Clinical Expert Series CME

Asthma in Pregnancy

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Asthma affects up to 10% of pregnancies and confers risk to both mother and child. Adverse maternal outcomes associated with asthma include preeclampsia, preterm labor, and increased risk of cesarean delivery. Maternal asthma also increases risks of low birth weight and small-for-gestational-age birth weight, as well as pediatric respiratory disease, including neonatal respiratory distress and early-onset asthma. Despite these risks, evidence suggests that both chronic asthma and acute asthma exacerbations remain undertreated in pregnancy. Recent landmark clinical trials in nonpregnant individuals have shown that, even for patients with mild disease, using as-needed inhaled corticosteroids combined with long-acting bronchodilators as rescue therapy dramatically reduces exacerbations. Inhaled corticosteroids are considered safe in pregnancy and are effective in reducing symptoms, preventing exacerbations, and mitigating some adverse pregnancy outcomes. Therefore, inhaled corticosteroids should be included as a mainstay in the treatment regimens of all pregnant women with asthma, preferably with an inhaled corticosteroid and rapid-onset bronchodilator combination inhaler for as-needed use and for daily maintenance use in those with more persistent asthma symptoms or risk factors for complications. Clinicians should actively discourage discontinuation or de-escalation of asthma therapies during pregnancy and educate women on the safety and importance of these medications for both themselves and their offspring. Asthma exacerbations during pregnancy confer additional risk, so they must be promptly recognized and treated with systemic corticosteroids and bronchodilators. This Clinical Expert Series article provides an overview of asthma in pregnancy, with a focus on its potential adverse health effects and the core principles of asthma evaluation and treatment in pregnancy.

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Asthma is the most common chronic respiratory disorder complicating pregnancy, affecting 3–10% of pregnant women in the United States.[1–3] Maternal asthma is associated with a number of adverse pregnancy outcomes that can affect the health of both pregnant mothers and their children. Despite advances in our understanding of asthma and its treatment, national surveys suggest that maternal asthma is often poorly controlled.[2] An analysis of U.S. health care claims databases found that 16–28% of asthma is poorly controlled during pregnancy.[3] Among pregnant women with poor asthma control, up to 40–50% do not use any controller inhaler therapy.[2,3] Up to 40% of pregnant women report an asthma exacerbation in the past year,[2] and nearly 20% experience an exacerbation requiring medical intervention.[4]

The course of asthma during pregnancy is variable. Pregnancy can influence asthma severity in unpredictable ways, with early studies suggesting that roughly equal proportions of women will worsen, improve, or have unchanged asthma control during pregnancy.[5–9] A more recent study of 308 pregnant women found that 40% experienced worsened asthma control with pregnancy, and it did not identify any whose control improved.[10] Subsequent pregnancies may follow a similar asthma course for a majority of women.[7]

Asthma treatment recommendations have been updated in recent years after several landmark clinical

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trials demonstrated the benefit of inhaled corticosteroid (ICS)–based regimens for all patients, even those with mild asthma.[11–14] In addition, increasing use of targeted biologic therapies in asthma raises questions about their role and safety in the treatment of severe asthma during pregnancy. This Clinical Expert Series article reviews the outcomes, evaluation, and treatment of asthma in pregnancy, with a focus on risk reduction through assessment of disease control and optimization of evidence-based asthma treatment strategies. The literature review methods for preparation of this article are outlined in Appendix 1, available online at http://links.lww.com/AOG/E147.

DEFINITIONS AND TERMINOLOGY

The terminology used to classify asthma severity and control varies depending on its context. *Disease control* refers to the burden of asthma symptoms and risk of complications such as exacerbations and impaired lung function, which may be mitigated by treatment and other interventions. *Uncontrolled disease* is that with a high symptom burden, frequent or serious exacerbations, or impaired lung function and may be related to inadequate treatment, comorbidities, environmental factors, or refractory disease. For the purposes of this review, classification of asthma severity is defined by the intensity of treatment required to achieve disease control. *Mild asthma* refers to disease controlled by only as-needed therapy or low-dose daily ICS. *Moderate asthma* is that controlled with low- or medium-dose ICS plus long-acting β agonist (ICS-LABA) combination therapy. *Severe asthma* is that which requires or remains uncontrolled by combination high-dose ICS-LABA therapy. These definitions are consistent with those used by national and international society guidelines,[15,16] although definitions used within individual studies referenced herein may differ slightly.

RESPIRATORY PHYSIOLOGY DURING PREGNANCY

During pregnancy, the respiratory system is influenced by numerous hormonal and mechanical changes. Progesterone and estrogen increase throughout gestation, affecting the respiratory system in several important ways. Beginning in the first trimester, there is a marked increase in minute ventilation attributed predominantly to the central effects of progesterone, increasing the tidal volume of each breath.[17] As a result, serum carbon dioxide (CO_2) levels decrease, producing a chronic and compensated respiratory alkalosis, which facilitates offloading of fetal CO_2. There is also a small increase in arterial oxygen tension, which compensates for increases in oxygen consumption and basal metabolic rate during pregnancy. It is important to recognize that although the volume of each breath increases in pregnancy, the respiratory rate is relatively unchanged. Progesterone also affects the airways, exerting a mild bronchodilatory effect and causing hyperemia and edema of the airway mucosa.[17] Increased prostaglandin levels during pregnancy can have variable effects on the airway smooth muscle, with some acting as bronchodilators and others causing bronchoconstriction.[18]

Pregnancy also changes respiratory system compliance through effects on the diaphragm and chest wall. As the gravid uterus expands, it causes an upward displacement of the diaphragm (up to 5 cm) and a resultant decrease in resting lung volumes.[17,19] To compensate, the rib cage expands and accessory muscles are recruited. These effects are most pronounced during the third trimester.[17]

As a result of these normal changes, up to 70% of women endorse a sensation of dyspnea by 30 weeks of gestation. Often called "physiologic dyspnea of pregnancy," it is most pronounced during the third trimester.[17,20] It is important to note that dyspnea of pregnancy is an isolated symptom, whereas dyspnea that occurs as part of asthma is typically paroxysmal and frequently accompanied by cough, chest tightness, wheezing, and responsiveness to rescue inhaler use.

PATHOPHYSIOLOGY OF ASTHMA

The hallmark of asthma is expiratory airflow limitation. This obstruction is typically episodic and reversible, although it may become fixed in those with long-standing asthma. Airflow limitation leads to the characteristic symptoms of wheezing, dyspnea, and cough experienced by most patients with asthma.

The pathophysiology of asthma is complex and varies significantly between patients. In general, airway inflammation causes bronchial smooth muscle constriction and excessive mucus production, leading to luminal narrowing and obstruction. For some patients, often referred to as those with T-helper cell type-2 high or allergic asthma, this inflammation is driven by pathways that involve eosinophils and inflammatory mediators such as immunoglobulin E (IgE), interleukin (IL)-4, and IL-5.[21] Recognition of these inflammatory pathways has led to the development of targeted biologic therapies, which are increasingly used in the treatment of severe asthma.

