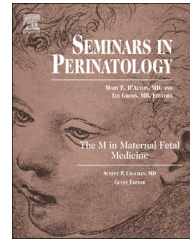


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Severe acute asthma

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ABSTRACT

Asthma is common among women of reproductive age and affects between 4% and 8% of pregnant women. Pregnancy outcomes are correlated to the degree of asthma severity and control. Approximately one-third of pregnant women with asthma remain stable, a third will have improvement of their asthma, and a third will have worsening of the disease. Pregnant women with severe asthma are at markedly increased risk of maternal and perinatal morbidity and mortality, preeclampsia, low-birth weight infants, and preterm delivery. A severe asthma exacerbation in a pregnant woman may be clinically daunting, however immediate intervention with appropriate supplemental oxygenation, medical therapy, and intubation if necessary can be life-saving. A focus on maternal well-being and pulmonary function in a pregnant asthmatic is essential to ensure optimal outcomes for both mother and her fetus. This article will provide an overview of asthma management, particularly in the acute care setting.

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1. Introduction

Asthma is a chronic inflammatory lung disorder that affects an estimated 4–8% of pregnant women^{1,2} and is frequently underdiagnosed and suboptimally treated.³ It is characterized by hyperresponsiveness of the airway to various precipitating triggers resulting in partially or completely reversible airway obstruction.⁴ Between 20% and 36% of patients with asthma will experience acute asthma exacerbations.^{5,6} A pregnant asthmatic who has continual symptoms during the day, frequent symptoms at night, and a peak expiratory flow rate (PEFR) or forced expiratory volume in 1 s (FEV1) $\leq 60\%$ predicted percentage of personal best is considered to have severe persistent or very poorly controlled asthma.⁴ Severe and poorly controlled asthma have been associated with an increased risk for spontaneous abortion, preeclampsia, intra-uterine growth restriction, preterm delivery, postpartum hemorrhage, and cesarean delivery.^{3,7–10}

Effective monitoring and treatment of the pregnant asthmatic will improve the outcomes for both mother and neonate. Pregnant patients presenting with acute asthma

exacerbations pose particular clinical challenges, as an accurate assessment of disease severity and prompt intervention can be life-saving. We will provide a brief overview of the diagnosis and treatment of asthma in general, and then discuss the treatment of severe, uncontrolled asthma in pregnant patients in the acute care setting.

2. Diagnosis

The characteristic symptoms of asthma include wheezing, shortness of breath, cough, and a sensation of tightness in the chest. Symptoms typically worsen at night and after exposure to triggers, such as environmental allergens, upper respiratory tract infections, tobacco, cold air, and exercise. The diagnosis of asthma in the pregnant woman is the same as in the nonpregnant patient and requires the presence of symptoms of airway obstruction or hyperresponsiveness, reversible hyperreactivity, and the exclusion of alternative diagnoses. Auscultation of the patient's lungs will generally reveal high-pitched wheezes except in patients with

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significant airway obstruction. Dyspnea of pregnancy, post-nasal drip, gastroesophageal reflux, and bronchitis should be considered in the differential diagnosis, but may also accompany or exacerbate asthma.¹¹

The medical history, the physical examination findings and the results of pulmonary function testing are all important in making the diagnosis of asthma. Pregnant women with signs and symptoms of asthma should undergo pulmonary function evaluation with spirometry to confirm the diagnosis of asthma. The “gold standard” diagnostic pulmonary function test is spirometry, particularly the forced expiratory volume in 1 s (FEV1) and the forced vital capacity (FVC), which can be scheduled as an outpatient with pulmonary medicine. A reduction in the percent of predicted FEV1 value or in the proportion of the FEV1 compared to the FEV1/FVC indicates obstruction.¹¹ At least 12% improvement of the FEV1 after use of a bronchodilator establishes reversibility. Alternatively a peak flow meter can be easily used in a physician's office to obtain a peak expiratory flow rate (PEFR), which is a measurement done during maximal exhalation after the patient has maximally inhaled.¹² There is excellent correlation between the PEFR and the FEV1. The PEFR is useful in establishing a patient's baseline (personal best), assessing the asthma severity, and monitoring the response to treatment. It is of paramount importance that acute asthma exacerbations are recognized promptly and treatment initiated. Moreover, it is reasonable to treat a pregnant patient based on clinical suspicion, and improvement in response to asthma medication is sufficient for diagnosis.^{4,11}

The range of asthma severity extends from intermittent, mild persistent, moderate persistent to severe persistent based on the frequency of daytime symptoms, nighttime awakening, impact on daily activities, and forced expiratory volume (FEV1) readings or PEFR via peak flow monitoring as summarized in Table 1.¹² According to the National Asthma Education and Prevention Program Asthma and Pregnancy Working Group, a pregnant woman with asthma who has continual symptoms during the day, frequent symptoms at night, a PEFR or FEV1 $\leq 60\%$ predicted percentage of personal best or PEFR variability $> 30\%$ is considered to have severe persistent or very poorly controlled asthma.¹² This definition of severe asthma in pregnancy is recognized by the American College of Obstetricians and Gynecologists.⁴ In contrast, the American Thoracic Society Workshop Consensus defined severe asthma as the need for daily high-dose inhaled corticosteroids and almost continuous use of oral corticosteroids ($> 50\%$) throughout the year.¹³

