# Chapter 18
# Asthma and Pregnancy

**Peg Strub**

## Asthma and Pregnancy

Asthma is one of the most common chronic diseases and affects up to 8 % of pregnancies. The "one-third rule" states that in pregnancies with asthma, a third of the patients will improve, a third will get worse, and a third will stay the same.

Asthma in two-thirds of pregnant women will either worsen or show no improvement; the importance of treating all persistent asthmatics with Inhaled corticosteroids (ICS) must be emphasized. One large study shows that in women using Inhaled corticosteroids (ICS) prior to pregnancy, the number of emergency department visits for asthma remained unchanged, and the rate of physician visits for asthma actually decreased after pregnancy.

Despite worsening or unchanged asthma in two-thirds of the patients, pregnant women in general report a decrease in asthma symptoms throughout the pregnancy particularly in the last 4 weeks of pregnancy. This perceived improvement may be explained by hormonal changes or other factors and may lead to difficulties with medication adherence.

### *Adverse Pregnancy Outcomes for Patients with Asthma*

Studies have shown that pregnant women with asthma are at increased risk for pregnancy-induced hypertension, preeclampsia, eclampsia, vaginal bleeding, perinatal mortalities, premature birth, low birth weights, and neonatal sepsis as well as

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pulmonary embolism and depression. For pregnancies complicated by moderate to severe asthma, studies report an increased incidence of cesarean section deliveries. Pregnancies with poorly controlled asthma are at risk for intrauterine growth retardation (IUGR).

## *Physiology*

During pregnancy, many physiologic changes occur in the mother. Understanding these changes is important not only for the care of the pregnant patient with asthma but also for the fetus.

## Maternal Respiratory Physiology

In early pregnancy, 60–70 % of women feel dyspneic due to hyperventilation. The mechanism of the hyperventilation is progesterone mediated with a resultant increase in tidal volume. As pregnancy progresses, an up to 50 % increase in minute ventilation occurs with a corresponding increase in oxygen consumption and carbon dioxide production. The increase in carbon dioxide production is partially blunted by an increase in renal excretion of bicarbonate (explaining the polyuria of early pregnancy), resulting in a mild compensatory respiratory alkalosis. During pregnancy, arterial blood gases (ABGs) typically have pH levels of 7.42–7.46, PCO2 levels of 26–30 mmHg, and PO2 levels of 99–106 mmHg.

The increased size and pressure of the uterus limits diaphragmatic excursion, lowering residual volume and functional residual capacity. Compensation occurs by increased mobility and flaring of the ribs as well as by progesterone-mediated relaxation of bronchial smooth muscle. The net result is that pulmonary function test results remain unchanged for forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), the forced expiratory volume in 1 s to forced vital capacity ratio (FEV1/FVC), and peak expiratory flow rate (PEFR) (Table 18.1).

## Maternal Cardiovascular Physiology

Although central venous pressure remains unchanged, there is a 40 % increase in maternal cardiac volume and cardiac output with a marked increase in left ventricular mass, compliance, and end-diastolic volume. Total blood volume increases by 40 %, but plasma volume increases more than red cell mass resulting in anemia of pregnancy or physiologic hemodilution (Table 18.2).

**Table 18.1** Maternal respiratory physiology

| |
|---|
| 60–70 % patients have dyspnea of early pregnancy due to hyperventilation |
| Progesterone-related tidal volume increase |
| Minute ventilation increases up to 50 % with increased O2 consumption and CO2 production |
| Compensatory respiratory alkalosis (pH 7.42–7.46, PCO2 26–30, and PO2 99–106) |
| Increased size and pressure of uterus limits diaphragmatic excursion |
| Increased mobility and flaring of ribs |
| Progesterone may relax bronchial smooth muscle |
| Pulmonary function tests remain essentially unchanged |

**Table 18.2** Maternal cardiovascular physiology

| |
|---|
| Central venous pressure remains unchanged |
| 40 % increase in maternal cardiac volume |
| 40 % increase in cardiac output |
| Increase in left ventricular mass, compliance, and end-diastolic volume |
| Plasma volume increases more than red cell mass: anemia of pregnancy |

**Table 18.3** Maternal gastroesophageal reflux

| |
|---|
| Common complaint during pregnancy |
| May be due to progesterone-mediated relaxation of smooth muscle of esophagus with resultant |
| Increase in intra-abdominal pressure |

## Maternal Gastroesophageal Reflux

Gastroesophageal reflux during pregnancy is a common complaint and may exacerbate asthma. The increase in gastroesophageal reflux may be due to progesterone-mediated relaxation of smooth muscle of the esophagus with a resultant increase in intra-abdominal pressure (Table 18.3).

## Fetal Physiology

The fetus functions by aerobic metabolism even though the PO2 level of the fetus is one-fourth of the PO2 level of the mother. Mechanisms allowing the fetus to thrive include an increase in hemoglobin content and the oxygen affinity of fetal hemoglobin, preferential blood flow to vital organs, high cardiac output, and leftward shift of the oxygen dissociation curve.

**Table 18.4** Fetal physiology

| |
|---|
| Fetus functions by aerobic metabolism |
| Mechanisms allowing fetus to thrive |
| Increase in hemoglobin content |
| Increase in oxygen affinity of fetal hemoglobin |
| Preferential blood flow to vital organs |
| High cardiac output |
| Leftward shift of oxygen dissociation curve |
| Low maternal PCo2 important to acid-base balance |
| Increase in maternal PCo2 may result in fetal acidosis, even with adequate oxygenation |

A low maternal PCO2 is important to normal fetal acid–base balance. An increase in maternal PCO2 may affect this balance and result in fetal acidosis, even with adequate oxygenation (Table 18.4).