DIAGNOSIS AND EVALUATION OF ASTHMA DURING PREGNANCY

The diagnosis of asthma is based on a combination of suggestive symptomatology and variable airflow obstruction on lung function testing. Symptoms are typically intermittent and include wheezing, cough, chest tightness, and dyspnea. They may be triggered by exposures such as allergens, smoke and other irritants, cold air, exercise, or respiratory viruses.[16] Symptoms at night or on waking are also common in asthma.[16,22]

Lung Function Testing in Pregnancy

Lung function testing most commonly involves spirometry, which measures expiratory volumes and flows, and can include measurements of lung volumes and diffusion capacity for carbon monoxide. Spirometric volumes and flows and diffusion capacity for carbon monoxide do not change significantly with pregnancy. However, subtle changes can occur in the measurement of resting lung volumes in the second and third trimesters as a result of upward displacement of the diaphragm by the gravid uterus, with mild reductions in functional residual capacity, expiratory reserve volume, and residual volume (Fig. 1).[17,23] The total lung capacity does not change because of an increase in the inspiratory capacity during pregnancy.[17]

In active asthma, airflow obstruction causes a slowed and prolonged exhalation. This can be measured by spirometry, which shows a decrease in the air exhaled in the first second (forced expiratory volume in 1 second [FEV_1]) relative to the total air exhaled (forced vital capacity [FVC]), reducing the FEV_1:FVC ratio to less than 0.7. This can be visualized with a flow–volume loop that is characteristically drawn out or "scooped." In asthma, the obstruction may be reversible, as evidenced by a significant improvement in FEV_1 or FVC after the administration of inhaled bronchodilators. Lung volumes in asthma are typically normal, although they can increase in severe cases as a result of hyperinflation and air trapping. The diffusion capacity for carbon monoxide is normal or even increased in asthma.

The presence of variable airflow obstruction on spirometry is important in confirming a diagnosis of asthma. However, obstruction may be absent at the time of testing for patients with intermittent disease. Thus, it is important to recognize that normal lung function tests do not rule out a diagnosis of asthma. Bronchoprovocation testing, wherein airway hyperresponsiveness is elicited by administration of a trigger (typically methacholine), is not recommended in pregnancy given the risk of precipitating severe bronchoconstriction.[16]

Evaluation of Asthma

Accurate assessment of disease severity and symptom control is imperative in the evaluation of asthma and should be monitored throughout pregnancy. Increased severity[24,25] and impairment from asthma symptom[26,27] are strong predictors of exacerbation risk, which is of heightened importance during pregnancy because asthma exacerbations increase the risk of poor outcomes.[4,28] A thorough asthma evaluation includes assessment of recent asthma symptoms, history of and risk factors for exacerbation, current treatment and adherence to treatment, inhaler technique, frequency of rescue inhaler use, related comorbidities, environmental conditions, and measurement of lung function with spirometry to determine the presence and extent of airflow obstruction (Fig. 2). Useful tools for assessing recent symptom control include the Asthma Control Test, Asthma Control Questionnaire, and Global Initiative for Asthma symptom control tool. Important comorbidities that may complicate asthma include allergy and atopic disease, rhinitis and nasal polyps, and gastroesophageal reflux disease (Table 1). All women should be screened for depression, regardless of asthma or pregnancy status, and studies show that depression in pregnancy is a risk factor for poor asthma control.[29]

In pregnancy, similar to the general population, we recommend obtaining spirometry at diagnosis of asthma or to establish a baseline in those without lung function tests within the past 2 years, in patients with new or increasing symptoms, and before the start or escalation of asthma therapy.[16] Although lung function measurements do not always correlate with asthma symptoms,[30] reduced FEV_1 percent predicted is associated with higher risk of exacerbation[31] and further lung function decline.[32] If clinicians are not familiar with obtaining or interpreting spirometry, it should be coordinated with local primary care or pulmonary practices that possess this capability.

Although poorly controlled asthma symptoms predict exacerbations, it is important to recognize that even patients with seemingly well-controlled asthma can have severe exacerbations. Therefore, evaluation and modification of exacerbation risk factors are necessary (Table 1). Particular attention should be paid to assessing medication adherence and inhaler technique. Individualized asthma education incorporating "teach-back" or "teach-to-goal" strategies empowers patients in asthma self-management, optimizes inhaler technique, and improves medication adherence,[33,34] which can lead to improved disease control.[35]