3. Effects of pregnancy on asthma

The course of asthma is variable in pregnancy and is likely linked to the degree of asthma control prior to pregnancy. A multicenter prospective trial was conducted by the Eunice Kennedy Schriver National Institutes of Child Health and Human Development Maternal Fetal Medicine Units Network, to evaluate the relationship between initial asthma severity classification and subsequent pregnancy morbidity in 1739 pregnant asthmatics at < 26 weeks of gestation.⁵ Of the 1739 pregnant women, 50% (873) were initially classified as having

mild asthma, 47% (814) had moderate asthma, and 3% (52) had severe asthma. Severity of disease directly correlated with the risk of asthma exacerbation. Although only 13% of those with mild asthma had acute exacerbations, the rate rose to 26% for exacerbations in moderate asthmatics. Acute exacerbations occurred in 52% of pregnant women who were classified as severe asthmatics. Up to 23% of patients initially classified as moderate–severe asthmatics demonstrated symptomatic improvement throughout the course of their pregnancy and were ultimately reclassified with mild disease. Conversely, 30% of patients had worsening symptoms during pregnancy and were reclassified from mild asthma to moderate or severe asthma.⁵

4. Effects of asthma on pregnancy

4.1. Outcomes

Asthma in pregnancy negatively impacts both short- and long-term maternal and fetal health. In a retrospective study evaluating the outcomes of 37,585 pregnant asthmatics and 243,434 pregnant women without asthma by Tata et al., asthma was associated with an increased risk of miscarriage (OR 1.10, 95% CI 1.06–1.13), cesarean delivery (OR 1.11, 95% CI 1.07–1.16), antepartum hemorrhage (OR 1.20, 95% CI 1.08–1.34), postpartum hemorrhage (OR 1.38, 95% CI 1.21–1.57), anemia (OR 1.06, 95% CI 1.01–1.12), and depression (OR 1.52, 95% CI 1.36–1.69).⁷ Their study included stratification by severity using medication status as a surrogate marker, including 17,604 women with “unmedicated asthma,” 3409 women with “short-acting beta agonist medicated asthma,” and 6305 women with “inhaled corticosteroid/long-acting beta agonist medicated asthma.” The authors could not find a consistent correlation between asthma severity and all adverse outcomes, particularly postpartum hemorrhage, delivery by cesarean, and risk of depression. Rather, all women with asthma appeared to be at increased risk for these outcomes compared to non-asthmatics. The authors concluded that women with asthma, “may have persisting immunologic, hormonal, or other yet unknown physiologic differences compared with women without asthma.”⁷ Demissie et al. compared maternal and fetal outcomes in pregnancies complicated by asthma in a case–control study.⁸ Asthma imparted increased risks of preterm birth (OR 1.36, 95% CI 1.18–1.55), preeclampsia (OR 2.18, 95% CI 1.68–2.83), low-birth weight infants (OR 1.32, 95% CI 1.10–1.58), and small for gestational age infants (OR 1.26, 95% CI 1.10–1.45). Additionally, they found an increased incidence of cesarean delivery (OR 1.62, 95% CI 1.46–1.80), placenta previa (OR 1.71, 95% CI 1.05–2.79), and congenital malformations (OR 1.37, 95% CI 1.12–1.68). These differences persisted despite controlling for age, marital status, education, race, parity, co-morbidity with diabetes mellitus or preexisting hypertension, smoking, alcohol, or drug use.⁸ Similarly, Källén et al. demonstrated an increased risk of low-birth weight offspring (OR 1.21, 95% CI 1.14–1.29), preeclampsia (OR 1.15, 95% CI 1.08–1.23), preterm delivery (OR 1.15, 95% CI 1.09–1.21), and perinatal mortality (OR 1.21, 95% CI 1.08–1.35).⁹ The impact was greatest among mothers whose asthma was most severe. The outcomes in

Table 1 – Classification of asthma severity and stepwise approach for managing asthma during pregnancy and lactation: treatment.

Classify severity	Clinical features before treatment or adequate control				Medications required to maintain long-term control
	Symptoms: day	Symptoms: night	PEF or FEV1	PEF variability	Daily medications
Step 4 severe persistent	Continual	Frequent	≤60%	>30%	Preferred treatment - High-dose inhaled corticosteroid AND - Long-acting inhaled beta-2 agonist AND, if needed, - Corticosteroid tablets or syrup long term (2 mg/kg/day, generally not to exceed 60 mg/day). (Make repeat attempts to reduce systemic corticosteroid and maintain control with high-dose inhaled corticosteroid[†]). Alternative treatment - High-dose inhaled corticosteroid[†] AND - Sustained-release theophylline to serum concentrations of 5–12 mcg/mL.
Step 3 moderate persistent	Daily	>1 night/week	>60%–<80%	>30%	Preferred treatment EITHER - Low-dose inhaled corticosteroid[†] and long-acting inhaled beta-2 agonist OR - Medium-dose inhaled corticosteroid[†] If needed (particularly in patients with recurring severe exacerbations): - Medium-dose inhaled corticosteroid[†] and long-acting inhaled beta-2 agonist. Alternative treatment - Low-dose inhaled corticosteroid[†] and either theophylline or leukotriene-receptor antagonist.[†] If needed - Medium-dose inhaled corticosteroid[†] and either theophylline or leukotriene-receptor antagonist.[†]
Step 2 mild persistent	>2 days/week but < daily	>2 nights/month	≥80%	20–30%	Preferred treatment - Low-dose inhaled corticosteroid.* Alternative treatment (listed alphabetically): - cromolyn, leukotriene-receptor antagonist.[†] OR sustained-release theophylline to serum concentration of 5–12 mcg/mL.