## Asthma Treatment During Pregnancy

Treatment goals are providing optimal therapy to maintain control of asthma for maternal health and quality of life as well as for normal fetal maturation. As per the National Asthma Education Prevention Program (NAEPP), asthma control is defined as follows:

- Minimal or no chronic symptoms day or night
- Minimal or no exacerbations
- No limitations on activities
- Maintenance of normal or near-normal pulmonary function
- Minimal use of short-acting inhaled B2-antagonist
- Minimal or no adverse effects from medications (always consult latest NAEPP guidelines)

## Assessment of Asthma

Pregnant women with asthma should have a thorough assessment of their asthma control. Patients should be asked about the frequency of their symptoms both during the day and at night/early morning, how often symptoms interfere with normal activities, and the usage of short-acting B2-agonists for symptom relief (not for exercise-induced bronchospasm prevention). Validated questionnaires such as the ATAQ, ACQ, and ACT are particularly helpful in classifying the level of asthma control.

In addition, a complete assessment of asthma must include objective measurements. All patients should have pulmonary function testing at their initial evaluation to determine disease severity. At subsequent office visits, repeat pulmonary function testing is preferable, but at a minimum, assessment of peak expiratory flow rates (PEERs) should be checked. Patients should be prescribed a peak flow meter or a portable FEV1 device to monitor asthma variability.

## Assessment of the Fetus

All pregnant women should be advised to be attentive to fetal activity. Serial ultrasound evaluations beginning at 32-week gestational age may be considered for women with moderate to severe asthma and women with poorly controlled asthma. In addition, after a severe exacerbation, an ultrasound evaluation may be reassuring.

## Medication Reassurance

Patients need to be reassured that asthma medications are safe and advised that the risks of treatment are much less than the risks of untreated asthma. Concern about side effects in the fetus may interfere with medication adherence and lead to undertreatment of asthma.

## Education

All pregnant women with asthma should receive asthma education emphasizing the important benefits of treatment and its impact on the fetus. Written and verbal instructions should be given for the proper use of medications, spacers, and peak flow meters. Patients should be taught how to monitor inhaler usage to avoid running out of medication. Patients should also be counseled on the dangers of overuse and over-reliance on short-acting B2-agonist (SABA) medications.

## Smoking

Any patient who is smoking should be advised to quit and be referred to a smoking cessation program. Besides adversely affecting asthma. In addition to adversely has deleterious effects on the mother and the fetus.

## Triggers

An assessment of common triggers with instructions on avoidance and control should be part of all patient evaluations. Patients with exposure to secondary smoke, including woodburning stoves and fireplaces, should also be counseled on the importance of avoidance. Patients should be advised to avoid exposure to irritants that trigger their symptoms including sprays, cleaning agents, and occupational sensitizers. Viral infections are the most common triggers causing severe exacerbations. Influenza vaccines and frequent hand washing are recommended, particularly during the flu season. Increased body weight and high-panic-fear state can worsen asthma and complicate treatment in asthma.

## Treatment Plans

Together with the patient, providers should develop medication regimens that are effective and easy to follow. Providers need to be aware that pregnant patients with asthma may have difficulty following complicated treatment regimens.

All patients should receive a written self-management plan. The plan should emphasize home management of exacerbations, including instructions on when to start oral steroids and when and where to call for help. Ideally, these plans should be based on both symptoms and peak flow meter readings.

In addition, it is important to include the obstetrical provider in the asthma care team early on. The obstetrical provider will be assessing the patient more frequently.

## Medications

### *Inhaled Short-Acting B2-Agonists (SABAs)*

Inhaled short-acting B2-agonists (SABAs) are one of the mainstays of therapy but should be administered only as needed. The preferred medication is albuterol, based on more published data on safety.

### *Inhaled Long-Acting B2-Agonists (LABAs)*

Inhaled long-acting B2-agonists (LABAs) have a profile similar to the inhaled short-acting B2-agonists (SABAs) with the exception that these drugs are retained longer in the lungs. The preferred medication is salmeterol (Serevent), due to the longer availability of the drug in the United States (Table 18.6).

There has been controversy about inhaled long-acting B2-agonists (LABAs) increasing risks of hospitalization and death in asthmatics. It would be prudent to use inhaled long-acting B2-agonists (LABAs) only as add-on therapy to medium- or high-dose inhaled corticosteroids (ICS), if asthma remains poorly controlled.

### *Inhaled Corticosteroids (ICS)*

Inhaled corticosteroids (ICS) are the cornerstone of therapy for the pregnant woman with persistent asthma. Multiple studies have emphasized the decrease in asthma exacerbations and the improvement in FEV1 with the use of inhaled corticosteroids (ICS). Even studies in large birth registries have failed to relate the use of inhaled corticosteroids (ICS) in low–moderate doses to any unfavorable perinatal outcome, including increased incidence of congenital malformations. However, a study that looked at higher doses of inhaled corticosteroids (ICS) (>1000 mcg/day) during the first trimester showed a 63 % increase in risk of all congenital malformations. This study had multiple issues including a small number of patients with a daily dose over 1000 mcg, and it was difficult to determine whether the increased incidence of malformations was due to inadequately controlled asthma or due to high-dose inhaled corticosteroids (ICS). More studies are needed. The preferred medication is budesonide (Pulmicort), based on published data (Table 18.7).

