respiratory symptoms is 10–11% in asthmatics compared to 2.5% in non-asthmatics. NSAID-induced asthma is thought to be caused by an inhibition of COX-1 in the airway of sensitized patients which results in a depletion of PGE2, a potent bronchodilator. As a result, patients with asthma may experience bronchoconstriction after exposure to these agents[23,26,27,43].

Highly selective COX-2 inhibitors may not exhibit the same bronchoconstrictive properties and, thus, may present a reasonable alternative if clinically indicated. In individuals for whom there is no alternative therapy to COX-1, it is possible to offer desensitization to COX-1 inhibitors. Medications such as acetaminophen and sodium salicylates are generally well tolerated and typically do not act as triggers for asthma symptoms[23,26,27,43].

Occupational triggers

Occupational triggers account for 5% of all asthma complaints and 26% of all work-related respiratory disease. Occupational induced asthma exacerbations are characterized by temporal as well as cyclic trends. Typically, upon arrival to work these individuals are symptom-free. As the work day continues, symptoms develop and become progressively worse only to remit or lessen after these individuals leave the work place. Remission is notable during holiday and vacation time, but resumption of work initiates the cycle anew[9,13].

Common occupational triggers include metal salts, wood products, residues from grain products and a variety of industrial chemicals. Exposure to these agents induces both an early and a late response, both of which are mediated by mast cell activation. Early responses are a result of histamine and leukotriene release resulting in bronchoconstriction. Late responses are a consequence of cytokine and chemokine production, which leads to inflammation of the tracheobronchial airway. Differences in the pathophysiology of these responses should be considered when deciding upon appropriate therapy[9,11,13].

Exercise-induced asthma

Exercise-induced asthma is characterized by acute bronchoconstriction during or immediately after exercise. Fifty to 90% of all asthmatics experience airway sensitivity related to physical activity. Clinically, exercise-induced asthma is defined as 10% or more decline in FEV1 following exercise. During exercise, the increase in inspired air overwhelms the body's ability to warm the air to body temperature prior to its reaching the distal airways. Bronchoconstriction is the result of cold (unwarmed) air reaching the distal bronchial tree[14].

Environmental allergens

Hypersensitivity responses to environmental allergens require prior extended exposure to the offending agent to produce sensitization.

Individuals who are sensitized to a particular agent mount an IgE-mediated response after which subsequent reintroduction to the agent leads to histamine production, which causes rhinitis and progressive bronchoconstriction.

Environmental allergenic triggers frequently follow seasonal patterns and 75–85% of asthmatics have positive skin tests to common environmental allergens. Environmental triggers include indoor and outdoor exposures. Outdoor triggers are usually related to climate conditions that promote increases in agents such as ozone, nitrogen dioxide and sulfur dioxide often resulting in respiratory symptoms in the general population. Often, however, the asthmatic population experiences an exaggerated response to subtle atmospheric changes. Indoor triggers include exposure to animals, tobacco smoke, dust mites, molds and cockroaches, and as such often are implicated in the development of childhood asthma. Activities that may be taken to lessen these symptoms include the removal of carpets/rugs, reduction of humidity in an effort to decrease mite growth, departure from the house during vacuuming, weekly bathing of pets (or removal of pets) and the control of cockroaches[1,12,23,33].

Emotional stress

Asthmatic patients experience changes in elastic recoil, ventilation distribution and pulmonary blood flow during times of high stress. Positive and negative emotional stresses stimulate vagal efferent activity, inducing changes in airway hyperactivity in some patients. These changes influence airway resistance by modifying smooth muscle contractions and respiratory secretions[15].

PHARMACOTHERAPY

Most medications used for asthma treatment outside of pregnancy are also not contraindicated during pregnancy. Below, we provide a discussion of the mechanism of action of each class of drug, special considerations for use during pregnancy, and specific examples of medications with their FDA classification for use in pregnancy[9,17,23,32,38]. Table 1 describes the FDA classification system for medications in pregnancy.

β_2 agonists

β_2 agonists bind to β_2 receptors on bronchial smooth muscles increasing cyclic AMP production, leading to bronchial relaxation and dilation. β_2 agonists also inhibit the release of mediators of immediate hypersensitivity from mast cells. They can be further classified as short acting agents used for acute exacerbations, and long acting agents used for main-

Table 1 FDA pregnancy classification of medications

Risk category	*Animal data*	*Human data*	*Recommendation*
A	Negative	Negative	Use approved
B	Negative	None available	Use approved
B	Positive	Negative	Use approved
C	Positive	None available	Use approved
C	None available	None available	Use approved
D	Positive/negative	Positive	Use approved
X	Positive	Positive	Contraindicated

tenance therapy in patients with moderate to severe persistent disease[5,9,17,36].

Short acting agents are considered first line therapy for the management of acute exacerbations as well as for patients with mild intermittent disease. Short acting β_2 agonists should not be used for maintenance therapy. These agents are not contraindicated during pregnancy or lactation and have not been associated with an increased risk of congenital malformation or adverse pregnancy outcome.

Long acting agents are best for patients with moderate to severe persistent disease who are not adequately controlled with inhaled steroids alone. Although human data are scant, they lack any evidence of an increased risk of congenital malformations. Risk–benefit considerations favor the use of these medications in select patient groups[5,9,17,36].