Step 1 mild intermittent	≤2 days/week	≤2 nights/ month	≥80%	<20%	- No daily medication needed. - Severe exacerbation may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroid is recommended.
Quick relief all patients	● Short-acting bronchodilator: 2–4 puffs <i>short-acting inhaled beta-2 agonist</i>[‡] as needed for symptoms. ● Intensity of treatment will depend on severity of exacerbation; up to 3 treatments at 20-min intervals or a single nebulizer treatment as needed. Course of systemic corticosteroid may be needed. ● Use of short-acting inhaled beta-2 agonist[‡] >2 times a week in intermittent asthma (daily, or increasing use in persistent asthma) may indicate the need to initiate (increase) long-term control therapy.				
 Step down Review treatment every 1–6 months; a gradual stepwise reduction in treatment may be possible.			Notes ● The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs. ● Classify severity: assign patient to most severe step in which any feature occurs (PEF is percent of personal best; FEV1 is percent predicted). ● Gain control as quickly as possible (consider a short course of systemic corticosteroid), then step down to the least medication necessary to maintain control. ● Minimize use of short-acting inhaled beta-2 agonist ‡ (e.g., use of approximately one canister a month even if not using it every day indicates inadequate control of asthma and the need to initiate or intensify long-term control therapy). ● Provide education on self-management and controlling environmental factors that make asthma worse (e.g., allergens and irritants). ● Refer to an asthma specialist if there are difficulties controlling asthma or if Step 4 care is required. Referral may be considered if Step 3 care is required.		
 Step up If control is not maintained, consider step up. First, review patient medication technique, adherence, and environmental control					
Goals of therapy: asthma control ● Minimal or no chronic symptoms day or night ● Minimal or no exacerbations ● No limitations on activities; no school/work missed ● Maintain (near) normal pulmonary function ● Minimal use of short-acting inhaled beta 2-agonist[‡] ● Minimal or no adverse effects from medications					
Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.¹² * There are more data on using budesonide during pregnancy than on using other inhaled corticosteroids. † There are minimal data on using leukotriene-receptor antagonists in humans during pregnancy, although there are reassuring animal data submitted to FDA. ‡ There are more data on using albuterol during pregnancy than on using other short-acting inhaled beta-2 agonists.					

pregnant women with mild asthma do not differ greatly from those without asthma,¹⁴ implying that disease severity and degree of control convey a significant proportion of risk to the pregnancy, as opposed to the mere presence of the disease. The timing of asthma exacerbations may further impact fetal outcomes; however, this association is less clear. For example, Blais and Forget reported that there was a small increased risk of congenital malformations in 321 asthmatic mothers whose asthma exacerbations occurred during the first trimester of pregnancy compared to 4023 patients with asthma who did not (OR 1.48, 95% CI 1.04–2.09).¹⁵ At least one anomaly was identified in 398 infants (9%) and a major anomaly was identified in 261 (6%) infants. Anomalies included a list of 33 ICD-9 codes, ranging from “anencephaly” to “other and unspecified congenital anomalies.” A geneticist classified anomalies as “major” if it could be life-threatening or cause major cosmetic defects and if there was at least one hospitalization related to the malformation in the first year for life, or as “minor,” for all others. The most frequent malformations were musculoskeletal, followed by cardiac. To exclude the effect of corticosteroid use on the rate of malformations, a sub-cohort analysis of 3062 women who did not fill a prescription for oral corticosteroids at any time in pregnancy was performed. From this group, 116 women had an exacerbation in the first trimester. The authors found an almost 2-fold risk of major congenital malformation in pregnant women with an exacerbation compared to those without (OR 1.95, 95% CI 1.03–

3.72).¹⁵ It is important to note, however, that this study used administrative databases to identify medication claims, and ICD-9 codes to identify malformations, and neither were independently validated using patient-level data, which may lead to significant confounding.

Recent studies indicate a significant impact of maternal asthma on fetal programming of adult disease.¹⁶ The impact of low-birth weight on future cardiovascular disease and metabolism is well described.¹⁷ In addition to these risks, the development of asthma in children prior to 5 years of age is associated with a maternal but not paternal history of asthma.¹⁸

Several mechanisms have been proposed to explain the adverse outcomes associated with severe asthma. Maternal hypoxemia resulting from acute asthma exacerbations leads to fetal hypoxia, particularly when maternal oxygenation levels are below 60 mmHg or the hemoglobin saturation is less than 90%.¹² Hypoxia is a potent vasoconstrictor and has been associated with impaired uteroplacental blood flow,¹⁹ which may result in fetal growth restriction or uteroplacental insufficiency. Beta 2-adrenergic receptor polymorphisms have been implicated in preterm labor and asthma.²⁰ The inflammatory milieu including maternal cytokines may impart signaling to the fetus that affects programming of disease later in life. Finally, medications commonly used to treat asthma are not without side effects, some of which may be undesirable in pregnancy.