## Oral Corticosteroids

Oral corticosteroids are used in the treatment of poorly controlled severe persistent asthma or for the treatment of asthma exacerbations. On occasion, a short course of oral corticosteroids may be necessary to gain control of asthma (Table 18.6). Studies have shown that oral corticosteroid use has been associated with a decrease in birth weight of approximately 200 g without an increased incidence of small for gestational age (SGA) infants. In addition, there is an association with an increased incidence of isolated cleft lip (without cleft palate) especially when oral corticosteroids are taken during the first trimester. Systemic steroid use has also been associated with an increased incidence of preterm births and preeclampsia. Hypertension and gestational diabetes are potential maternal complications. The preferred drugs are prednisone and prednisolone due to limited placental transfer.

## Cromolyn Sodium

Cromolyn sodium is safe for pregnancy. It is considered an alternative but not a preferred option for mild persistent asthma (Table 18.6). The availability of this drug is limited.

## Nedocromil

Animals' studies have been reassuring on the use of nedocromil in pregnancy. It is considered an alternative, but not a preferred, option for mild persistent asthma. The availability of this drug is limited (Table 18.6).

## Theophylline

Theophylline is safe for pregnancy in the usual therapeutic serum level range of 5–12 ug/mL. However, theophylline has many side effects and drug–drug interactions. Studies have shown that women treated with theophylline have a high rate of discontinuance of the drug. Inhaled corticosteroids (ICS) have greater efficacy with fewer side effects. Oral theophylline would be an alternative but not preferred option for the treatment of mild or moderate persistent asthma (Table 18.6).

## Leukotriene Receptor Antagonists (LTRAs)

There are limited studies on treatment with leukotriene receptor antagonists during pregnancy available for review. There is more data on montelukast in pregnancy than zafirlukast and zileuton; montelukast is considered the preferred leukotriene receptor antagonist option. Animal data on zafirlukast shows no teratogenicity at high doses. Animal studies on zileuton do not support its use in pregnancy. Leukotriene receptor antagonists would be an alternative but not preferred option for the treatment of mild or moderate persistent asthma (Table 18.6).

## Ipratropium

There are reassuring animal studies for ipratropium (Atrovent, Atrovent HFA). Inhaled ipratropium is considered safe for pregnancy. Note that when atropine is administered systemically to the mother, the fetus can develop tachycardia (Table 18.9).

## Tiotropium

Tiotropium may be an option for asthma that is not well controlled during pregnancy on inhaled corticosteroids (ICS) and long-acting B2-agonists (LABAs). However, there is currently no safety data on the use of tiotropium during

pregnancy. Caution needs to be used and the benefits versus the risks need to be weighed if considering tiotropium during pregnancy (Table 18.6).

## Anti-immunoglobulin E

Omalizumab is an IgG monoclonal antibody (recombinant DNA derived) which inhibits IgE binding to the high-affinity IgE receptors on mast cells and basophils. It is considered a potential option for add-on therapy for moderate to severe persistent asthma only when asthma is inadequately controlled. No human studies have been performed, but the Xolair Pregnancy Registry (EXPECT) has shown no differences in outcomes with omalizumab use during pregnancy. However, further studies are needed. Patients who are pregnant with inadequately controlled asthma on high-dose steroids who may be candidates for anti-immunoglobulin E therapy should be referred to a specialist (Table 18.6).

## Treatment Guidelines

The pharmacologic treatment approach for pregnant woman with asthma is based on stepwise asthma care. This approach follows established guidelines for intermittent asthma and mild, moderate, and severe persistent asthma (Table 18.5). It recommends controller mediations for all levels of persistent asthma. Doses of medications used in pregnancy and lactation are included in Tables 18.6 and 18.7. These guidelines may be modified to fit the needs of individual patients (Table 18.8).

## Intermittent Asthma (Step 1)

Patients with intermittent asthma should be treated with inhaled short-acting B2-agonists (SABAs), preferably albuterol, as needed. However, it is important to note that even patients with intermittent asthma can experience life-threatening exacerbations and should have treatment plans for exacerbations that include oral corticosteroids (Tables 18.5, 18.8, and 18.9).

## Mild Persistent Asthma (Step 2)

Patients with mild persistent asthma should be treated with low-dose inhaled corticosteroids (ICS), preferably budesonide (Pulmicort), with inhaled short-acting B2-agonists (SABAs), preferably albuterol, used as needed. The alternative but less preferable treatments include leukotriene receptor antagonists (LTRAs), sustained-release theophylline, cromolyn, and nedocromil (Tables 18.5, 18.6, 18.7, and 18.8).