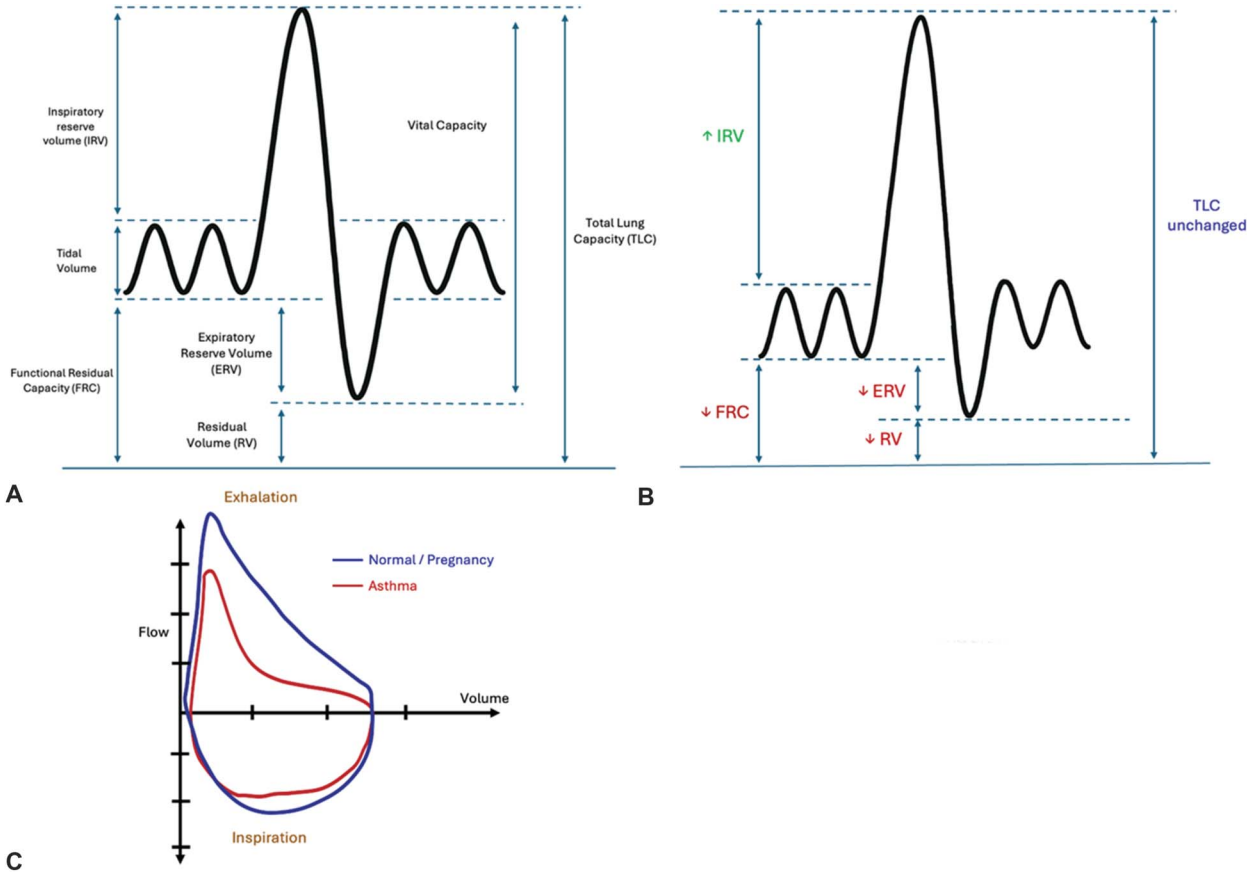

Fig. 1. Pulmonary function testing in pregnancy and asthma. **A.** Representation of normal lung volumes. Two cycles of tidal breathing are followed by a maximal inspiratory effort and then a maximal forced expiration, ending with a return to tidal breathing. **B.** Pregnant women breathe at lower resting lung volumes, best represented by a reduced functional residual capacity (the sum of expiratory reserve volume and residual volume, also reduced), predominately because of mechanical effects of the gravid uterus. Note that total lung capacity is unchanged as a result of an increase in inspiratory reserve volume. These changes begin during the second trimester and are most evident in the third trimester. **C.** Illustration of spirometry, comprising inspiration followed by a forced expiratory maneuver, on a flow–volume loop. Spirometry is typically normal in pregnancy. In asthma, there is a characteristic "scooping" of the expiratory limb when obstruction is present, depicting the expiratory flow limitation.

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MATERNAL AND OFFSPRING OUTCOMES

Literature comparing pregnant women with asthma with those without asthma demonstrates that maternal asthma is associated with adverse maternal, perinatal, and pediatric outcomes. Reasons for these observed associations are not fully understood. Possible explanations include chronic or intermittent maternal hypoxia influencing placental oxygen delivery and fetal oxygenation, adverse effects of increased inflammatory mediators in maternal asthma, or even underlying dysfunction of smooth muscle common to both the airways and myometrium.[36]

Maternal Outcomes

Observational studies have found an association between maternal asthma and increased risk of preeclampsia,[37,38] further demonstrated in a 2011 meta-analysis (relative risk [RR] 1.54, 95% CI, 1.32–1.81).[36] Contemporary studies have also linked maternal asthma to increased risk of placental abruption,[37–39] placenta previa,[37,39] and both antepartum and postpartum maternal hemorrhage.[37–40] Women with asthma more frequently experience preterm contractions[36,38] and premature rupture of membranes[38,39] and have higher risk for cesarean delivery.[37–40] One study also found higher rates of maternal intensive care unit admission in women with asthma (adjusted odds ratio 1.34, 95% CI, 1.04–1.72).[37]

Maternal asthma is associated with numerous pregnancy-related comorbidities. Although results of cohort studies are conflicting, a 2014 meta-analysis

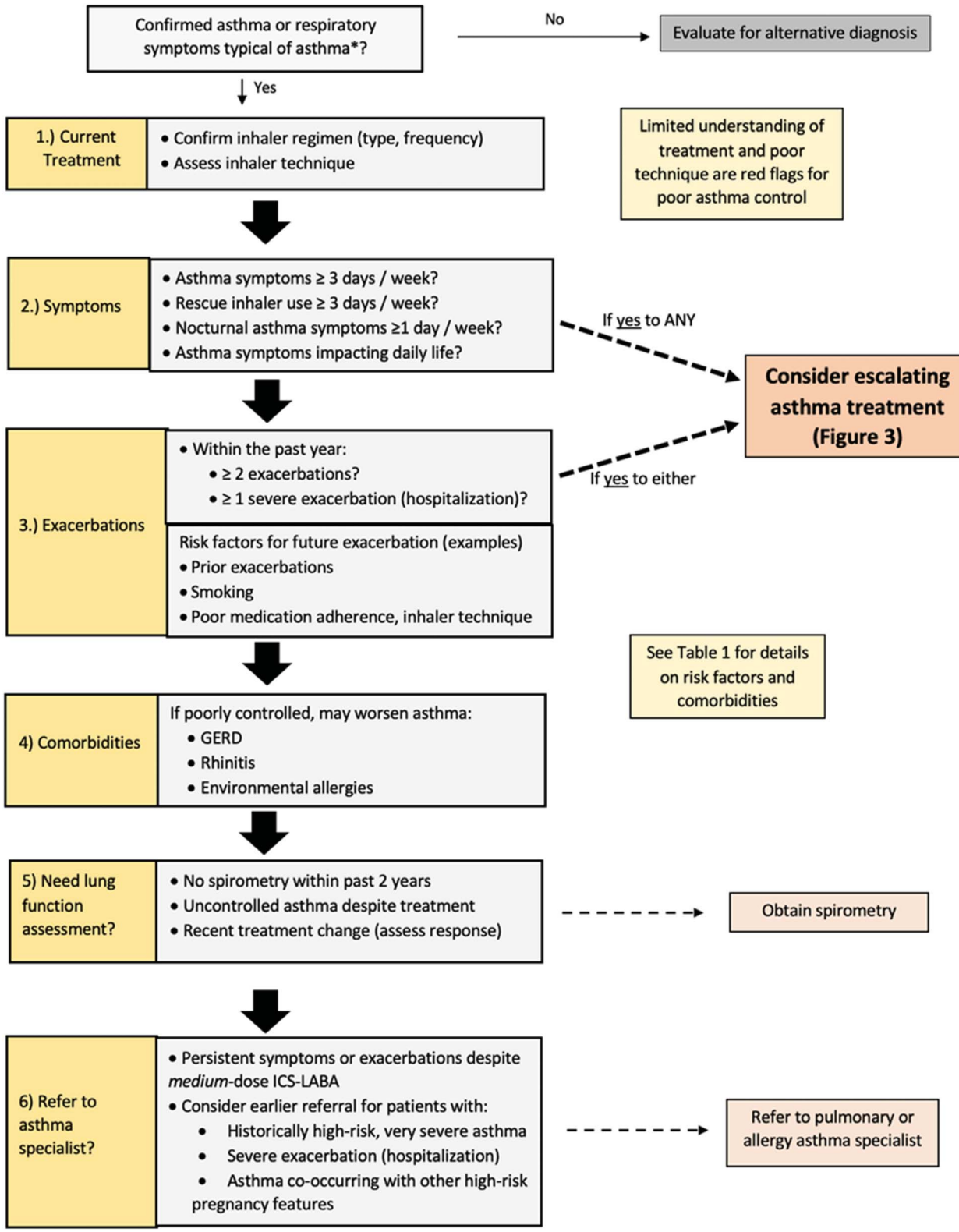

Fig. 2. Clinical evaluation of asthma in pregnancy. Thorough asthma evaluation during pregnancy aims to identify risk factors for poor outcomes and opportunities for intervention. *Typical asthma symptoms include intermittent and variable cough, wheeze, chest tightness, and dyspnea. Asthma symptoms often have predictable triggers and often occur at night and on waking. GERD, gastroesophageal reflux disease; ICS-LABA, inhaled corticosteroid–long-acting β agonist.

