

Acute Asthma During Pregnancy

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The prevalence of asthma in pregnant women will increase as the prevalence of asthma in the general population increases [1]. Many of these patients will suffer acute asthma during pregnancy. A prospective study from Finland suggested that 9.3% of 504 pregnant women who had asthma and who were followed in a pulmonary clinic required emergency treatment for asthma during pregnancy [2]. A more recent and larger prospective study from this country included 1739 pregnant asthmatic women who were followed in obstetric clinics; 5.1% of patients were hospitalized and 15.8% required an unscheduled visit for an asthma exacerbation during pregnancy [3]. These exacerbations were more common in patients who had persistent asthma and were especially common in patients who had severe persistent asthma, 26.9% of whom required a hospitalization and 36.5% had an unscheduled visit for acute asthma during pregnancy.

Data indicate that the course of asthma during pregnancy improves in one third, worsens in one third, and remains unchanged in one third [4–9]. Asthma symptoms and exacerbations tend to peak during the second trimester [3,4,7–9]. In the study from Finland, exacerbations occurred most frequently between 17 and 24 weeks of pregnancy [2]. Exacerbation during labor and delivery is uncommon, usually is treated easily, and is more likely to occur in patients in whom asthma is controlled inadequately or in those who acquire an infection [8].

Limited data suggest that pregnant asthmatic African American women experience more morbidity than do white women. They are 1.35 times more likely to receive a course of rescue corticosteroids, 1.89 times more likely to visit an emergency department, and 1.73 times more likely to be hospitalized during pregnancy [10].

Asthma exacerbations can harm the fetus in several ways. Poor control of asthma during pregnancy is associated with several poor outcomes for mother

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and baby, including perinatal mortality, preeclampsia, preterm birth, and low birth weight [9,11–15]. Maternal hypoxia may cause fetal hypoxia directly [16,17]. In addition, other consequences of poorly controlled asthma, such as hypocapnia and alkalosis, may cause fetal hypoxia indirectly by reducing uteroplacental blood flow [16,17]. Therefore, acute asthma exacerbations during pregnancy should be managed aggressively in the home, emergency department, and hospital.

Treatment goals

Home management of asthma exacerbations

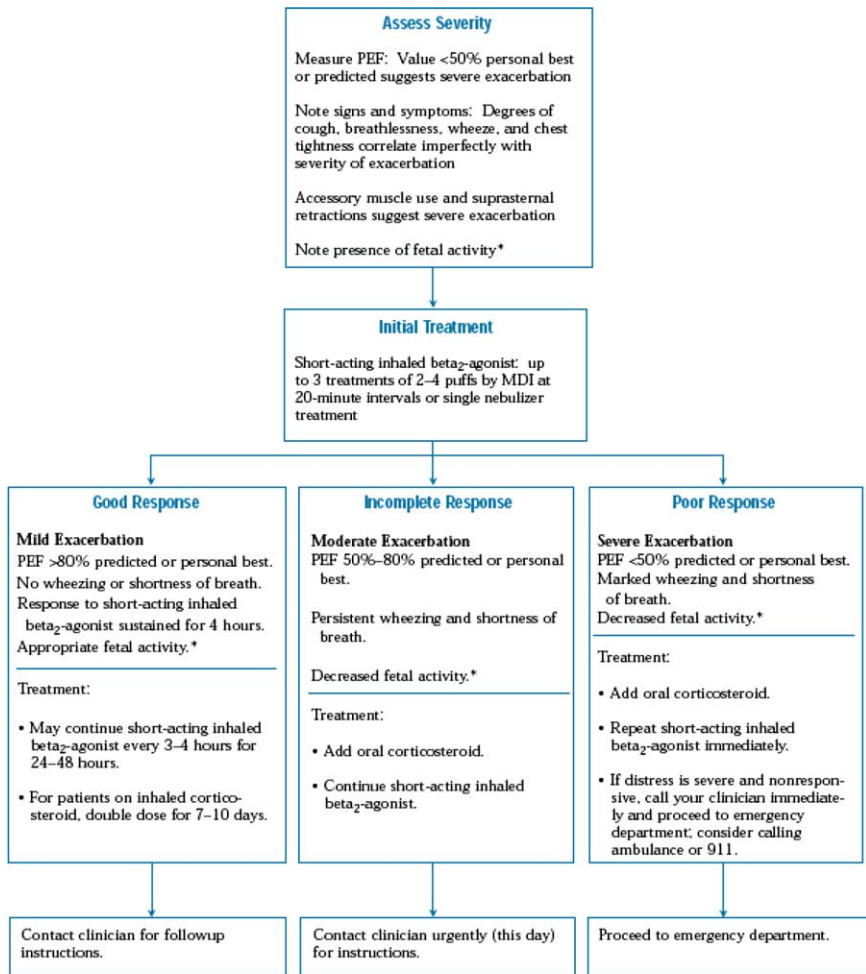
Pregnant asthmatics must be admonished to be diligent in monitoring their asthma symptoms and vigilant in recognizing early signs and symptoms of acute asthma exacerbation. An increase in cough, the appearance of chest tightness, dyspnea, wheezing, decrease in fetal movement, or a 20% decrease in peak expiratory flow rate (PEFR) may signal the worsening of asthma and should warrant immediate attention. All patients should have a personal action plan for initiating home therapy and for seeking medical attention [18].