**Table 18.5** Guide to asthma severity

| Components of severity | Category | #Symptoms | #Symptoms/night | SABA use | Activity | FEV1 or PEFR | FEV1/FVC | Step |
|---|---|---|---|---|---|---|---|---|
| Impairment normal Fev1/FVC: 8– to 19 years 85 % | Intermittent | ≤2 days/week | ≤2 nights/month | ≤2 days/week | None | ≥80 % | Normal | 1 |
| 20–39 years, 80 % | Mild persistent | >2 days/week but not daily | 3–4×/month | >2 days/week not daily and not more than 1×/day | Minor | ≥80 % | Normal | 2 |
| 40–59 years, 75 % | Moderate persistent | Daily | >1×/week but not nightly | Daily | Some | >60–<80 % | Reduced 5 % | 3 |
| 60–80 years, 70 % | Severe persistent | Continual | Often 7×/week | Several times/day | Extremely | ≤60 % | Reduced >5 % | 4, 5 or 6 |

Adapted from NAEPP Guidelines, 2007

**Table 18.6** Usual dosages for long-term medications during pregnancy and lactation

| Medication | Dosage form | Adult dose |
|---|---|---|
| *Inhaled corticosteroids* (*see estimated comparative daily dosages for inhaled corticosteroids* (Table 18.8)) | | |
| *Systemic corticosteroids* (*applies to all three 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 mL | Short-course "burst" to achieve control: 40–60 mg/day |
| | 15 mg/5 mL | |
| Prednisone | 1-,2.5-,5-,10-,20-,50-mg tablets | As single dose or two divided doses for 3–10 day |
| | 5 mg/mL, 5 mg/5 mL | |
| *Long-acting inhaled B2-agonists* (*note*: *should not be used for symptom relief or for exacerbations. Use with inhaled corticosteroids*) | | |
| Salmeterol<br>Formoterol | DPI 50 μg/blister<br>DPI 12 μg/single-use capsule | 1 blister q 12 h<br>1 capsule q 12 h |
| *Combined medication* | | |
| Fluticasone/salmeterol | DPI 100 mcg/50 mcg<br>250 mcg/50 mcg<br>Or 500 mcg/50 mcg<br>HFA 45 mcg/21 mcg<br>115 mcg/21 mcg<br>230 mcg/21 mcg | 1 inhalation bid; dose depends on level of severity or control |
| Budesonide/formoterol | HFA MDI<br>80 mcg/4.5 mcg<br>160 mcg/4.5 mcg | 2 puffs bid; dose depends on level of severity or control |
| Mometasone/formoterol | HFA MDI 100 mcg/4.5 mcg<br>200 mcg/4.5 mcg | |
| *Cromolyn*<br>Cromolyn | MDI 5 mg/puff<br>Nebulizer 20 mg/ampule | 2–4 puffs qid<br>1 ampule qid |
| *Nedocromil* | MDI CFC free<br>2 mg/puff | 2 puffs qid |
| *Leukotriene receptor antagonists* | | |
| Montelukast<br>Zafirlukast | 10-mg tablet<br>20-mg tablet | 10 mg q h<br>40 mg daily (20-mg tablet bid) |
| *Methylxanthines* (*serum monitoring is important* [*serum concentration of 5–12 μg/mL at steady state*]) | | |
| Theophylline | Liquids, sustained release | Starting dose, 10 mg/kg/day up to usual maximum; 16 mg/kg/day |
| | Tablets and capsules | |

(continued)

**Table 18.6** (continued)

| Medication | Dosage form | Adult dose |
|---|---|---|
| *Immunomodulators* | | |
| Omalizumab (anti-IgE) | Subcutaneous injection, 150 mg/1.2 mL, following reconstitution with 1.4 mL sterile water for injection | 150–375 mg SC q 2–4 weeks, depending on body weight and pretreatment serum IgE level |
| | | Note: no human studies have been performed, but the Xolair Pregnancy Registry (EXPECT) has shown no differences in outcomes with omalizumab use during pregnancy. Further studies are needed and the benefits versus the risks need to be weighed |
| *Anticholinergics* | | |
| Tiotropium | 18-mcg capsule 2.5 mcg/puff | 18-mcg capsule by inhalation qd |
| | | 2 puffs qd |
| | | Note: tiotropium may be an option for asthma that is not well controlled during pregnancy on ICS/LABA. Note there is currently no safety data on the use of tiotropium during pregnancy. Caution needs to be used and the benefits versus the risks need to be weighed |

Adapted from NAEPP Guidelines, 2007

## Moderate Persistent Asthma (Step 3)

Patients with moderate persistent asthma should be treated with medium-dose inhaled corticosteroids (ICS), preferably budesonide (Pulmicort). If control is difficult or cannot be achieved, inhaled corticosteroids (ICS) can be supplemented with an inhaled long-acting B2-agonist (LABA), preferably salmeterol (Serevent). Inhaled short-acting B2-agonists (SABAs), preferably albuterol, should be added as needed. Alternative, but less preferable, treatments include low-dose inhaled corticosteroids (ICS) with an inhaled long-acting B2-agonist (LABA), preferably salmeterol (Serevent). For those intolerant of long-acting B2-agonists (LABAs), either low-dose or medium-dose inhaled corticosteroids (ICS) can be supplemented with the addition of sustained-release theophylline or leukotriene receptor antagonist (LTRA) therapy (Tables 18.5, 18.6, 18.7, and 18.8).