Table 2 – Usual dosages for long-term control medications during pregnancy and lactation.*

Medication	Dosage form	Adult dose
Inhaled corticosteroids (see estimated comparative daily dosages for inhaled corticosteroids (Table 3)		
Systemic corticosteroids (Applies to all 3 corticosteroids.)		
Methylprednisolone	2, 4, 8, 16, 32 mg tablets	● 7.5–60 mg daily in a single dose in AM or qod as needed for control
Prednisolone	5 mg tablets, 5 mg/5 cc, 15 mg/5 cc	● Short-course “burst” to achieve control: 40–60 mg/day as single dose or 2 divided doses for 3–10 days
Prednisone	1, 2.5, 5, 10, 20, 50 mg tablets 5 mg/cc, 5 mg/5 cc	
Long-acting inhaled beta-2 agonists (Should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids.)		
Salmeterol	MDI 21 mcg/puff DPI 50 mcg/blister	2 puffs q 12 h 1 blister q 12 h
Formoterol	DPI 12 mcg/single-use capsule	1 capsule q 12 h
Combined medication		
Fluticasone/ salmeterol	DPI 100, 250, or 500 mcg/50 mcg	1 inhalation bid; dose depends on severity of asthma
Cromolyn		
Cromolyn	MDI 1 mg/puff Nebulizer 20 mg/ampule	2–4 puffs tid-qid 1 ampule tid-qid
Leukotriene-receptor antagonists		
Montelukast	10-mg tablet	10 mg qhs
Zafirlukast	10 or 20-mg tablet	40 mg daily (20 mg tablet bid)
Methylxanthines (Serum monitoring is important [serum concentration of 5–12 mcg/mL at steady state].)		
Theophylline	Liquids, sustained-release tablets, and capsules	Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day

DPI, dry powder inhaler; MDI, metered-dose inhaler.

Notes:

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy.
- Some doses may be outside package labeling, especially in the high-dose range.

Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.¹²

* Adapted from EPR—Update 2002.

Table 3 – Estimated comparative daily dosages for inhaled corticosteroids.*

Drug	Adult low daily dose (mcg)	Adult medium daily dose (mcg)	Adult high daily dose (mcg)
Beclomethasone CFC 42 or 84 mcg/puff	168–504	504–840	> 840
Beclomethasone HFA 40 or 80 mcg/puff	80–240	240–480	> 480
Budesonide DPI 200 mcg/inhalation	200–600	600–1200	> 1200
Flunisolide 250 mcg/puff	500–1000	1000–2000	> 2000
Fluticasone MDI: 44, 110, or 220 mcg/puff	88–264	264–660	> 660
DPI: 50, 100, or 250 mcg/inhalation	100–300	300–750	> 750
Triamcinolone acetonide 100 mcg/puff	400–1000	1000–2000	> 2000

DPI, dry powder inhaler; MDI, metered-dose inhaler.

Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.¹²

* Adapted from EPR—Update 2002.

On the whole, studies regarding the safety of inhaled beta-adrenergic agonists, such as albuterol, have been reassuring.^{21,22} Oral glucocorticoids on the other hand, have been linked to cleft palate, preterm birth, low-birth weight, and preeclampsia.^{21,23,24} Inhaled corticosteroids appear to be safer in pregnancy. Källén et al. assessed 2014 women who used inhaled budesonide in pregnancy and did not find an associated increased risk for congenital anomalies when compared to the rest of the population.²⁵ Similarly, Norjavaara and de Verdier did not find any associations between budesonide and adverse fetal outcomes, gestational age at birth, or birth weight.²⁶ A thorough review of the studies of medications used for asthma treatment in pregnancy is compiled in tabular format by the National Asthma Education and Prevention Program from the National Heart, Lung, and Blood Institute, and is available online at http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg_etbls.htm.²⁷