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Table 1. Additional Considerations in Asthma Evaluation

	Considerations
Risk factors for asthma exacerbation[100]	
Prior exacerbations	1 or more exacerbations in past year History of ICU or intubations for asthma
Severity of asthma	Severe>moderate>mild
Insufficient ICS	Not prescribed or discontinued Poor adherence Poor technique
Smoking	Cigarettes, vaping Cessation may improve symptoms, lung function, and neonatal outcomes
Comorbid psychiatric illness	Depression or anxiety
Impaired lung function	Low FEV_1 Large bronchodilator response
Increased maternal age	Age older than 35 y
Multiparity	
Multiple gestation	Twin and triplet pregnancies increase risk compared with singletons
Obesity	Prepregnancy or postpregnancy weight loss may mitigate risk Excess weight gain during pregnancy not shown to increase risk
Social determinants of health	Black and Latinx Americans have higher asthma morbidity in general Studies suggest that Black patients have higher exacerbation risk in pregnancy Health care access and quality, environmental exposures, chronic stress, and other socioeconomic factors
Comorbid conditions	
Gastroesophageal reflux disease[123–125]	Very common (40–85% of pregnancies) Lifestyle modification and dietary changes are first line Antacids and H2 blockers generally considered safe PPIs typically reserved for refractory or severe disease
Atopy and allergies[126]	Trigger avoidance is key Intranasal steroids, montelukast, or certain antihistamines can be used Continuation of allergen immunotherapy is generally considered safe but should be discussed with allergist
Rhinitis (allergic and nonallergic)[127]	Safe treatment options include intranasal steroids, montelukast, certain antihistamines Avoid decongestants if possible

ICU, intensive care unit; ICS, inhaled corticosteroid; FEV_1, forced expiratory volume in 1 second; H2 blocker, histamine type 2 receptor antagonist; PPI, proton pump inhibitor.

found maternal asthma to be associated with an increased risk of gestational diabetes (RR 1.39, 95% CI, 1.17–1.66).[39] Pregnant women with asthma report increased respiratory viral infections[41,42] and may have higher rates of pulmonary embolism[37] and urinary tract infections.[42] In addition, a recent cohort study found an association between maternal asthma and postpartum depression (adjusted odds ratio 1.58, 95% CI, 1.50–1.67).[43]

Offspring Outcomes

Children of mothers with asthma are also at increased risk of adverse outcomes. A study from Sweden of more than 260,000 pregnancies found associations between maternal asthma and low birth weight (less than 2,500 g) and small-for-gestational-age (SGA) birth weight (birth weight more than 2 SDs below the mean), as well as moderate-to-late preterm birth between 32 and 36 weeks of gestation.[38] A large cohort study from the United States also found an increased risk of indicated preterm birth in women with asthma.[37] Maternal asthma has been associated with small increases in risk of neonatal hospitalization and death, neonatal respiratory distress, transient tachypnea of the newborn, and congenital malformations, including cleft lip.[44–46]

In addition to these neonatal outcomes, large cohort studies have shown that uncontrolled maternal asthma confers increased risk of bronchiolitis and early-onset asthma in their children.[47,48] This risk of wheezing and atopy may

be further increased by respiratory viral infections during pregnancy.[49]

Effect of Asthma Severity and Treatment on Outcomes

The severity of maternal asthma has been shown to correlate with some poor pregnancy outcomes but not others. Some studies have found the risks of preterm delivery, cesarean delivery, and gestational diabetes to be associated with moderate and severe asthma only.[39,40] Risk of having a neonate with SGA birth weight has also been correlated with increasing severity of maternal asthma.[50]

Certain adverse outcomes appear to be mitigated by asthma treatment. A 2011 meta-analysis found that active treatment significantly reduced the risk of preterm labor (RR reduction 0.44, 95% CI, 0.25–0.77) and delivery (RR reduction 0.71, 95% CI, 0.57–0.89) compared with no active treatment.[36] In another meta-analysis, bronchodilator use was found to reduce the risk of gestational diabetes for women with asthma to that of the general population, stressing the importance of appropriate therapy.[39]

ANTENATAL SURVEILLANCE

Although the association of maternal asthma with adverse pregnancy and neonatal outcomes is clear, there are currently no formal recommendations or guidelines for antenatal surveillance specific to women with asthma. In the absence of such information, we recommend an emphasis on routine obstetric care with a heightened clinician suspicion for both maternal complications and adverse neonatal outcomes, particularly for those with moderate and severe asthma. In cases of moderate-to-severe asthma, a growth ultrasonogram in the third trimester would be reasonable to consider given the increased risk of having a neonate with SGA birth weight. A thorough asthma evaluation should be performed for all pregnant women with asthma (Fig. 2), and symptom control should be reassessed at each visit. Maternal asthma alone should not dictate mode of delivery.

ASTHMA TREATMENT IN PREGNANCY

Asthma management during pregnancy parallels that of nonpregnant patients. Goals of treatment are to alleviate symptoms, prevent exacerbations, and reduce risk of adverse pregnancy outcomes. Treatment of asthma should be personalized and guided by repeated evaluations of symptoms, exacerbations, and periodic lung function testing. Therapy is escalated in a stepwise manner until disease control is achieved (Fig. 3). Recent landmark studies have led to notable changes in modern asthma treatment.[11–14] Most critical is an increased emphasis on ICS, to be used as part of both as-needed rescue and daily maintenance inhaler regimens to prevent exacerbations. Currently, ICS-containing regimens are recommended for all patients, regardless of asthma severity.

Avoidance or discontinuation of asthma medications during pregnancy remains common, likely because of hesitancy on the part of patients and health care professionals for fear of adverse medication effects. As we will show, studies of the safety of essential asthma medications are largely reassuring. Moreover, any medication risks are typically outweighed by the risks of uncontrolled asthma during pregnancy.

