1 Pulmonary disease in pregnancy

Lucia Larson[1], *Niharika Mehta*[2], *Michael J. Paglia*[1], *Ghada Bourjeily*[2] *with Warwick D. Ngan Kee*[3]

[1]Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women & Infants' Hospital of Rhode Island, Providence, RI, USA
[2]Department of Medicine, Warren Alpert Medical School of Brown University, Women & Infants' Hospital of Rhode Island, Providence, RI, USA
[3]Department of Anesthesia and Intensive Care, Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China

Introduction

The respiratory system undergoes a number of changes during pregnancy so that the gravid woman can meet the metabolic needs of both the mother and the fetus. The implications of these changes for the diagnosis and management of specific pulmonary diseases as well as for pregnancy will be considered in this chapter.

Physiologic adapations to pregnancy

Anatomic changes

Many anatomic changes occur in and around the respiratory system. In the upper airway, hyperemia and glandular hyperactivity are observed in pregnancy and are associated with edema and friability. These changes are likely the result of the expansion of plasma volume that starts early in pregnancy and progresses with increasing gestational age. Also contributing to this is the indirect effect of the elevated levels of estrogens. Consequently, up to 30% of pregnant women suffer from nasal congestion and epistaxis. This condition is known as gestational rhinitis and it usually resolves very quickly after delivery. Other consequences of mucosal edema of the upper airway include difficulties in airway management and failed endotracheal intubations as well as problems with the introduction of nasogastric tubes, necessitating liberal lubrication and extreme care. The higher propensity to snoring in pregnancy as compared to the nonpregnant population is also related to these changes.

Changes also occur in the chest wall. The lower ribcage widens, leading to an increase in the anteroposterior and transverse diameters of the chest, resulting in an overall increase of 5–7 cm in the chest wall circumference and a widening of the costal angle by about 50%. However, impaired chest wall compliance related to the enlarging uterus can occur late in pregnancy, causing decreased total lung compliance.

Physiologic measurements in pregnancy

Flow rates are relatively unchanged in pregnancy. Forced expiratory volume in 1 second (FEV_1), a helpful measurement in obstructive lung diseases, is not affected by pregnancy. In addition, peak expiratory flow rates are unchanged. Therefore, the interpretation and monitoring value of these tests in patients with asthma, for instance, are unchanged in pregnancy. The major effect of pregnancy on lung physiology occurs on volumes. There is an increase in tidal volume (TV) and a reduction in functional residual capacity (FRC) secondary to a decreased residual volume and expiratory reserve volume. FRC is further reduced in the supine position late in gestation. The inspiratory capacity is increased so that total lung capacity remains the same in the pregnant and nonpregnant state (Figure 1.1).

Ventilation

Minute ventilation, a product of tidal volume and respiratory rate, is increased by about 40% in pregnancy. This increase is achieved mainly by a proportional increase in tidal volume from 500 mL to 700 mL (about 40%). There is minimal change in the respiratory rate in pregnancy and any change should be interpreted as pathologic rather than physiologic.

This increase in ventilation leads to a reduction in $PaCO_2$ levels from 35–40 mmHg in the pre-pregnant state to an average of 30 mmHg during pregnancy. The drop in $PaCO_2$ is matched by an increased renal excretion of bicarbonate, leading to lower plasma bicarbonate levels. The end result is a plasma pH that is not significantly changed but there may be less buffering capacity in the face of an acidosis.

More profound changes occur in pregnancy at high altitude. Ventilation usually increases at high altitudes to compensate

de Swiet's Medical Disorders in Obstetric Practice, 5th edition. Edited by R. O. Powrie, M. F. Greene, W. Camann.

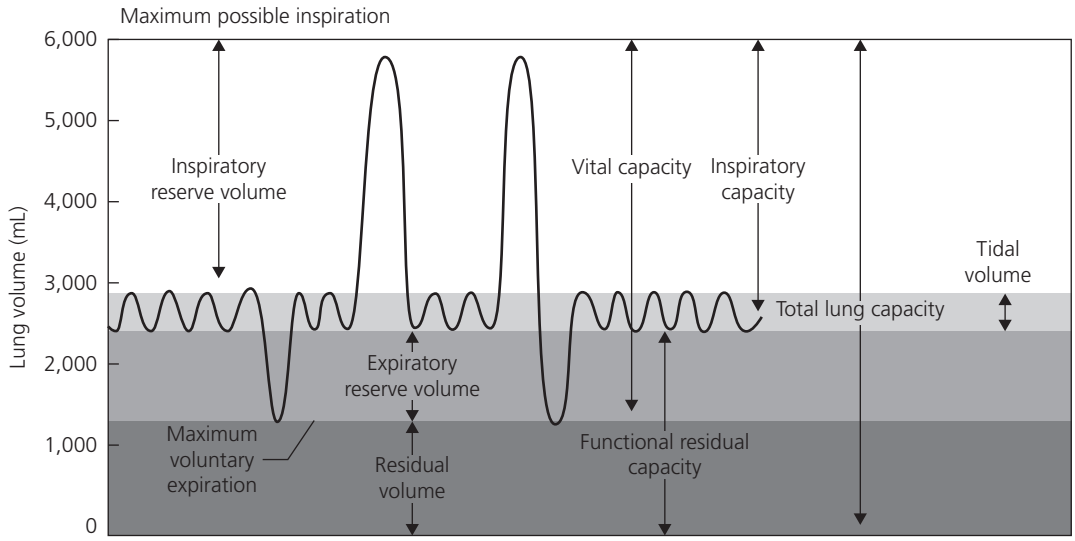


Figure 1.1 Lung volumes and capacities. Reproduced with permission of Anaesthesia UK Image Library.