The goal of treatment is prevention of maternal and fetal hypoxia and quick reversal of airway obstruction. An algorithm for home therapy is presented in Fig. 1. Home treatment should begin with inhaled β -2 agonist treatment (eg, albuterol, two to four puffs or single nebulizer treatments every 20 minutes for up to 1 hour). Quick resolution of symptoms, ability to resume normal activity, and return of PEFR to greater than 80% of personal best indicate a good response. Prompt further medical attention, such as a visit to the doctor or emergency department, is indicated if there is an incomplete response to initial therapy or a decrease in fetal movement.

Emergency department and physician/hospital-based management

Emergency department and other acute interventions should be guided by pulmonary function tests (forced expiratory volume in 1 second [FEV₁], PEFR), vital signs, chest and heart examinations, and the patient's subjective assessment of dyspnea. The goals of emergency treatment are to ensure adequate oxygenation for mother and fetus and to relieve airflow obstruction. An ideal therapy does not exist, and the use of multidrug regimens is common. Supplemental oxygen, inhaled β -2 agonists, systemic corticosteroids, and, when indicated, inhaled anticholinergic agents are the mainstays of asthma treatment in the emergency department.

An algorithm that outlines recommendations for assessment and care of acute asthma exacerbation in the emergency department and hospital is presented in



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

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

Fig. 1. Home management of acute asthma exacerbation during pregnancy. *From* National Asthma Education and Prevention Program Working Group report on managing asthma during pregnancy. Recommendations for pharmacologic treatment. Bethesda (MD): US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2005. p. 53. NIH Publication #05–5236.

Fig. 2. Medications and dosages for acute asthma exacerbations are presented in Table 1. The safety of medications during pregnancy is discussed elsewhere in this issue. A recent review of the literature indicates that human gestational studies have been conducted for the inhaled corticosteroids (ICSs), beclomethasone, budesonide, and triamcinolone, and for cromolyn sodium, theophylline, and salmeterol [19]. No asthma medication has been placed in category A, which