**Table 18.7** Estimated comparative daily dosages for inhaled corticosteroid

| Medication – daily dose | Low | Medium | High |
|---|---|---|---|
| *Beclomethasone MDI* | 80–240 mcg | More than 240–480 mcg | More than 480 mcg |
| 40 mcg per puff | 1–3 puffs twice a day | 4–6 puffs twice a day | |
| 80 mcg per puff | 1 puff a.m.<br>2 puffs p.m. | 2–3 puffs twice a day | 4 or more puffs twice a day |
| *Budesonide DPI* | 180–540 mcg | More than 540–1,080 mcg | More than 1,080 mcg |
| 90 mcg per inhalation | 1–3 inhalations twice a day | | |
| 180 mcg per inhalation | 1 inhalation a.m.<br>2 inhalations p.m. | 2–3 inhalations twice a day | 4 or more inhalations twice a day |
| *Budesonide Nebules* | Not applicable | Not applicable | Not applicable |
| 0.25 mg | Not applicable | Not applicable | Not applicable |
| 0.5 mg | Not applicable | Not applicable | Not applicable |
| 1.0 mg | Not applicable | Not applicable | Not applicable |
| *Ciclesonide MDI* | 160–320 mcg | More than 320–640 mcg | More than 640 mcg |
| 80 mcg per puff | 1–2 puffs twice a day | 3–4 puffs twice a day | |
| 160 mcg per puff | | 2 puffs twice a day | 3 or more puffs twice a day |
| *Flunisolide MDI* | 320 mcg | More than 320–640 mcg | More than 640 mcg |
| 80 mcg per puff | 2 puffs twice a day | 3–4 puffs twice a day | 5 puffs or more twice a day |
| *Fluticasone MDI* | 88–264 mcg | More than 264–440 mcg | More than 440 mcg |
| 44 mcg per puff | 1–3 puffs twice a day | | |
| 110 mcg per puff | | 2 puffs twice a day | 3 puffs twice a day |
| 220 mcg per puff | | 1 puff twice a day | 2 or more puffs twice a day |
| *Fluticasone DPI* | 100–300 mcg | More than 300–500 mcg | More than 500 mcg |
| 50 mcg per inhalation | 1–3 inhalations twice a day | | |
| 100 mcg per inhalation | | 2 inhalations twice a day | 3 or more inhalations twice a day |
| 250 mcg per inhalation | | 1 inhalations twice a day | 2 or more inhalations twice a day |
| *Mometasone DPI* | 110–220 mcg | More than 220–440 mcg | More than 440 mcg |
| 110 mcg per inhalation | 1–2 inhalations p.m. | 3–4 inhalations p.m. or 2 inhalations twice a day | 3 or more inhalations twice a day |

(continued)

**Table 18.7** (continued)

| Medication – daily dose | Low | Medium | High |
|---|---|---|---|
| 220 mcg per inhalation | 1 inhalation p.m. | 1 inhalation twice a day or 2 inhalations p.m. | 3 or more inhalations divided in two doses |
| *Mometasone HFA* | 100–200 mcg | More than 200–400 mcg | More than 400 mcg |
| 100 mcg per puff | 2 puffs once a day | 2 puffs twice a day | |
| 200 mcg per day | 1 puff a day | 2 puffs a day | 2 puffs twice a day |

Adapted from NAEPP Report (17.27)

**Table 18.8** Stepwise approach for managing asthma during pregnancy and lactation: treatment

| | Step 1 | Step 2 | Step 3 | Step 4 | Steps 5 and 6 |
|---|---|---|---|---|---|
| Preferred controller choice | None needed | Low dose ICS | Med dose ICS | High ICS/ LABA | Refer for add-on treatment, e.g., anti-IgE[b] |
| Other controller options | Consider low-dose ICS | LTRA, low-dose theophylline, nedocromil, cromolyn | Low-dose ICS/ LABA, low-dose ICS + LTRA (or +theophylline) Med-dose ICS/ LABA | High-dose ICS +LTRA (or + theophylline) consider tiotropium although no safety studies on usage during pregnancy[a] | Add low-dose OCS; consider tiotropium although no safety studies on usage during pregnancy[a] |
| Reliever | As-needed short-acting beta 2-agonist (SABA) | | As-needed SABA | | |

Modified from National Heart, Lung, and Blood Institute: National Asthma Education and Prevention Program Asthma and Pregnancy Working group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment-2004 update. *J Allergy ClinImmunol*. 2005;115 (1):36.q

Remember to …

Note presence of fetal activity

Provide guided self-management education (self-monitoring + written action plan + regular review)

Treat modifiable risk factors and comorbidities, e.g., smoking, obesity, and anxiety

Advise about nonpharmacological therapies and strategies, e.g., physical activity, weight loss, and avoidance of sensitizers where appropriate

Consider stepping up if…uncontrolled symptoms, exacerbations, or risks, but check diagnosis, inhaler technique, and adherence first

Consider stepping down if…symptoms controlled for 3 months + low risk for exacerbations. Ceasing ICS is not advised

[a]Tiotropium may be an option for asthma that is not well controlled during pregnancy on ICS/ LABA. Note there is currently no safety data on the use of tiotropium during pregnancy. Caution needs to be used and the benefits versus the risks need to be weighed

[b]No human studies have been performed, but the Xolair Pregnancy Registry (EXPECT) has shown no differences in outcomes with omalizumab use during pregnancy. The benefits versus the risks need to be weighed. Patients should be referred to an asthma specialist