for the drop in ambient oxygen. This response in pregnancy further accentuates the drop in $PaCO_2$ and levels of 24–28 mmHg have been reported at high altitude. Although residence at high altitude is associated with decreased maternal PaO_2, intrauterine growth restriction and pre-eclampsia, modern aircraft are pressurized to about 2500 m (8200 ft) and at these pressures Huch found no evidence of ill effects on mother or fetus in 10 pregnancies studied during commercial flights [1].

The increase in ventilation and associated fall in $PaCO_2$ occurring in pregnancy are probably due to progesterone, which may act via a number of mechanisms. Progesterone lowers the threshold and increases the sensitivity of the respiratory center to CO_2. It is also possible that progesterone acts as a primary stimulant to the respiratory center independently of any change in CO_2 sensitivity or threshold. Not only does progesterone stimulate ventilation, but it also increases the level of carbonic anhydrase B in the red blood cell. An increase in carbonic anhydrase will facilitate CO_2 transfer, and also tends to decrease $PaCO_2$ independently of any change in ventilation.

Oxygenation

Maternal PaO_2 increases in pregnancy to 100–105 mmHg at sea level. This increase is in part secondary to an increment in cardiac output leading to an improvement in ventilation/perfusion matching in the upper lobes. The alveolar–arterial gradient (the difference between PO_2 in the alveoli and that measured in the arterial blood) has been reported to increase slightly in the late stages of pregnancy from 15 to about 20. Position can also have an important effect on maternal arterial blood gases late in pregnancy. PaO_2 has been shown to decrease and the alveolo-arterial gradient to increase in the supine position in pregnancy. This has been attributed to a reduction in functional residual capacity and earlier airway closing during normal tidal breathing. Alterations in cardiac output between the sitting and the supine position may also contribute to that reduction in arterial oxygen tension. Therefore, arterial blood gases are ideally obtained while pregnant women are in the sitting position.

Oxygen consumption is increased in pregnancy by about 20% and increases further during labor and delivery. About one-third of the increased oxygen consumption is necessary for the metabolism of the fetus and placenta. The remainder is supplied for the extra metabolism of the mother, in particular the extra work of increased secretion and reabsorption by the kidney.

Breathlessness in pregnancy

Approximately 50% of normal pregnant women will note dyspnea before 19 weeks gestation and 76% by 31 weeks [2]. Reasons for experiencing the sensation during normal pregnancy may be related to the effect of progesterone on the respiratory center, mechanical changes associated with weight gain or decreased venous return, and/or the demands of the fetus. Women often describe their symptoms as "needing to take a deep breath." Since these women are otherwise normal, there should be no suggestion of cardiopulmonary disease on history or physical exam such as sudden onset of symptoms, cough, chest pain or wheezing and patients should be able to perform activities of daily living. Likewise, physical exam is normal and oxygen saturation is normal at rest and with exertion. The presence of an anemia should be sought as this is common in pregnancy. If there is no underlying disease as a cause of dyspnea, the patient can be reassured that there is no increased risk for complications during pregnancy or labor and delivery.

Specific conditions

The remainder of this chapter discusses the most common and the most serious respiratory problems that may complicate a pregnancy. Although each requires specific management, a general approach to the care of the pulmonary patient can be found at the end of this chapter in Table 1.12.

Asthma

Asthma is characterized by heightened airway responsiveness to triggers and reversible airway obstruction. According to the National Asthma Education and Prevention Program, it is defined as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. . ." In susceptible individuals, this inflammation causes recurrent coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment [3].

Epidemiology

Asthma affects 3.7–8.4% of all pregnancies and is one of the most common serious medical complications encountered in pregnancy in the United States [4]. Other estimates from both the United Kingdom and Australia show rates close to 12–13% in pregnancy [5]. It is estimated that 10% of the population has airway hyper-responsiveness. The prevalence of asthma has significantly increased since the 1980s and cannot be solely explained by an increased awareness of the disease since the rate of death from asthma has also increased. Asthma has become the leading cause of hospitalization of children under 15 and is emerging as the most common chronic and potentially life-threatening disease of childhood, affecting one in seven children in Great Britain. Pregnant women and their children are also more likely to experience asthma than any other chronic disease.