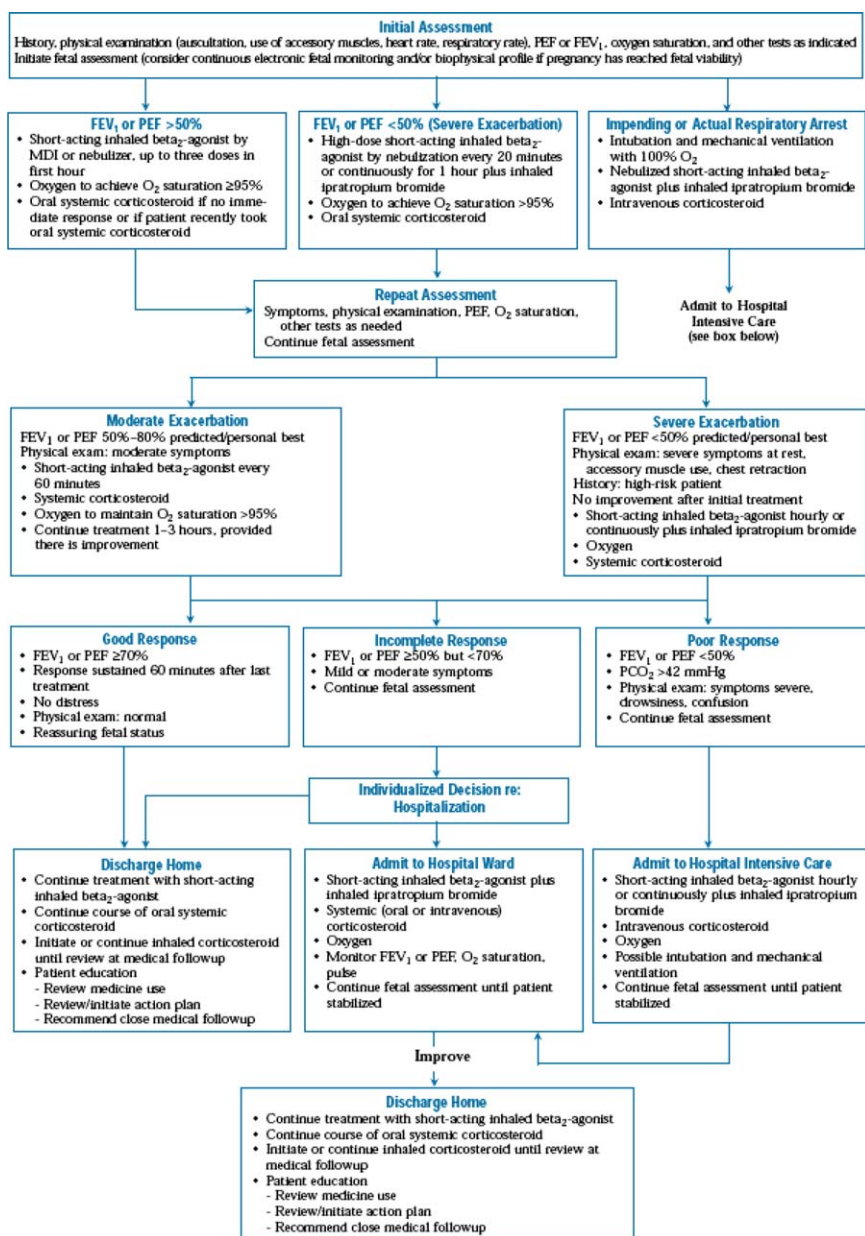


Fig. 2. Emergency department/hospital-based management of acute asthma exacerbation during pregnancy. From National Asthma Education and Prevention Program Working Group report on managing asthma during pregnancy. Recommendations for pharmacologic treatment. Bethesda (MD): US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2005. p. 54. NIH Publication #05–5236.

requires adequate and controlled human data and reassuring animal studies. Human pregnancy data support a U.S. Food and Drug Administration pregnancy category B rating for budesonide. Pregnancy category B ratings for cromolyn, nedocromil, montelukast, and zafirlukast are based primarily on safety in animal reproduction studies. ICSs other than budesonide, theophylline, zileuton, and long-acting β -2 adrenergic agonists are pregnancy category C. Human pregnancy data for many asthma controllers are lacking; nonetheless, data support a range of choices among medications that are rated pregnancy category B [19].

Assessment

The goal of therapy is prevention of maternal and fetal hypoxia [16,17]. A focused history and physical examination should be performed rapidly and treatment should be initiated promptly. Attention to vital signs and work of breathing should be supplemented with objective measures of response to therapy, such as assessment of oxygen saturation and FEV₁ or PEF. If possible, fetal monitoring should be performed once the fetus is potentially viable because it may provide an early indicator of fetal distress.

Oxygen should be administered as needed to maintain oxygen saturation (S_pO_2) of at least 95% saturation. Hypoxemia is not common during most acute asthma exacerbations [20,21]. Arterial blood gas measurements need to be obtained only in patients who experience severe or prolonged attacks. In the nonpregnant patient, hypercapnia, severe hypoxemia, or metabolic acidosis does not occur until the PEF or FEV₁ is less than 25% of predicted values [22–24]. The degree of hypoxemia that is determined by arterial blood gas generally reflects the extent of ventilation–perfusion mismatch. As pregnancy progresses, the normal $PaCO_2$ decreases to 27 to 32 mm Hg [16]. Thus, a $PaCO_2$ of more than 35 mm Hg indicates severe airway obstruction and impending ventilatory failure during pregnancy, and needs to be addressed immediately.