Examples include:

- Short acting: albuterol (category C)
- Long acting: salmeterol (category C).

Inhaled corticosteroids

Inhaled corticosteroids counteract the inflammatory response that takes place during asthma exacerbations. In addition, inhaled corticosteroids act to modify the immune response by inhibiting the activation of numerous cell types including mast cells, eosinophils, neutrophils, macrophages and lymphocytes.

Inhaled corticosteroids should be initiated as maintenance therapy in patients with persistent asthma symptoms. They are not contraindicated in pregnancy and have not been associated with an increased risk of congenital malformation or adverse pregnancy outcome[5,17,35,43].

Examples include:

- Beclomethasone (category C)
- Budesonide (category B)
- Fluticasone (category C)
- Flunisolide (category C).

Systemic corticosteroids

As with inhaled corticosteroids, systemic corticosteroids act as anti-inflammatory agents to reverse the inflammatory response characteristic of asthma exacerbations. They also modify the body's immune response to stimuli by inhibiting the activation of numerous cell types including mast cells, eosinophils, neutrophils, macrophages and lymphocytes[5,9,35,36].

A number of clinical studies have found an association between chronic systemic steroid use during pregnancy and adverse pregnancy outcome including preterm delivery, preeclampsia and intrauterine growth restriction. However, it is not clear to what extent these outcomes are related to the disease process *per se* and not to the drugs used to treat it. For example, reports suggest that infants of mothers treated with corticosteroids during the first trimester have an increased risk of facial clefts (0.1–0.3%). Despite this, due to the documented increase in maternal and fetal morbidity and mortality associated with poorly controlled asthma, and the important role that systemic steroids may provide in asthma control, the American College of Obstetrics and Gynecology recommends that systemic steroids be used when clinically indicated and that benefits for maternal and fetal health are perceived to outweigh risks. Systemic steroids should be administered in short bursts for patients with severe asthma exacerbations. A select group of patients will require chronic use of systemic steroids to adequately manage asthma symptoms[5,9,23,35,36].

Examples include:

- Prednisone (category C)
- Methylprednisone (category C)
- Dexamethasone (category C).

Anticholinergics

Anticholinergics act by binding to acetylcholine receptors, thereby reducing the action of acetylcholine. This reduction in acetylcholine activity results in an inhibition of secretions from serous and seromucous glands and a reduction of symptoms associated with asthma exacerbations. These agents should be considered as add-on therapy to β_2 agonists for the treatment of acute asthma exacerbations. Anticholinergics have not been associated with an increased risk of congenital malformation or adverse pregnancy outcome[23,26,32,34,40].

Examples include:

- Ipatropium (category B).

Methylxanthines

Methylxanthines work by promoting smooth muscle relaxation. They also suppress the hypersensitivity reaction of the airways to stimuli. Theophylline, the most commonly used methylxanthine, is not commonly prescribed during pregnancy due to multiple drug interactions, the need to monitor levels and bothersome side-effects. Side-effects such as insomnia, heart burn, palpitations and nausea all decrease patient tolerability. It is, however, not contraindicated in pregnancy, as it has not been associated with an increased risk of congenital malformations or adverse maternal outcome[23,26,32,34,40].

These agents should be considered as add-on therapy to inhaled corticosteroids therapy regimens. To ensure efficacy and safety serum levels should be titrated and maintained to levels between 5 and 12 μg/ml.

Examples include:

- Theophylline (category C).

Cromoglycates

Cromoglycates block the activation of chloride channels which results in an inhibition of airway inflammatory cells including mast cells. Cromoglycates are effective in preventive therapy for individuals with persistent asthma.

Cromoglycates should not be used as a first line therapy as their efficacy is generally considered less than that of inhaled corticosteroids. Patients with mild persistent asthma who are effectively managed with cromolyn sodium prior to pregnancy may be maintained on their current regimens. Cromolyn sodium use has not been associated with an increased risk of congenital malformations or adverse maternal outcome[5,23,32,34,38].

Examples include:

Table 2 FDA recommendations for asthma therapy

Asthma classification	*Recommended therapy*
Mild intermittent	Inhaled β_2 agonist as needed
Mild persistent	1st scheduled inhaled corticosteroids 2nd scheduled inhaled cromolyn
Moderate persistent	Scheduled inhaled corticosteroids plus theophylline or salmeterol
Severe persistent	Scheduled inhaled corticosteroids plus theophylline or salmeterol plus oral corticosteroids prescribed in short bursts or daily dosing as needed

- Cromolyn sodium (category B)

Leukotriene inhibitors

Leukotriene inhibitors act to antagonize leukotriene activity, thereby inhibiting bronchial smooth muscle contractions as well as the reactive inflammatory response.

Leukotriene inhibitors are effective in mild–moderate asthma management. Information regarding the use of leukotriene inhibitors during pregnancy is limited, and they should only be used in patients with intractable asthma who require them for adequate symptom control. Zileuton should be avoided in pregnancy due to unfavorable results observed in animal studies that demonstrated increased rates of miscarriage, stillbirth, low birth weight and skeletal abnormalities associated with its use[5,23,32,34,38].

Examples include:

- Zafirlukast (category B)
- Montelukast (category B)
- Zileuton (category C – not recommended).

A summary of the current FDA recommendations for initiation of therapy is included in Table 2.

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