**Table 18.9** Medications and dosages for asthma exacerbations during pregnancy and lactation

| Medications | Adult dosages | Comments |
|---|---|---|
| Short-acting inhaled β2-agonists | | |
| Albuterol<br>Nebulizer solution (5 mg/mL, 2.5 mg/3 mL, 1.25 mg/3 mL, 0.63 mg/3 mL)<br>HFA (90 μg/puff) | 2.5–5 mg q 29 min for doses, then 2.5–10 mg q 1–4 h PRN, or<br>10–15 mg/h continuously<br>4–8 puffs q 20 min up to 4 h, then q 1–4 h as needed | Only selective β2-agonists are recommended. For optimal delivery, dilute aerosols to minimum of 3 mL at gas flow of 6–8 L/min<br>As effective as nebulized therapy if patient is able to coordinate |
| *Levalbuterol* (*R-albuterol*)<br>Nebulizer solution (0.63 mg/3 mL, 1.25 mg/3 mL)<br>HFA 45 μg/puff | 1.25–2.65 mg q 20 min for three doses, then 1.25–5 mg q 1–4 h as needed, or 5–7.5 mg/h continuously<br>See albuterol dose | 0.63 mg of levalbuterol is equivalent to 1.25 mg of racemic albuterol for both efficacy and side effects |
| Systemic (injected) β2-agonists | | |
| *Epinephrine*<br>1:1000 (1 mg/mL) | 0.3–0.5 mg q 20 min for three doses sq | No proven advantage of systemic therapy over aerosol |
| Terbutaline (1 mg/mL) | 0.25 mg q 20 min for three doses sq | No proven advantage of systemic therapy over aerosol |
| Anticholinergics | | |
| *Ipratropium bromide*<br>Nebulizer solution (0.25 mg/mL)<br>HFA (17 μg/puff) | 0.5 mg q 30 min for three doses, then every 2–4 h as needed<br>4–8 puffs as needed | May mix in same nebulizer with albuterol. Should not be used as first-line therapy; should be added to β2-agonists therapy |
| *Ipratropium with albuterol*<br>Nebulizer solution (each 3-mL vial contains 0.5 mg ipratropium bromide and 2.5 mg albuterol) | 3 mL q 30 min for three doses, then every 2–4 h as needed | Contains EDTA to prevent discoloration. This additive does not induce bronchospasms |
| *Ipratropium with albuterol*<br>MDI (each puff contains 18 μg ipratropium bromide and 90 μg albuterol) | 4–8 puffs as needed | |
| Systemic corticosteroids (dosages and comments apply to all three corticosteroids) | | |
| *Prednisone*<br>*Methylprednisolone*<br>*Prednisolone* | 10–80 mg/d in 1 or 2 Divided doses until PEF reaches 70% of predicted or personal best | For our outpatient "burst," use 40–60 mg in 1 or 2 divided doses for 5–10 days in adults |

Modified from the NAEPP Report. Child doses taken off table
*MDI* metered dose inhaler, *PEF* peak expiratory flow, *PRN* as needed

## Severe Persistent Asthma (Step 4)

For patients with severe persistent asthma, the treatment of choice is high-dose inhaled corticosteroid therapy, preferably budesonide (Pulmicort), and an inhaled long-acting B2-agonist (LABA), preferably salmeterol (Serevent). Inhaled short-acting B2-agonists (SABAs), preferably albuterol, should be added as needed. Alternative but less preferable treatment would be high-dose inhaled corticosteroids (ICS) with sustained-release theophylline or leukotriene receptor antagonists (LTRAs). If control cannot be achieved with these drugs, oral corticosteroids should be added, as needed, to maintain control (Tables 18.5, 18.6, 18.7, and 18.8).

Tiotropium may be an option for moderate and severe persistent asthma that is not well controlled during pregnancy on dose inhaled corticosteroids (ICS) and long-acting B2-agonists. However, there is currently no safety data on the use of tiotropium during pregnancy. Caution needs to be used, and the benefits versus the risks need to be weighed (Tables 18.5, 18.6, and 18.8).

### *Addition of Anti-IgE Therapy to Moderate and Severe Persistent Asthma (Step 5 or 6)*

For patients with moderate to severe asthma that is inadequately controlled on inhaled corticosteroids (ICS) and long-acting B2-agonists (LABAs), anti-IgE therapy is an option for add-on therapy. No human studies have been performed, but the Xolair Pregnancy Registry (EXPECT) has shown no differences in outcomes with omalizumab use during pregnancy. However, further studies are needed and caution is advised. Patients who may be candidates for anti-immunoglobulin E therapy should be referred to a specialist (Tables 18.5, 18.6, 18.7, and 18.8).

### *Addition of Oral Steroids to Severe Persistent Asthma (Step 5 or 6)*

For patients with severe persistent asthma that is inadequately controlled on inhaled corticosteroids (ICS) and long-acting B2-agonists (LABAs), low dose oral corticosteroids are an option for add-on therapy. Patients who may be candidates for oral corticosteroid therapy should be referred to a specialist (Tables 18.5, 18.6, 18.7, and 18.8).

## Assignment of Severity Step

All patients should be assigned to the highest step in which any single feature occurs. For example, nighttime symptoms twice a week will increase the severity assignment to moderate persistent asthma, even if all other symptoms and objective measures are in the mild persistent asthma category (Tables 18.5 and 18.8).

## Overuse of Albuterol

Patients need to be specifically asked about their use of albuterol or other inhaled short-acting bronchodilators (SABAs). Overuse of albuterol indicates inadequate asthma control and the need to increase the asthma severity assignment to a higher level. Pharmacy records, if available, can be invaluable in analyzing refill patterns and determining if patients are refilling their inhaled short-acting B2-agonists (SABAs) too frequently (Table 18.5).