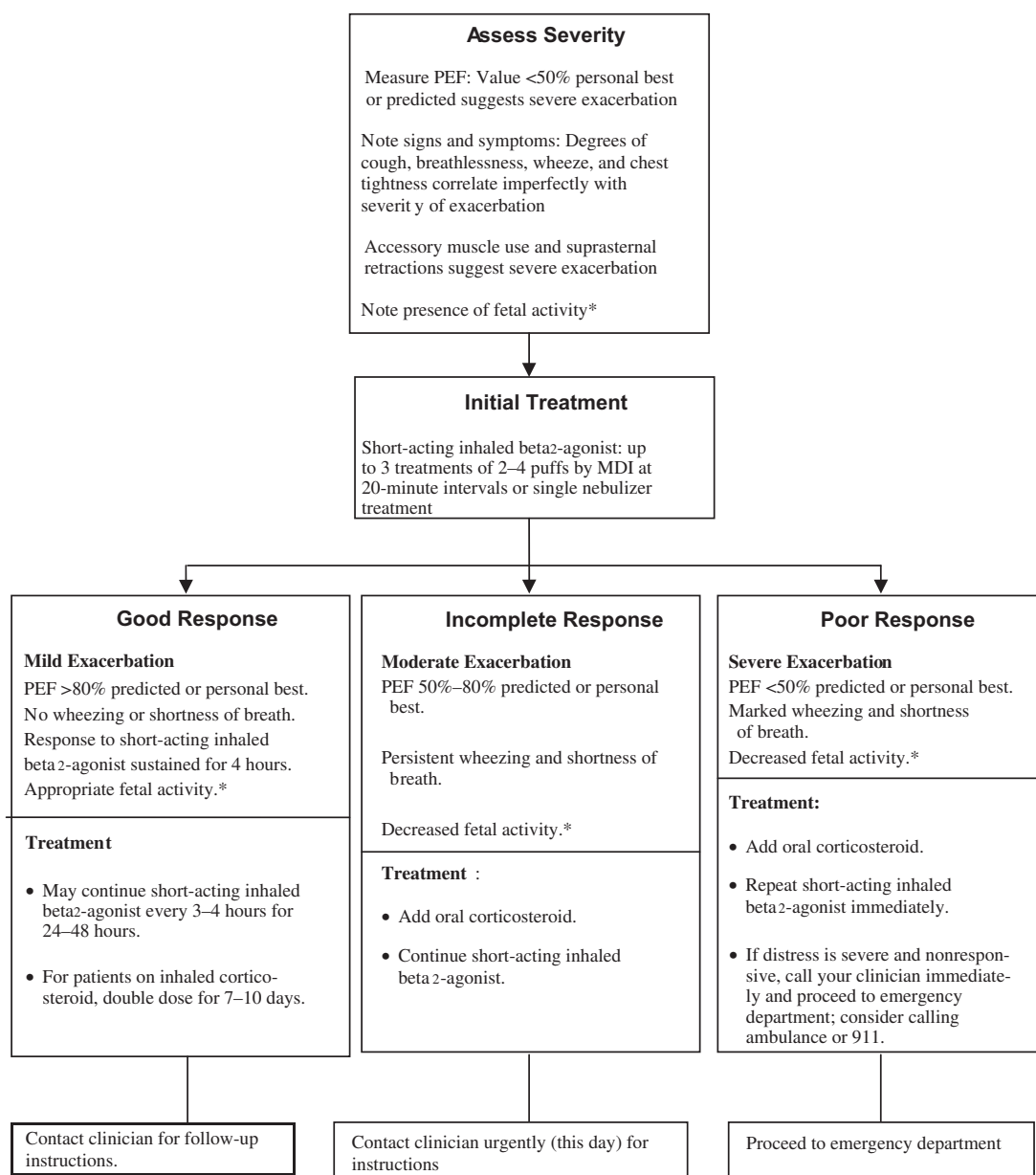
4.2. Management

According to the National Asthma Education and Prevention Program, uncontrolled asthma is far more deleterious than exposure to commonly used asthma medications,¹² therefore poorly controlled asthma and acute exacerbations should be treated aggressively during pregnancy with a goal of achieving the PEFR or FEV1 of >70% predicted. The pregnant asthmatic's initial evaluation of pulmonary function should ideally be done by spirometry at the first prenatal visit or as soon as possible to classify the severity of their asthma, to assess their degree of control, to document their baseline function, and to treat accordingly. It is also reasonable to check the moderate persistent to severe persistent asthmatic's PEFR at each prenatal visit. Pregnant women should be seen every 1–2 weeks until good asthmatic control is achieved. Afterward, monthly visits for evaluation of pulmonary function and asthma symptoms are recommended.

Asthmatic pregnant women with frequent symptoms should ideally measure their PEFR 2 times a day, first thing in the morning and 12 h later. Exacerbating factors should be identified and controlled. Irritants, such as cigarette smoke,

and allergens, including animal dander, dust mites, pollen, molds, and cockroaches, should be eliminated from the mother's environment. Clinicians should offer administration of the influenza vaccine to all pregnant patients with asthma as influenza and other upper respiratory infections can trigger acute exacerbations.^{28,29} Starting at 32-weeks gestation, pregnant women with moderate to severe asthma or poorly controlled asthma are candidates for serial ultrasound examinations every 3–4 weeks to assess fetal growth and weekly antenatal fetal testing.^{4,12} Pregnant women with asthma should be instructed to monitor fetal movement daily via kick counts.¹²

Pharmacologic management should be initiated in a stepwise manner according to the severity of asthma symptoms as shown in Table 1.¹² Intermittent asthma should be managed with short-acting inhaled beta-2 agonists, preferably albuterol, on an as-needed basis. No daily maintenance medication is required. For mild persistent asthma, a daily, low-dose inhaled corticosteroid, such as budesonide, can be used. Pregnant asthmatics with adequate control prior to pregnancy using another inhaled corticosteroid, such as beclomethasone, flunisolide, or fluticasone, do not need to switch medications. Additionally, montelukast or zafirlukast can be used to optimize control with or instead of inhaled corticosteroids. These are not first-line agents, but continuation is acceptable in women who were stable while on them prior to pregnancy. For moderate persistent asthma, use of either a low-dose inhaled corticosteroid in conjunction with a long-acting inhaled beta-2 agonist or an increased dose of the inhaled corticosteroid to a medium level dose is appropriate. Salmeterol is the most commonly used long-acting beta-2 agonist compared to others in its class. Severe persistent asthma is best treated with a high-dose inhaled corticosteroid and a long-acting inhaled beta-2 agonist. Long-acting beta-2 agonists should never be used alone for maintenance therapy. Finally, short courses of oral corticosteroids may be added if needed. Care should be taken not to exceed 2 mg/kg/day or 60–80 mg/day of prednisone, or an equivalent dose of an alternate steroid.^{12,28} A short-acting beta 2-adrenergic agonist should be used as a rescue medication if



MDI, metered-dose inhaler; PEF, peak expiratory flow.

*Fetal activity is monitored by observing whether fetal kick counts decrease over time.

Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services¹²

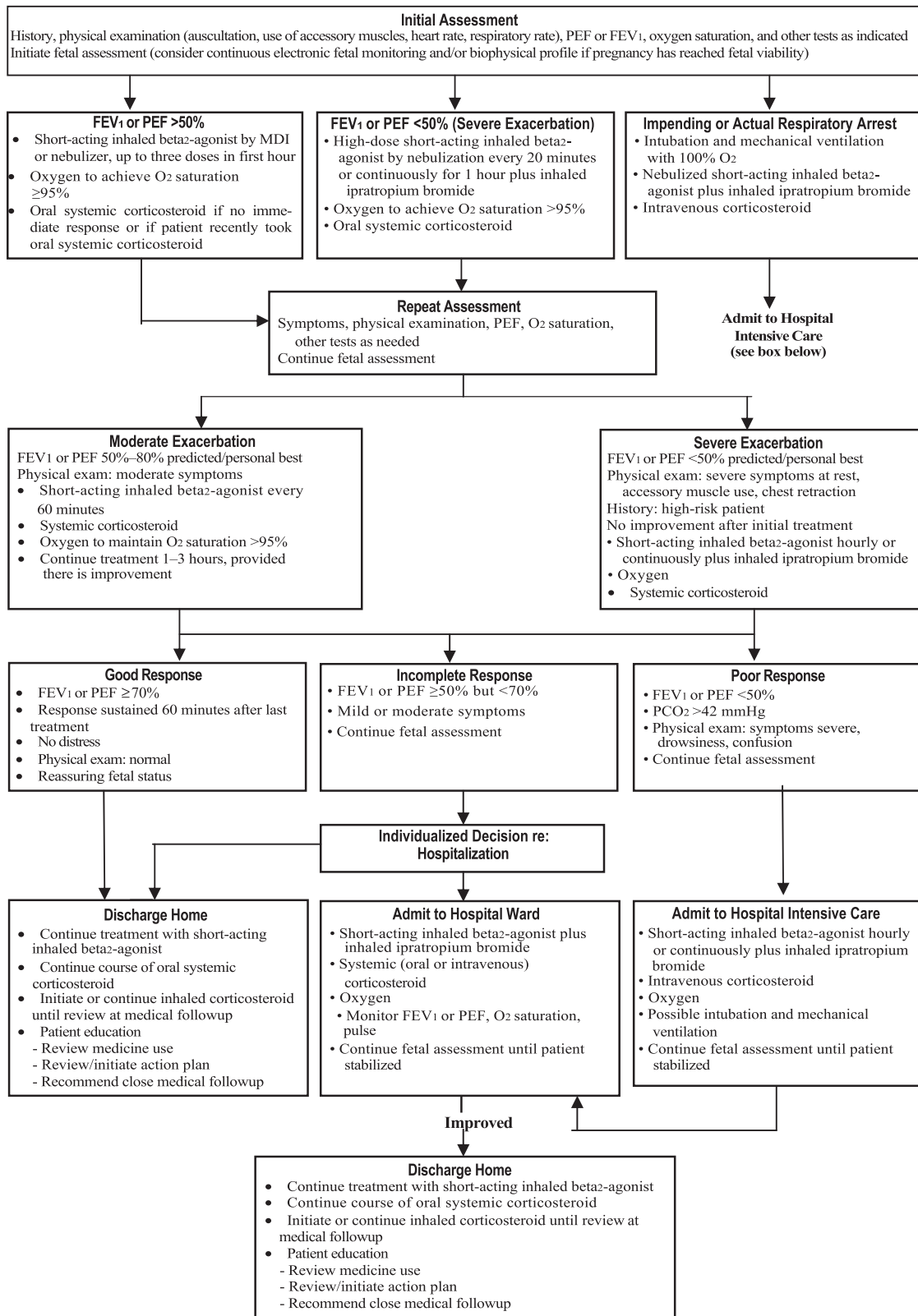
Fig. 1 – Management of asthma exacerbations during pregnancy and lactation: home treatment.

an asthma flare occurs. Common asthmatic medications used for long-term control during pregnancy and postpartum are summarized in Tables 2 and 3.¹²

5. Treatment of asthma exacerbations

A “home-action plan,” with step-up therapy should be developed for each pregnant asthmatic patient based on her frequency of symptoms and FEV1 or PEF measurements as depicted in Figure 1.¹² Patient asthma-action plan forms, like

those developed by the National Asthma Education and Prevention Program, listing green, yellow, and red zones based on symptoms and PEF value with explicit instructions detailing medication names, doses, and times for the patient, may be useful to engage the pregnant woman in her own care. The course of asthma in pregnancy can be variable and the need for medication changes and adjustments are common.⁵ A short-acting beta 2-adrenergic agonist, such as albuterol or levalbuterol, is employed as a first step in the management of an acute asthma exacerbation. It is important to counsel asthmatic grvida that rescue medication



FEV₁, forced expiratory volume in 1 second; MDI, metered-dose inhaler; PCO₂, carbon dioxide partial pressure; PEF, peak expiratory flow.

*Adapted from EPR-2 1997.