Inhaled Corticosteroids

Inhaled corticosteroids are the backbone of asthma treatment and supported by decades of literature. By directly targeting airway inflammation, ICSs reduce symptoms, prevent exacerbations, and slow decline in lung function. In pregnancy, ICS use is associated with reduced risk of preterm delivery[35] and reduced asthma exacerbations (RR 0.22, 95% CI, 0.11–0.44).[51,52] Inhaled corticosteroids should be initiated at the time of diagnosis of asthma,[16] even for patients with mild disease, because studies suggest that early ICS therapy improves lung function recovery.[53,54]

For patients with mild asthma, an as-needed ICS-formoterol combination inhaler can be used alone. If symptoms are not controlled or a patient experiences exacerbation or a decline in lung function, treatment is escalated to a daily low-dose ICS-LABA combination (preferably containing formoterol so that the same inhaler can be used for both daily maintenance and rescue). From there, the ICS dose can be increased further if disease remains poorly controlled. For asthma symptoms that remain uncontrolled despite adherence to daily medium-dose ICS-LABA or for patients who experience severe exacerbations despite treatment, we recommend referral to an asthma specialist to consider additional treatment strategies.[16]

In addition to their importance for daily asthma treatment, recent studies have shown the benefits of using ICS-combination inhalers for as-needed use. When combined with formoterol, a rapid-onset LABA, these inhalers provide prompt bronchodilatation and symptom relief. Multiple large, randomized trials of adults with asthma compared use of ICS-LABA with short-acting β agonist (SABA) for rescue inhaler therapy. Use of ICS-LABA instead of SABA for as-needed therapy reduced exacerbation risk,

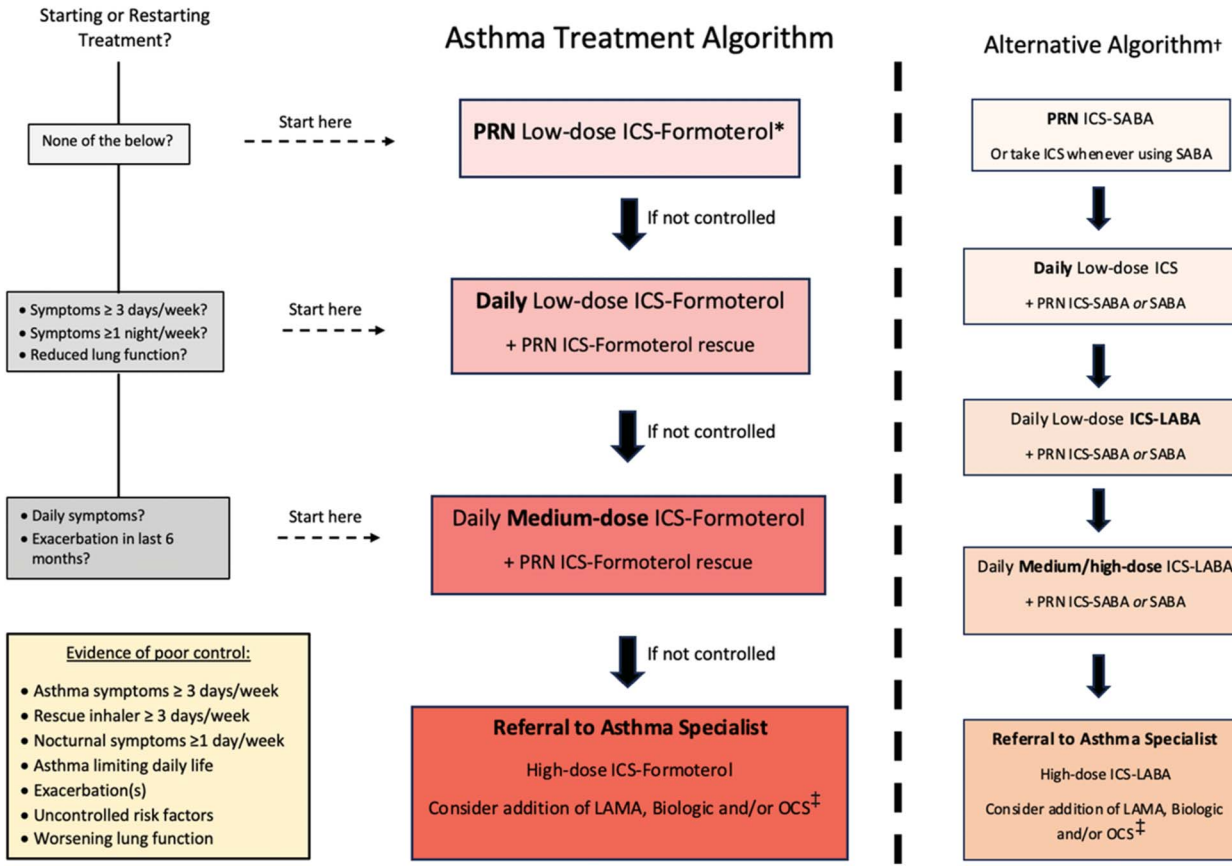

Fig. 3. Treatment algorithm for asthma in pregnancy. Treatment should be escalated in stepwise manner until asthma control is achieved as indicated by periodic reassessments of disease status. Inhaled corticosteroid (ICS) should be included in all treatment regimens given their proven efficacy in reducing exacerbations. *ICS total daily dose (micrograms) with formoterol: budesonide 200–400 (low-dose), 400–800 (medium), and more than 800 (high); mometasone 200–400 (low–medium), and more than 400 (high). †Alternative treatment strategy may be considered for patients who have a strong preference for a specific alternative (nonformoterol) maintenance or short-acting β agonist (SABA) rescue inhaler. ‡Adjunctive treatments to be considered under guidance of asthma specialist. Chronic oral corticosteroid (OCS) is not typically preferred because of its side-effect profile. PRN, as needed; SABA, short-acting β agonist; LABA, long-acting β agonist; LAMA, long-acting muscarinic antagonist.

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regardless of asthma severity or use of a maintenance inhaler.[11–13] A 2018 trial of nearly 4,000 adult patients found a 64% reduction in rates of severe asthma exacerbations with as-needed ICS-LABA compared with SABA (RR 0.36, 95% CI, 0.27–0.49), with a number needed to treat of 11.5 to prevent one severe exacerbation.[11] A recent meta-analysis found that as-needed ICS-LABA reduced exacerbations requiring oral corticosteroids by 55% and risk of emergency department (ED) visits or hospitalizations for asthma exacerbation by 65% compared with as-needed SABA.[55] Updated guidelines recommend ICS-LABA combination inhalers as first-line rescue therapy for asthma,[16,56] a significant change for many patients given the ubiquity of the SABA albuterol.