A chest radiograph is necessary only if pneumonia, pneumothorax, pneumomediastinum or other pulmonary pathology is suspected or if the patient fails to respond to aggressive bronchodilator therapy [25,26]. Generally, electrocardiography is not helpful, except to rule out suspected cardiac problems. Blood tests, including a complete blood count, also are unlikely to help guide the acute management of an asthma attack.

Treatment

β -2 Agonists. β -2 agonists relax airway smooth muscle by stimulating β -2 receptors and increasing cyclic cAMP. Data from human studies indicate that the use of β -2 agonists are safe during pregnancy [27–30]. Treatment should be initiated with a β -2 agonist, such as albuterol, 2.5 to 5.0 mg delivered by nebulizer or MDI with spacing device every 20 minutes for three doses, or continuously at 10 to 15 mg/h if obstruction is severe. Current evidence indicates that administration by nebulizer and multi-dose inhaler (MDI) with spacer are

Table 1
Medications and dosages for asthma exacerbation during pregnancy.^a

Medications	Adult dose	Child dose	Comments
<i>Short-acting inhaled beta₂-agonists</i>			
Albuterol			
Nebulizer solution (5.0 mg/mL, 2.5 mg/3mL, 1.25 mg/3mL, 0.63 mg/3 mL)	2.5–5 mg every 20 minutes for 3 doses, then 2.5–10 mg every 1–4 hours as needed, or 10–15 mg/hour continuously	0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for 3 doses, then 0.15–0.3 mg/kg up to 10 mg every 1–4 hours as needed, or 0.5 mg/kg/hour by continuous nebulization	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 µg/puff)	4–8 puffs every 20 minutes up to 4 hours, then every 1–4 hours as needed	4–8 puffs every 20 minutes for 3 doses, then every 1–4 hours inhalation maneuver; use spacer/holding chamber	As effective as nebulized therapy if patient is able to coordinate.
Bitolterol			
Nebulizer solution (2 mg/mL)	See albuterol dose.	See albuterol dose, thought to be half as potent as albuterol on a mg basis.	Has not been studied in severe asthma exacerbations. Do not mix with other drugs.
MDI (370 µg/puff)	See albuterol dose.	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 minutes for 3 doses, then 1.25–5 mg every 1–4 hours as needed, or 5–7.5 mg/hour continuously	0.075 mg/kg (minimum dose 1.25 mg) every 20 minutes for 3 doses, then 0.075–0.15 mg/kg up to 5 mg every 1–4 hours as needed, or 0.25 mg/kg/hour by continuous nebulization	0.63 mg of levalbuterol is equivalent to 1.25 mg of racemic albuterol for both efficacy and side effects.

Pirbuterol MDI (200 µg/puff)	See albuterol dose.	See albuterol dose, thought to be half as potent as albuterol on a mg basis.	Has not been studied in severe asthma exacerbations.
<i>Systemic (injected) beta₂-agonists</i>			
Epinephrine 1:1000 (1 mg/mL)	0.3–0.5 mg every 20 minutes for 3 doses sq	0.01 mg/kg up to 0.3–0.5 mg every 20 minutes for 3 doses sq	No proven advantage of systemic therapy over aerosol.
Terbutaline (1 mg/mL)	0.25 mg every 20 minutes for 3 doses sq	0.01 mg/kg every 20 minutes for 3 doses, then every 2–6 hours as needed sq	No proven advantage of systemic therapy over aerosol.
<i>Anticholinergics</i>			
Ipratropium bromide Nebulizer solution (0.25 mg/mL)	0.5 mg every 30 minutes for 3 doses, then every 2–4 hours as needed	0.25 mg every 20 minutes for 3 doses, then every 2 to 4 hours	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 µg/puff)	4–8 puffs as needed	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 minutes for 3 doses, then every 2–4 hours as needed	1.5 mL every 20 minutes for 3 doses, then every 2–4 hours	Contains EDTA to prevent discoloration. This additive does not induce bronchospasm.
MDI (Each puff contains 18 µg ipratropium bromide and 90 µg albuterol)	4–8 puffs as needed	4–8 puffs as needed	

(continued on next page)

Table 1 (continued)