The extent of albuterol overuse can be easily estimated by multiplying the number of canisters used by 200 (puffs per canister) and dividing the result by the number of days between refills. The use of one canister, every 2 months, indicates an average of more than 3 puffs of albuterol per day, suggesting suboptimal control that should be evaluated (Tables 18.5 and 18.8).

Patients often experience worsening of asthma symptoms during exercise. These patients may require albuterol use prior to exercise as well as during and after exercise. Ideally, patients with asthma that is well controlled won't require additional albuterol. A step-up in the asthma medication regimen may be required to allow for exercise without additional albuterol (Table 18.8).

## Gaining Control of Asthma

Most asthma specialists start a patient at a higher dose of medication to gain control quickly and even consider a short course of oral steroids if needed. Once control is gained, the dosage should be lowered to the minimal medication needed to maintain good control. Reassessment should occur frequently to determine if control can be maintained at a lower dose of medications (Table 18.8).

## Specialty Care

The NAEPP guidelines recommend that pregnant women with asthma be referred to an asthma specialist if there is difficulty controlling their asthma. The guidelines specifically advise that patients with severe persistent asthma or those requiring step 4 treatment be referred to an asthma clinic or a specialist. Patients with moderate persistent asthma or who require step 3 treatment should be considered for referral. If anti-IgE therapy is being considered, the patient should be referred for specialty care (Table 18.8).

### *Exacerbations*

During the course of their pregnancy, studies show that 20 % of asthma patients have exacerbations severe enough to seek urgent medical care. Approximately 6 % require hospital admissions. Severe exacerbations such as those requiring hospital

admission, urgent physician visits, or systemic corticosteroids are significantly more likely to occur with severe asthma.

Exacerbations are most common in the late second trimester to early third trimester. The most common reasons for exacerbation are viral infections and noncompliance with inhaled corticosteroid treatment. The importance of regular usage of inhaled corticosteroids (ICS) for persistent asthma cannot be overemphasized. Studies show that for patients using inhaled corticosteroids (ICS) before pregnancy, the rate of asthma-related physician visits decreased and the number of emergency department visits was unchanged after pregnancy.

## Management of Exacerbations

The management of the pregnant woman having an asthma exacerbation is set forth in Figs. 18.1 and 18.2. Treatment depends on the severity of the exacerbation with inhaled albuterol and oral steroids used as the primary treatment, particularly at home. For pregnant women with severe exacerbations in the emergency department, nebulized ipratropium can be added to albuterol. Table 18.9 lists the doses of medications for acute exacerbations.

## Mechanical Ventilation

Fortunately, it is rare for a pregnant woman to require intubation and mechanical ventilation. If needed, intubation should be oral instead of nasal due to airway narrowing. Preoxygenation with 100 % oxygen prior to intubation is important to avoid a precipitous drop in oxygen that may occur after even a short period of apnea. Studies show that it is important to maintain cricoid pressure before and after intubation to avoid aspiration and gastric insufflation. Patients should be ventilated with respiratory rates of 8–12 breaths per minute, tidal volumes of 6–8 mL/kg, and high inspiratory flow rates of 100–120 per minute. Hyperventilation should be avoided because a respiratory alkalosis may decrease uterine blood flow and impair oxygenation of the fetus. In addition, it is important to avoid volutrauma and barotrauma.

## Evidence-Based Medicine

Global Strategy for Asthma Management and Prevention 2015. Retrieved 11 Aug 2015. http://www.ginasthma.org/local/uploads/files/GINA_Report_2015_May19.pdf. Accessed 1/16