Source: National Heart, Lung, and Blood Institute: National Institutes of Health; U.S. Department of Health and Human Services.¹²

Fig. 2 – Management of asthma exacerbations during pregnancy and lactation: emergency department and hospital-based care.*

Table 4 – Medications and dosages for asthma exacerbations during pregnancy and lactation.*

Medications	Adult dose	Comments
Short-acting inhaled beta-2 agonists		
Albuterol		
Nebulizer solution (5.0 mg/mL, 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)	2.5–5.0 mg every 20 min for 3 doses, then 2.5–10 mg every 1–4 h as needed, or 10–15 mg/h continuously	Only selective beta-2 agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min.
MDI (90 mcg/puff)	4–8 puffs every 20 min up to 4 h, then every 1–4 h as needed	As effective as nebulized therapy if patient is able to coordinate.
Bitolterol		
Nebulizer solution (2 mg/mL)	See albuterol dose.	Has not been studied in severe asthma exacerbations. Do not mix with other drugs.
MDI (370 mcg/puff)	See albuterol dose.	Has not been studied in severe asthma exacerbations.
Levalbuterol (R-albuterol)		
Nebulizer solution (0.63 mg/3 mL, 1.25 mg/3 mL)	1.25–2.5 mg every 20 min for 3 doses, then 1.25–5 mg every 1–4 h as needed, or 5–7.5 mg/h continuously	0.63 mg of levalbuterol is equivalent to 1.25 mg of racemic albuterol for both efficacy and side effects.
Pirbuterol		
MDI (200 mcg/puff)	See albuterol dose	Has not been studied in severe asthma exacerbations.
Systemic (injected) beta-2 agonists		
Epinephrine		
1:1000 (1 mg/mL)	0.3–0.5 mg every 20 min for 3 doses sq	No proven advantage of systemic therapy over aerosol.
Terbutaline		
(1 mg/mL)	0.25 mg every 20 min for 3 doses sq	No proven advantage of systemic therapy over aerosol.
Anticholinergics		
Ipratropium bromide		
Nebulizer solution (0.25 mg/mL)	0.5 mg every 30 min for 3 doses, then every 2–4 h as needed	May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to beta-2 agonist therapy.
MDI (18 mcg/puff)	4–8 puffs as needed	Dose delivered from MDI is low and has not been studied in asthma exacerbations.
Ipratropium with albuterol		
Nebulizer solution (Each 3 mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol)	3 mL every 30 min for 3 doses, then every 2–4 h as needed	Contains EDTA to prevent discoloration. This additive does not induce bronchospasm.
MDI (Each puff contains 18 mcg ipratropium bromide and 90 mcg albuterol)	4–8 puffs needed	
Systemic corticosteroids		
	(Dosages and comments apply to all 3 corticosteroids)	
Prednisone	120–180 mg/day in 3 or 4 divided doses for 48 h, then 60–80 mg/day until PEF reaches 70% of predicted or personal best	For outpatient “burst” use 40–60 mg in single or 2 divided doses for adults.
Methylprednisolone		
Prednisolone		

Notes:

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy.
- No advantage has been found for higher dose corticosteroids in severe asthma exacerbations, nor is there any advantage for intravenous administration over oral therapy provided gastrointestinal transit time or absorption is not impaired. The usual regimen is to continue the frequent multiple daily dose until the patient achieves an FEV1 or PEF of 50% of predicted or personal best and then lower the dose to twice daily. This usually occurs within 48 h. Therapy following a hospitalization or emergency department visit may last from 3 to 10 days. If patients are then started on inhaled corticosteroids, studies indicate there is no need to taper the systemic corticosteroid dose. If the follow-up systemic corticosteroid therapy is to be given once daily, one study indicates that it may be more clinically effective to give the dose in the afternoon at 3 PM, with no increase in adrenal suppression.

Source: National Heart, Lung, and Blood Institute; National Institutes of Health; U.S. Department of Health and Human Services.¹²

* Adapted from EPR—Update 2002.

should be used if they experience worsening symptoms or if their PEFR decreases by 20%. If the patient improves symptomatically and her PEFR improves to at least 80%, no further action is indicated. Otherwise, she should be instructed to seek immediate medical care. Patient education and

compliance is crucial as avoidance of triggers and use of controller medications can improve maternal symptoms and, therefore, pregnancy morbidity.²⁹

Management of an acute asthma exacerbation during pregnancy and the postpartum period is summarized in

Figure 2.¹² When a pregnant asthmatic presents with acute worsening of symptoms, her pulmonary status should be assessed immediately. Physical examination may reveal posturing, use of accessory muscles of respiration, and wheezes. In some cases, inflammation, thick secretions, and bronchospasm are sufficiently severe to prohibit air movement, and wheezes may be absent until after initiation of treatment. Patients may be unable to speak in complete sentences, or have a pulse rate elevated above 120 beats/min. A FEV1 or PEFR measurement may show marked decrease from the patient's goal or personal best, and impairment in oxygen saturation is common. During pregnancy, there is a physiologic reduction in the functional residual capacity by 20%, which predisposes pregnant women to rapid decompensation compared to the nonpregnant state.³⁰ Maternal oxygenation status should be monitored by pulse oximetry and/or arterial blood gas evaluations. Chest X-rays are rarely needed unless additional pulmonary comorbidities, such as pneumonia, are strongly suspected. The fetus should be continuously monitored or biophysical profiles performed, if viability has been reached, until the mother has clinically improved.