Medications	Adult dose	Child dose	Comments
<i>Systemic corticosteroids</i>			
Prednisone	(Dosages and comments apply to all three corticosteroids)	1 mg/kg every 6 hours for 48 hours, then	For outpatient "burst" use 40–60 mg
Methylprednisolone	120–180 mg/day in 3 or 4 divided	1–2 mg/kg/day (maximum = 60 mg/day)	in single or 2 divided doses for adults
Prednisolone	doses for 48 hours, then 60–80 mg/day	in 2 divided doses until PEF is 70% of	(children: 1–2 mg/kg/day, maximum
	until PEF reaches 70% of predicted	predicted or personal best	60 mg/day) for 3–10 days.
	or personal best		

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 percent of predicted or personal best and then lower the dose to twice daily. This usually occurs within 48 hours. 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 followup 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.

^a Adapted from EPR—Update 2002.

From National Asthma Education and Prevention Program Working Group report on managing asthma during pregnancy. Recommendations for pharmacologic treatment. Bethesda (MD): US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute; 2005. NIH Publication #05–5236; Appendix B; p. 55.

equivalent [31,32]. Continuous therapy may offer a slight advantage in patients who have severe obstruction [33,34].

Systemic corticosteroids. All patients should receive systemic corticosteroids—preferably oral—early in their treatment regimen, because data indicate that patients who receive glucocorticoids early require fewer hospital admissions and sustain fewer relapses after discharge from the emergency department [35]. Studies have revealed conflicting evidence about the safety of oral corticosteroids during pregnancy [15,27,29,36–39]. Oral corticosteroid use during the first trimester seems to be associated with a slight increased risk for oral clefts. It is difficult to separate the other adverse effects that are associated with corticosteroid use, such as preeclampsia, preterm delivery, and low birth weight, from the effects of uncontrolled asthma. Systemic corticosteroids may be withheld in patients who immediately and completely respond to β -2 agonists or in those who took an adequate dose of systemic corticosteroids before arrival for medical care. Intravenous corticosteroids should be administered to patients who have impending respiratory failure to ensure adequate absorption. Studies to support the use of high-dose ICSs in lieu of systemic corticosteroids during acute asthma exacerbation in pregnancy are lacking, and therefore, they cannot be recommended [35,40–42].

Ipratropium bromide. Ipratropium bromide is a quaternary amine anticholinergic agent that is minimally absorbed from the lungs [43]. Data from multiple studies indicated that the addition of ipratropium to β -2 agonist agents resulted in modest improvement in bronchodilation and decreased need for hospitalization among patients who presented with severe obstruction [44–46]. Although there are no published data on the use of anticholinergic agents in pregnancy, the National Asthma Education and Prevention Program (NAEPP) Working Group on Asthma in Pregnancy recommends the use of ipratropium bromide during acute asthma exacerbation [47–51].

Other asthma medications. Nedocromil and cromolyn inhibit the release of inflammatory cytokines from mast cells, but they have no role in acute management. The role of leukotriene modifiers in acute asthma exacerbation has yet to be defined. Two studies, one using intravenous montelukast [52] and the other using oral zafirlukast [53], demonstrated some benefit of leukotriene receptor antagonist therapy when added to standard therapy during emergency care. Leukotriene modifiers have not been studied in the treatment of acute asthma exacerbations during pregnancy. The benefits of ketamine and halothane remain largely anecdotal; they have not been substantiated in controlled trials and have not been studied in pregnant asthmatics [47–50].

Magnesium sulfate. Magnesium sulfate, a physiologic regulator of intracellular calcium flux, is an effective bronchodilator. In addition to preventing histamine release from mast cells and opposing the action of acetylcholine, magnesium

directly inhibits bronchial smooth muscle contraction. High-dose magnesium has been used as a treatment for eclampsia for decades [54,55]. Although only a single case report has documented the use of intravenous magnesium in the treatment of severe asthma in pregnancy [56], substantial evidence exists to support its use in severely obstructed nonpregnant asthmatic patients [35,57–62]. Aerosolized magnesium (0.66 g in 10 mL of saline) and intravenous magnesium solutions (1.2 g over 20 minutes) have been used investigationally to treat patients who have asthma for whom maximal standard therapy has failed, although neither form is approved for this indication in the United States. Bronchodilation is observed within 2 to 5 minutes after administration, but it disappears rapidly after treatment is discontinued; therefore, additional bronchodilator therapy must accompany the use of magnesium. Side effects include hypotension, malaise, and a warm sensation. Cardiac rhythm, blood pressure, pulse, neurologic status, and renal function must be monitored closely.