The ICS-SABA combinations can also be used as rescue inhalers. There is emerging evidence for their efficacy, with a 2022 randomized trial finding that use of combination albuterol-budesonide as rescue therapy reduced rates of severe asthma exacerbations by 26% compared with albuterol alone.[14] These combination inhalers may be particularly useful for patients who are reluctant to stop albuterol while still providing the benefits of ICS. An alternative treatment pathway is proposed for patients who have a strong preference for a nonformoterol inhaler (Fig. 3). Note that this pathway also emphasizes use of ICS for both as-needed and maintenance therapy.[16]

It must be recognized that contemporary trials of asthma treatment during pregnancy are lacking and

that the aforementioned trials evaluating as-needed ICS-LABA excluded pregnant patients.[11–14] Nevertheless, the results of these trials are compelling and have changed modern asthma treatment. Considering the safety and known benefits of ICS in pregnancy along with the dramatic risk reduction seen in studies of nonpregnant individuals, we strongly recommend incorporating as-needed ICS-formoterol or ICS-SABA into the asthma treatment regimens of pregnant individuals, as do the Global Initiative for Asthma guidelines.[16]

De-escalating asthma treatment is not recommended during pregnancy, even for patients with well-controlled symptoms, given the heightened importance of tight disease control.[16]

Safety of Inhaled Corticosteroids in Pregnancy

Studies are reassuring about the safety of ICS throughout all stages of pregnancy (Table 2). A randomized trial of more than 300 pregnant women with asthma found no adverse fetal outcomes associated with the use of inhaled budesonide.[57] Retrospective cohort studies evaluating ICS use in the first trimester of pregnancy show no increased risk of low birth weight, prematurity, stillbirth, or congenital malformations.[58,59] One study identified increased rates of cesarean delivery in mothers exposed to ICS in early pregnancy, although this may be attributable to the underlying asthma itself.[59] Inhaled corticosteroids do not increase risk of gestational diabetes, gestational hypertension, or preeclampsia.[60,61] These reassuring findings are strengthened by additional cohort studies[62–65] and meta-analyses concluding that ICSs appear safe throughout pregnancy.[66,67] Combination ICS-LABA inhalers appear similarly safe, although safety data are more limited.[68]

Inhaled β Agonist Bronchodilators for Chronic Asthma

Short-acting β agonists have long been the rescue inhalers used to alleviate asthma symptoms. However, studies show that overuse of SABAs not only reflects poor disease control but also carries risk, including increased risk of asthma-related death. Many patients continue to overuse SABAs and underuse ICS, a practice that asthma specialists are trying to correct by encouraging the use of ICS-LABA or ICS-SABA combinations for rescue therapy.[69]

The LABAs are useful for treating asthma when combined with an ICS as both rescue (using the rapid-onset LABA formoterol) and maintenance therapy. Long-acting β agonists should not be used as monotherapy without ICS according to a 2006 trial that showed increased risk of life-threatening exacerbations and asthma-related deaths with LABA monotherapy compared with placebo.[70]

Although there are reports of increased risk of malformations and pregnancy complications with β-agonist exposure, these studies are difficult to interpret because they do not adequately control for the effect of underlying asthma. A 2013 meta-analysis of 21 studies was not able to reach a conclusion on any association between inhaled β agonists and risk of congenital malformations, premature birth, or low birth weight, citing underpowered and methodologically flawed studies.[71]

Leukotriene Receptor Antagonists

Drugs inhibiting the actions of leukotrienes, endogenous mediators of bronchoconstriction and airway inflammation, are common adjunct therapies for asthma. They may be particularly useful for patients with asthma symptoms related to allergies, exercise, or nonsteroidal anti-inflammatory drugs.[72] Leukotriene receptor antagonists may improve asthma symptoms, reduce rescue inhaler use, prevent exacerbations, and improve lung function.[73–75]

Studies suggest that leukotriene receptor antagonists have a relatively favorable safety profile in pregnancy. Studies show no significant difference in rates of congenital malformations or pregnancy loss compared with disease-matched cohorts,[76–81] although there is conflicting evidence on associations with preterm birth and low birth weight. Several retrospective cohorts found increased risk of low birth weight in neonates of mothers exposed to leukotriene receptor antagonists,[76,77] and a meta-analysis of five studies found small increases in risk of preterm birth and low birth weight,[80] although underlying maternal asthma may have confounded these results. A more recent prospective cohort study of more than 200 women exposed to leukotriene receptor antagonists in the first trimester found no increased risk of preterm birth or low birth weight.[81] It should also be recognized that montelukast carries a U.S. Food and Drug Administration black-box warning for the uncommon but serious risks of adverse behavioral and mood-related changes, as well as sleep disturbance, seen in studies of nonpregnant individuals.[82]

Monoclonal Antibody Therapies (Biologics)

The landscape of therapy for severe asthma has changed in recent years with the development of targeted monoclonal antibody therapies against specific inflammatory mediators such as IgE, IL-4, and IL-5. Randomized trials of several available biologic

Table 2. Common Asthma Medications in Pregnancy

Drug Class	Medication	Dosage (Adult)	Frequency and Route	Safety in Pregnancy
Inhaled corticosteroids	Budesonide	200–400 micrograms (low) 400–800 micrograms (medium) More than 800 micrograms (high)	1–2 puffs 1–2 times daily	Best studied of ICS in pregnancy Safe throughout pregnancy by consensus of numerous trials, large cohort studies, and meta-analyses
	Fluticasone	100–250 micrograms (low) 251–500 micrograms (medium) More than 500 micrograms (high)	1–2 puffs 1–2 times daily	Large cohort studies demonstrate overall safety and similar safety to those of budesonide[128,129] Included in meta-analyses of ICS class as whole, which suggests safety
	Mometasone	200–400 micrograms (low–medium) More than 400 micrograms (high)	1–2 puffs 1–2 times daily	Included in meta-analyses of ICS class as whole, which suggests safety Few drug-specific studies available
	Beclomethasone	100–200 micrograms (low) 201–400 micrograms (medium) More than 400 micrograms (high)	1–2 puffs 2 times daily	Drug-specific meta-analysis mostly reassuring about its safety[130] Included in meta-analyses of ICS class as whole, which suggests safety
	Ciclesonide	80–160 micrograms (low) 161–320 micrograms (medium) More than 320 micrograms (high)	1–2 puffs 2 times daily	No drug-specific studies
Rapid-onset ICS-LABA	Budesonide-formoterol	80–4.5 micrograms (low) 160–4.5 micrograms (medium)	1–2 puffs 2 times daily or PRN	More limited data, but cohort studies suggest ICS-LABA combination has pregnancy safety profile similar to that of ICS
	Mometasone-formoterol	100–5 micrograms (low-medium) 200–5 micrograms (high)	2 puffs 2 times daily or PRN	

(*continued*)

Table 2. Common Asthma Medications in Pregnancy (*continued*)