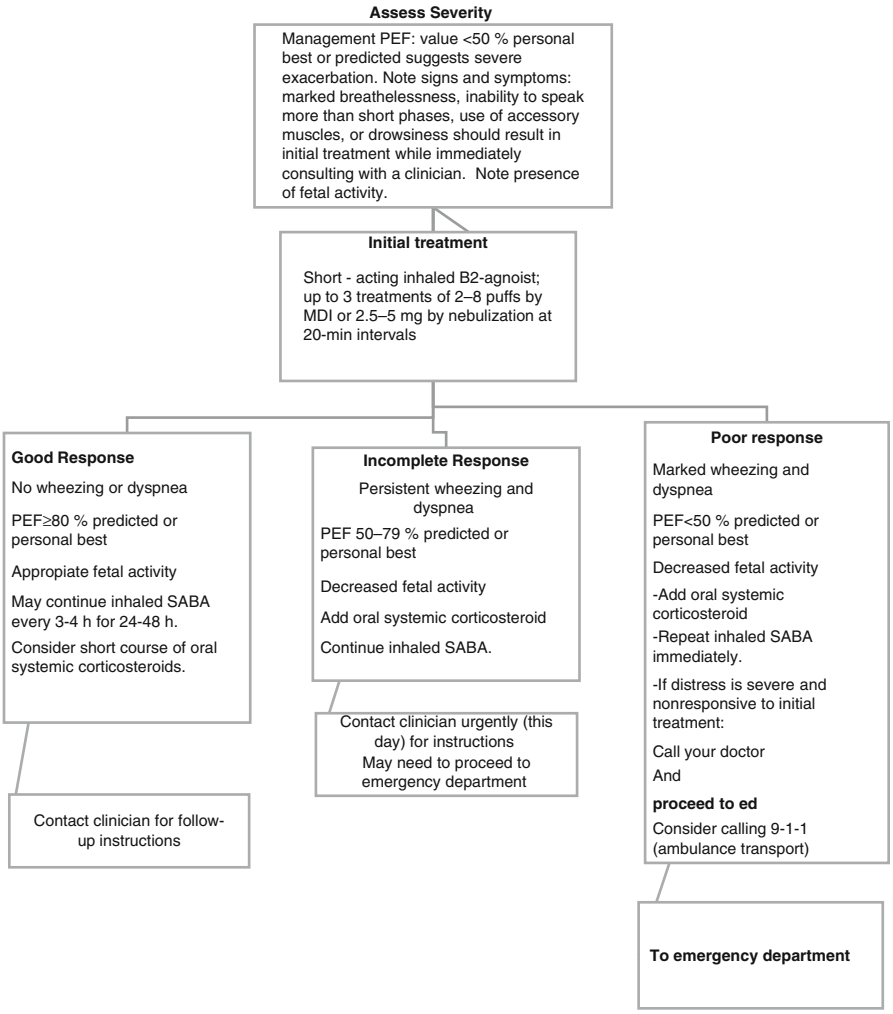


**Fig. 18.1** Management of asthma exacerbations: home treatment (Adapted from NAEPP Guidelines, 2007)

This is an updated guideline from the GINA Report 2015 and is a systemic evidenced review of asthma. This is a very thorough, well-presented guideline. There are several changes from the NAEPP 2007 Guidelines.

Blais L, Beauchesne MF, Lemière C, Elftouh N. High doses of inhaled corticosteroids during the first trimester of pregnancy and congenital malformation. *J Allergy Clin Immunol*. 2009;124(6):1229.

This is a very interesting study that looked at higher doses of inhaled steroids (>1000 mcg/day) during the first trimester and showed a 63 % increase in risk of all congenital malformations. This study had multiple issues including a small number

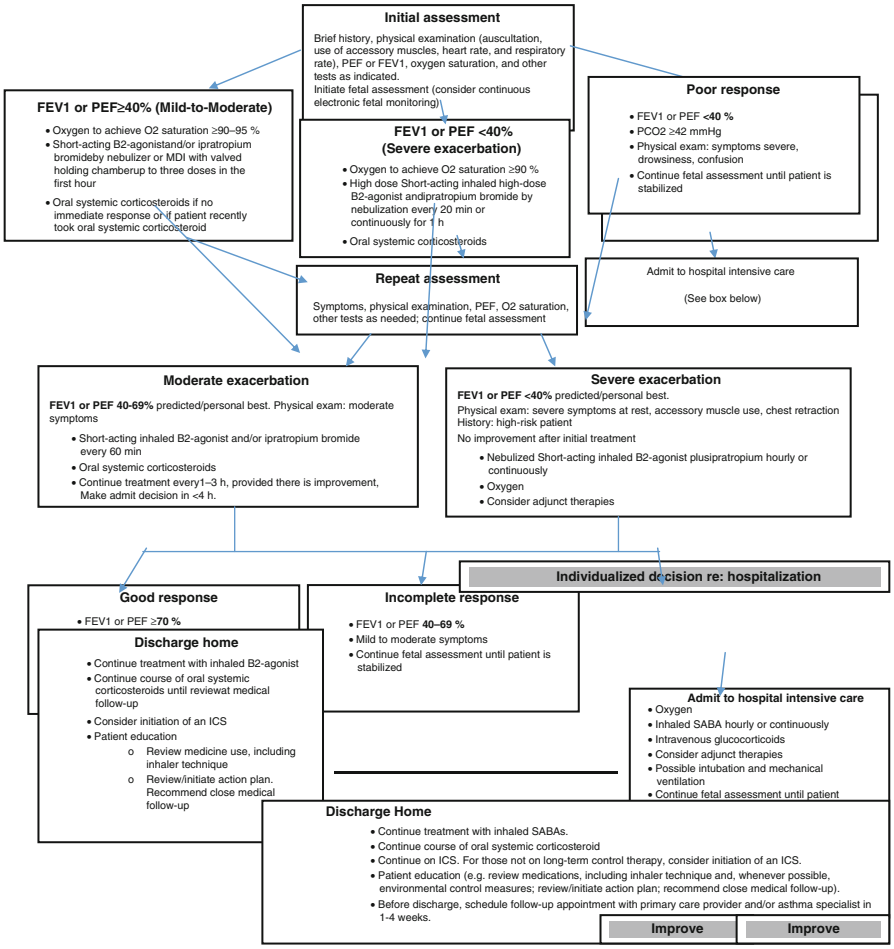


**Fig. 18.2** Management of asthma exacerbations: emergency department and hospital-based care (Modified from NAEPP Asthma Guidelines, 2007)

of patients with a daily dose over 1000 mcg, and it was difficult to determine whether the increased incidence of malformations was due to inadequately controlled asthma or due to high-dose inhaled steroids.

## Conclusion

Optimal asthma control during pregnancy is very important for both the mother and the fetus. To achieve this goal, thorough assessments and evaluations are critical, including monitoring with pulmonary function testing and peak flow meters. Avoidance and control of common triggers needs to be addressed with an emphasis on smoking cessation. Effective treatment must include asthma education and

reassurance that treatment is much safer for the fetus than maternal asthma exacerbations and symptoms. The obstetrical provider should be involved as part of the asthma care management team from the start of pregnancy.

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