The maintenance of good maternal oxygenation is vital for fetal well-being. Supplemental oxygen should be administered to maintain maternal oxygen saturation above 95% to ensure adequate fetal oxygen content. If the FEV1 or PEFR is greater than or equal to 50%, the patient usually responds to treatment with a short-acting beta-2 agonist either via nebulizer treatments or metered-dose inhaler. Oral corticosteroids can be added if deemed clinically necessary. If the FEV1 or PEFR is less than 50% (<200 L/min), the exacerbation is severe. When the PEFR is <25% of predicted or personal best (<100–150 L/min), the exacerbation is truly life-threatening. Moreover, if the patient is unable to speak or use the PEFR meter her exacerbation should be considered life-threatening. Status asthmaticus, the most severe manifestation of the disease, occurs when bronchioles constrict sufficiently to prohibit air flow, and is associated with life-threatening complications including respiratory arrest, pneumothorax, cardiac arrhythmias, pneumomediastinum, and acute cor pulmonale.

When the exacerbation is severe, treatment should begin with a high-dose short-acting inhaled beta-2 agonist, such as albuterol or levalbuterol, by nebulizer or metered-dose inhaler (up to 3 doses in the first hour) and systemic corticosteroids, such as prednisone, prednisolone, or methylprednisolone, which may be given orally or intravenously. Inhaled ipratropium bromide can be added if necessary. Medications used during acute exacerbations during pregnancy and the postpartum period are summarized in [Table 4](#).¹² Nebulizer treatments may be repeated every hour as needed. If, 1–2 h after treatment, the FEV1 or PEFR improves to 70% or more, the patient is feeling better and the fetal heart rate pattern or biophysical profile is reassuring, she can be discharged home at the discretion of the physician.

If the FEV1 or PEFR remain at less than 50% or symptoms are unresponsive to treatment, the patient should be hospitalized.³¹ Reassessment of the patient's condition and response to ongoing therapy should be performed every 60–90 min. Importantly, if pCO₂ levels are greater than

42 mmHg, the patient becomes exhausted, or she has altered consciousness, respiratory arrest is imminent, and the patient should be admitted to the intensive care unit and may require mechanical ventilation.^{4,12} In select patients who refuse intubation, or who may be compliant with mask therapy, BiPAP may be an adequate non-invasive therapeutic option, however, intubation should not be delayed. Intubation should be performed under controlled, semi-elective manner, by highly skilled personnel.^{4,31} Indications to intubate and mechanically ventilate a pregnant woman include altered mental status, inability to manage secretions, respiratory rate >35 breaths/min, hypercapnia defined as a PaCO₂ > 42 mmHg, progressive exhaustion, persistent acidosis despite treatment, or signs of impending or actual cardiorespiratory arrest.³² Maternal and perinatal mortality is significantly increased when mechanical ventilation is required.

In patients with poor response to medical management, the addition of helium to delivered oxygen reduces the gas density and may facilitate gas delivery through the narrowed bronchioles.³² There are rare case reports of a lack of response to aggressive medical and airway management.^{33,34} Cesarean delivery was performed as an intervention of last resort for the treatment of status asthmaticus. In these cases, rapid clinical improvement occurred after delivery. We have also observed significant clinical improvement after delivery in cases of status asthmaticus and respiratory compromise due to other causes. Most patients will respond to medical management, however, and cesarean delivery is routinely performed only for obstetrical indications.^{33,34}

During labor and delivery, asthmatic medications should be continued in the gravida as needed to maintain adequate maternal oxygenation and respiration. Patients taking systemic steroids in high doses, or for prolonged periods preceding delivery, should receive 100-mg hydrocortisone intravenously every 8 h for 24 h to avoid adrenal insufficiency. Equally important, some medications routinely given in the peripartum period must be used with caution in patients with unstable respiratory status or severe disease. Oxytocin is safe in the asthmatic patient for induction of labor and postpartum hemorrhage. Indomethacin for tocolysis should be used judiciously, as it may exacerbate symptoms in patients sensitive to aspirin or other NSAIDs, and analogs of prostaglandin F₂-alpha used for cervical ripening have been reported to cause bronchospasm. Most notably, hemabate may result in severe bronchospasm and respiratory arrest in asthmatic patients. Conversely, magnesium sulfate and terbutaline both relax bronchiolar smooth muscle, therefore are safe for asthmatic patients. Prostaglandin E1 or E2 may be used for cervical ripening, induction of labor, or postpartum hemorrhage. Epidural analgesia is a preferable method for intrapartum pain relief as it is associated with reduction in oxygen consumption and minute ventilation during labor, however, it has been associated with a 2% rate of bronchospasm.¹²

During the postpartum period, women should continue to be maintained on the same dose of their asthma medications used during pregnancy. Those women who were on oral corticosteroids may require intravenous steroids until they can tolerate oral medications. In general, asthma

medications are not a contraindication to breastfeeding (Tables 2–4).¹²

6. Conclusions

Asthma is a common medical condition affecting pregnant women with far-reaching impact on maternal and fetal health if uncontrolled. Pregnancy outcomes are correlated with the severity of disease, and may be similar to patients without asthma when well controlled. It is of paramount importance for physicians to educate and engage pregnant patients with asthma in their care. Adherence to a home-action plan, frequent outpatient clinical assessment, and step-up therapy may minimize the need for acute emergency care. Prompt recognition and appropriate treatment of acute asthma exacerbations, even when severe can truly protect the health of the mother and thereby, her fetus.

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