Drug Class	Medication	Dosage (Adult)	Frequency and Route	Safety in Pregnancy
Leukotriene receptor antagonist	Montelukast	10 mg	Oral Once daily	Relatively reassuring pregnancy safety profile overall, with no difference in rates of congenital anomalies or pregnancy loss Cohort studies with conflicting results on association with low birth weight and preterm birth[76,77,82] Note: Food and Drug Administration black-box warning for adverse neuropsychiatric effects and sleep disturbance
Targeted monoclonal antibodies (biologics)	Omalizumab (anti-IgE)	75–375 mg	SC every 2–4 wk	Best studied of the biologics in pregnancy EXPECT cohort (230 exposed) found no difference in rates of malformations or low birth weight. Increased rates of premature birth seen but may be attributable to severity of asthma or higher obesity rate in exposed cohort[91]
	Dupilumab (anti–IL-4Rα)	400- to 600-mg load followed by 200- and 400-mg maintenance	SC every 2 wk	Insufficient evidence with small cohort studies and case reports or series
	Mepolizumab (anti–IL-5)	100 mg	SC every 4 wk	Insufficient evidence, only limited case reports
	Benralizumab (anti–IL-5Rα)	30 mg	SC every 4–8 wk	Insufficient evidence, only limited case reports
	Reslizumab (anti–IL-5)	3 mg/kg	IV every 4 wk	No studies or case reports
	Tezepelumab (anti-TSLP)	210 mg	SC every 4 wk	No studies or case reports

(*continued*)

Table 2. Common Asthma Medications in Pregnancy (*continued*)

Drug Class	Medication	Dosage (Adult)	Frequency and Route	Safety in Pregnancy
Systemic corticosteroids	Prednisone Methylprednisolone Dexamethasone	Acute exacerbations: Prednisone 40–50 mg (or equivalent) for 5–7 d[16] assess response and consider extending course with taper if needed	Oral IV	Benefits of corticosteroids for acute exacerbations strongly outweigh risks, particularly given shorter duration of treatment Fetal drug exposure lowest with prednisone, prednisolone Epidemiologic studies of chronic corticosteroid exposure during pregnancy, mostly in patients with autoimmune disease, have found: Inconsistent associations with cleft lip and palate[131] Increased rates of low birth weight and preterm delivery[131] Possible increased risk of gestational diabetes (very limited body of evidence)[131,132]

ICS, inhaled corticosteroid; LABA, long-acting β agonist; PRN, as needed; Ig, immunoglobulin; SC, subcutaneous; EXPECT, Xolair Pregnancy Registry; IL, interleukin; IV, intravenous; TSLP, thymic stromal lymphoprotein.
Table is not exhaustive; individual formulations vary in dose and frequency. Dosing provided is that typical for adult patients and as indicated for asthma.

agents have demonstrated that they prevent exacerbations, reduce symptoms, and improve lung function in selected patients with severe asthma.[83–89]

Literature on the safety of biologic therapies in pregnancy is limited. Omalizumab, an anti-IgE–targeted monoclonal antibody injection and the first biologic approved by the U.S. Food and Drug Administration for the treatment of asthma, has the most robust safety data in pregnancy. The EXPECT (Xolair Pregnancy Registry) registry, a prospective cohort including 230 patients who received omalizumab for asthma during pregnancy or within 8 weeks of becoming pregnant, found no difference in rates of congenital malformations, fetal death, or stillbirth compared with a disease-matched cohort. There were higher rates of preterm birth in the omalizumab group, although this could be related to the severity of the underlying asthma or the high rates of obesity in the exposed cohort. Although there was a higher incidence of neonates with low birth weight in the omalizumab group, this may reflect the differences in preterm birth between cohorts given that they found no difference in rates of SGA birth weight.[90]

There are numerous case reports and series on the safety of dupilumab, an IL-4 receptor α-subunit inhibitor, in pregnancy. One small cohort study of 29 pregnant women who were exposed to dupilumab for the treatment of severe atopic dermatitis showed no

increase in adverse pregnancy or neonatal outcomes. However, all women in this study discontinued the medication on realization of pregnancy after a median exposure duration of 6 weeks gestation.[91] Studies of benralizumab and mepolizumab are limited to sparse case reports or series,[92–96] and there are currently no reports on pregnancy safety for tezepelumab or the intravenous biologic reslizumab.[97]

Further study of these targeted monoclonal antibodies in pregnancy is needed before consensus can be reached as to their safety. Deciding whether to continue biologic therapy during pregnancy must be done on a case-by-case basis with input from an asthma specialist, weighing the risks of uncertain drug safety with the importance of asthma control. We would not typically recommend initiating biologic therapies during pregnancy except in exceptional circumstances as determined by an asthma specialist.

Empiric Treatment of Suspected Asthma During Pregnancy

Normal spirometry does not necessarily rule out a diagnosis of asthma, as noted previously. If a pregnant woman has a clinical history suggestive of asthma but spirometry is nondiagnostic, it is recommended to treat empirically for asthma with an ICS-containing regimen (Fig. 3).[16] Clinicians should not delay treatment while waiting for repeat lung function assessment, which can be deferred until after delivery.

ACUTE ASTHMA EXACERBATIONS DURING PREGNANCY

Asthma exacerbations are serious and potentially life-threatening complications if not recognized and addressed promptly. Up to 20% of women with asthma will experience an exacerbation requiring intervention during pregnancy, with nearly one-third of these resulting in hospital admission.[4] Exacerbations can occur at any stage of pregnancy but are most common during the second trimester.[4,8,98] Increased disease severity,[4,98] active smoking, and the absence of or poor adherence to ICS are major risk factors for exacerbation.[4,98,99] Pregnancy-specific risk factors for asthma exacerbation include increased maternal age older than 35 years, multiparity, and multiple gestations. Comorbid depression, anxiety, and social determinants of health also are associated with exacerbation risk during pregnancy.[100] Respiratory viral infections and treatment interruptions are common triggers. Severe exacerbations in pregnancy increase the likelihood of low birth weight and preterm delivery.[4,28] Studies show that routine ICS use in pregnancy can reduce exacerbation risk by more than 75%,[51] and among those hospitalized for an asthma exacerbation, discharge with an ICS reduces readmission by 55%.[52]

Recognizing Acute Asthma Exacerbations

Asthma exacerbations are characterized by increased severity and persistence of symptoms such as breathlessness, cough, wheezing, and chest tightness. Warning signs for severe exacerbations requiring emergent management include difficulty speaking in full sentences, labored breathing with accessory muscle use, tachypnea, tachycardia, diaphoresis, and failure to respond to bronchodilator treatments. Hypoxemia, relative or frank hypercapnia (remembering that in pregnancy serum CO_2 levels should be low), and a "quiet" chest without air movement are signs of respiratory failure requiring emergency intervention.

Treatment of Asthma Exacerbations

Mild exacerbations often are managed in the outpatient setting, whereas more serious exacerbations require ED evaluation and potential hospital admission. During pregnancy, clinicians should have a low threshold to monitor patients in a health care setting while they receive initial treatment.