Heliox. Heliox, an 80:20 mixture of helium and oxygen, sometimes is considered for treatment in patients who have respiratory acidosis and who fail conventional therapy. Helium is a low-density, biologically inert gas that lowers airway resistance and decreases respiratory work. Significant improvement may be noted within 10 to 20 minutes of initiating therapy, but there are insufficient data on whether heliox can avert tracheal intubation, change intensive care and hospital admission rates and duration, or affect mortality [63,64]. One case report described the use of heliox in a pregnant, intubated asthmatic [65,66], but otherwise, the use of heliox has not been studied in pregnancy.

Assisted ventilation. Noninvasive respiratory therapies, such as continuous positive airway pressure and biphasic positive airway pressure, have been shown to reduce the work of breathing and to improve oxygenation for some causes of respiratory failure. More data are needed to support this intervention in acute asthma exacerbation [51,65,66].

If the patient's condition deteriorates or fails to improve despite intensive therapy, the use of intubation and mechanical ventilation must be considered. Although there are no absolute criteria other than respiratory arrest and coma, patients who have the following symptoms should be considered for intubation and mechanical ventilation: worsening pulmonary function tests, despite vigorous bronchodilator therapy; decreasing PaO_2 , increasing PaCO_2 , or progressive respiratory acidosis; declining mental status; and increasing fatigue.

Randomized controlled trials to evaluate methods of ventilation during treatment of severe, life-threatening acute asthma are lacking. Because airflow obstruction can result in air trapping and higher lung volumes in mechanically ventilated asthmatics, it is suggested that asthmatics who require intubation be ventilated using "permissive hypercapnia." This technique usually avoids the development of auto-PEEP (positive end-expiratory pressure) by using a rapid inspiratory flow rate, a reduced respiratory frequency, and a prolonged expiratory phase [67,68]. Should auto-PEEP develop and result in a continuously increased

intrathoracic pressure that may decrease venous return and cause hypotension, it can be treated by disconnecting the patient from the ventilator and allowing the lungs to deflate completely before reconnecting.

Disposition decisions

All patients should be observed and re-evaluated frequently during and after treatment. The disposition decision should be based on duration, course, and severity of symptoms; severity of airflow obstruction; course and severity of previous exacerbations; medication use at the time of the exacerbation; access to medical care and medications; and adequacy of support and home conditions (see Fig. 2). If in doubt, it is advisable to err on the side of caution and observe the patient longer in the emergency department, observation unit, or hospital. Although there are no reliable criteria to predict who will be discharged successfully and who will relapse [21,69–73], careful discharge planning may help to avoid future problems.

Patients should be provided with a schedule for ongoing short-acting β -2 agonist use and a 3- to 10-day burst of oral corticosteroids [74]. Data indicate that emergency physicians are less likely to prescribe systemic corticosteroids to pregnant asthmatic women who experience exacerbation than to nonpregnant asthmatic women, and that pregnant asthmatic women are three times more likely to report ongoing exacerbation at 2 weeks after emergency department discharge [21].

Patients who are on ICSs should be advised to continue their use, whereas asthmatics who have persistent disease and who are not already on ICSs should be advised to begin taking them. One observational study suggested that inhaled steroids prevented asthma exacerbations during pregnancy [9]. In addition, a randomized controlled trial showed that discharge on ICSs, in addition to oral steroids and β -2 agonists, reduced repeat asthma exacerbations in pregnant women who were hospitalized for asthma [75]. Finally, patient education, a personalized action plan for worsening of symptoms, and advice for close follow-up should be provided.

Summary

In addition to preventing maternal and fetal hypoxia, the goals of treating acute asthma exacerbation during pregnancy mirror those in the nonpregnant patient: rapid reversal of airflow obstruction with aerosolized bronchodilators, reduction of likelihood of recurrence by the addition of corticosteroids, and ongoing assessment of mother and fetus. Disposition decisions are multifaceted and must take into account the health and well-being of the pregnant patient and that of her fetus. Discharge planning includes prescription of scheduled β -2

agonist treatments until symptoms resolve, intensification of daily treatment as needed, prescriptions for systemic and ICSs, as well provision of patient education, a personalized action plan, and close follow-up.

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