Treatment of exacerbations in pregnancy parallels that of nonpregnant patients (Table 3). Clinicians should promptly administer short-acting bronchodilators and systemic corticosteroids. Oral prednisone is generally the preferred corticosteroid for asthma exacerbation, with studies showing that oral treatment is equivalent to intravenous therapy, regardless of exacerbation severity.[101–104] Prednisone is administered in dose ranges of 40–60 mg every 24 hours. Intravenous corticosteroids such as methylprednisolone in equivalent doses may be considered for severe or life-threatening exacerbations, although this practice is not evidence based.[105] Among corticosteroids, prednisone and prednisolone have the additional benefit of lower fetal drug exposure because of placental inactivation.[106,107] Short courses of systemic corticosteroids are likely safe in pregnancy, and any potential risk from corticosteroid exposure is outweighed by the benefits of promptly treating an acute asthma exacerbation (Table 2).

Unfortunately, there is clear evidence that pregnant women with acute asthma are undertreated. A 2011 study found that pregnant women were both less likely to receive systemic corticosteroids in the ED for acute asthma exacerbation (51% vs 72%) and less likely to receive a prescription for prednisone on ED discharge (41% vs 69%).[108] Pregnant women are more likely to be discharged with ongoing symptoms of an

Table 3. Management of Asthma Exacerbations in Pregnancy

Intervention	Considerations
Inhaled bronchodilators	Nebulized solution preferred, if possible Albuterol 0.083% 2.5–5 mg With or without ipratropium bromide Can give initially up to 3 successive doses every 20 min, then every 1–4 h as needed Continuous nebulized albuterol considered for life-threatening cases (10–15 mg/h)
Systemic glucocorticoids	Administer promptly Prednisone 40–60 mg once daily is typical IV methylprednisolone can be considered for life-threatening cases
Supplemental oxygen	Target O_2 saturation 95% or higher
Volume assessment	Hypovolemia often accompanies asthma exacerbation Low threshold for IV fluids
Systemic bronchodilators	Inhaled bronchodilators are the priority, but trials of adjuncts are reasonable for severe cases IV magnesium sulfate (2 g infusion over 20 min) Terbutaline (SC): 0.25 mg every 20 min, up to 3 doses
Noninvasive ventilation	Consider trial only under supervision of experienced clinicians Prepare for intubation in case of failure Contraindicated if severe distress, hemodynamic instability, altered mental status, high aspiration risk, unable to tolerate interface, or craniofacial fractures
Endotracheal intubation and mechanical ventilation	Indicated for those with severe distress, refractory hypoxemia or hypercarbia, poor response, or contraindications to NIV Ideally performed by clinician with expertise in obstetric airway management
Ventilatory strategies	Allow complete exhalation to avoid dynamic hyperinflation Low respiratory rate (8–12 breaths/min) High inspiratory flow rate Avoid decelerating breath waveform Low TV Lung protective ventilation TV 6–8 mL/ideal body weight Titrate to arterial blood gas goals $PaCO_2$ 28–32 mm Hg (normal for pregnancy) PaO_2 70 mm Hg or higher
Venovenous ECMO	For extreme respiratory failure unresponsive to intubation and ventilator strategies above (very rare) Continuous fetal monitoring required Position in lateral decubitus position
Obstetric consultation	Low threshold to involve obstetrics team, particularly for severe exacerbations and other high-risk scenarios Determine need for and frequency of fetal monitoring Assess safety of continuing pregnancy and, if viable, consider timing and method of delivery For critical cases, preparations for emergency delivery should be in place Regular, open communication between ICU and obstetrics teams are strongly recommended

IV, intravenous; SC, subcutaneous; NIV, noninvasive ventilation; TV, tidal volume; $PaCO_2$, arterial partial pressure of carbon dioxide; PaO_2, arterial partial pressure of oxygen; ICU, intensive care unit.

exacerbation.[109] Health care professional education, highlighting the importance of prompt and aggressive management of acute asthma in pregnancy, is crucial to closing this treatment gap.

Management of Status Asthmaticus and Life-Threatening Exacerbations

As in any exacerbation, prompt and repeated bronchodilator treatments and systemic corticosteroids are imperative; however, patients with life-threatening asthma exacerbations frequently require additional forms of respiratory support. Supplemental oxygen should be given to maintain an oxygen saturation above 95%,[110] a higher target for pregnant women than other adults given the added importance of maintaining fetal oxygen delivery. Severe maternal hypoxia can have devastating effects on the fetus, including fetal or neonatal death and ischemic brain injury.[111]

Noninvasive ventilation is sometimes applied for patients with established or impending respiratory failure attributable to asthma, but the evidence regarding this application of NIV remains uncertain.[112] Although there are reports of successful use of noninvasive ventilation for acute respiratory failure

in pregnancy, its safety and efficacy are not well established.[113] Noninvasive ventilation should be performed only under the observation of experienced clinicians and for patients who are alert, cooperative, and hemodynamically stable and can protect their airway given the increased aspiration risk in pregnancy. Patients with respiratory distress or who are not responding appropriately to noninvasive respiratory support must be emergently considered for endotracheal intubation and invasive ventilation. Intubation should be performed by clinicians experienced in obstetric airway management given the higher failure rates[114] resulting from anatomic and physiologic changes of pregnancy, most notably oropharyngeal and tracheal hyperemia and edema, and the increased risk of aspiration.[114–116]

Ventilatory support for pregnant patients must be titrated to achieve the lower serum CO_2 of 28–32 mm Hg that is physiologic during pregnancy[117] to allow fetal offloading of CO_2. In rare cases, patients who are unable to be adequately oxygenated or ventilated despite invasive mechanical ventilation may be considered for extracorporeal membrane oxygenation (ECMO) at centers with this expertise. Limited evidence indicates that ECMO can be performed safely during pregnancy as a form of life support[118,119] but requires continuous fetal monitoring and positioning in the lateral decubitus position to optimize circuit flows.[120] Successful use of ECMO in pregnant women with treatment refractory status asthmaticus has been reported.[121,122]

CONCLUSIONS

Asthma is common in pregnancy and can negatively affect both maternal and neonatal outcomes. Asthma is diagnosed through a combination of characteristic symptoms and variable obstruction on lung function testing. Treatment of asthma in pregnancy should prioritize the use ICS combination inhalers, which are safe and effective in reducing symptoms and risk of exacerbation. Disease control should be reassessed throughout pregnancy, with treatment adjusted accordingly. Asthma exacerbations during pregnancy must be recognized promptly and treated aggressively with bronchodilators and systemic corticosteroids, with a low threshold for monitoring in a health care setting, to minimize health risks to mother and the fetus. In patients with more severe asthma, joint care by an asthma specialist and obstetrics will result in the safest, most efficacious care.

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