Physiology

Asthma is a chronic inflammatory disease characterized by a reversible airway obstruction and airway hyper-reactivity. Reversible airway obstruction is defined as an obstruction on spirometry which is documented during acute attacks with normal physiology between attacks. Reversibility may also be documented by complete resolution of obstruction following the administration of a short-acting bronchodilator. Airway hyper-responsiveness, an exaggerated bronchospastic response to nonspecific agents such as methacholine and histamine or specific antigens, is the physiologic cornerstone of this disorder. Multiple factors lead to narrowing of the airway, resulting in reduced air flow, such as smooth muscle contraction, thickening of the airway wall and the presence of secretions within the airway lumen.

Pathophysiology

The predominant causes of airway obstruction in asthma include airway inflammation, cellular infiltration, and subsequent cytokine production.

Airway inflammation has many components involving cellular infiltration with Th2 lymphocytes as well as eosinophils, the former playing an important role in initiating and perpetuating inflammation through cytokine release as well as by affecting IgE production. When Th2 lymphocytes are stimulated by the appropriate antigens, they release interleukins (IL) such as IL-3, IL-4 and IL-5 as well as granulocyte macrophage-colony stimulating factor (GM-CSF). Airway cells such as smooth muscle cells and secretory cells undergo hypertrophic and hyperplastic changes whereas mast cells become sensitized with IgE and secrete tumor necrosis factor alpha (TNF-alpha), a pleiotropic inflammatory cytokine that plays a role in airway hyper-responsivess. Remodeling of the airway structure occurs as a result of collagen deposition in the basement membrane and thickening of the subepithelial connective tissue.

Clinical manifestations

Typically, patients with asthma present with periodic symptoms of shortness of breath, wheezing or chest tightness that occur in response to various stimuli. Common stimuli include exercise, cold temperatures, allergens or irritants. Common allergens could be indoor or outdoor allergens and include grass, pollen, pet dander, cockroaches, mice, dust mites and mold. A careful history should be taken regarding possible triggers and the history needs to include questioning about the home, work or even school environment.

During attacks, patients usually have expiratory wheezing which typically resolves once the symptoms improve. Depending on the severity of the attack, patients may use their accessory respiratory muscles (the parasternal, scalene, sternocleidomastoid, trapezius, and pectoralis muscles that do not normally contract with respiration) and even have paradoxic breathing (normally the abdomen should expand with inspiration but in paradoxic breathing, the abdomen may retract with inspiration, indicating marked respiratory muscle fatigue). In severe attacks leading to hyperinflation, there may be some compromise to the venous return and subsequent hypotension.

Diagnosis

The diagnosis of asthma is usually suggested by the history of episodic symptoms that follow specific triggers. The physical exam is suggestive during attacks but not when the attacks have resolved. The diagnosis is usually established by the

documentation of a reversible obstruction on spirometry. Obstruction is defined on spirometry by a reduced FEV_1 forced vital capacity (FVC) (normally the ratio of FEV_1 to FVC should be about 75%, meaning that 75% of the total volume of a breath can be exhaled within 1 second) with variable degrees of FEV_1 reduction. Normalization of FEV_1 following administration of bronchodilators determines reversibility.

Spirometry is often normal in patients with asthma outside an acute attack. Establishing a diagnosis may be difficult in that case and an airway challenge may be performed to trigger an obstructive physiology. The most commonly used challenge in making the diagnosis of asthma is performed with methacholine chloride but other challenges can be used such as cold air and allergen challenges. Methacholine is a quaternary ammonium compound and likely does not cross the placenta. There are no human studies looking at the safety of methacholine in pregnancy. Advantages obtained from testing during the pregnancy should be weighed against the potential risks.

Effect of pregnancy on asthma

The course of asthma is usually unpredictable in pregnancy and numerous studies have suggested that one-third of patients improve, one-third remain the same and the last third worsen [6]. Factors contributing to improvement may be the pregnancy-associated rise in serum cortisol, an anti-inflammatory hormone, or the increase in progesterone which acts as a potent smooth muscle relaxant. However, more is known in terms of factors that predispose to worsening of asthma during pregnancy. There is clear evidence linking upper airway and nasal symptoms and asthma control. The course of asthma seems to parallel that of gestational rhinitis and those patients who have an improvement in their symptoms of rhinitis during pregnancy also have improvements in their asthma symptoms [7]. These findings suggest that the same systemic factors may be affecting both upper and lower airways. In addition, the rate of bacterial sinusitis is 5–6 times higher in pregnant women and may contribute to worsening of asthma symptoms. Gastroesophageal reflux disease (GERD), common in pregnancy, may also play a role in worsening asthma control during pregnancy both through reflux of gastric acid into the airway and through a reflex bronchoconstriction that can occur following acidification of the lower esophagus.

How hormonal factors related to pregnancy affect asthma control is not as well understood. There are many studies of premenstrual asthma that suggest changes in beta-agonist receptor density in the airways that occur during the menstrual cycle. Declines in FEV_1 have been shown to occur in the luteal phase in women with premenstrual exacerbations of their symptoms. Emergency room visits were more frequent in the premenstrual period than in the pre-, peri- or postovulatory periods of the menstrual cycle but these findings were not consistent in other studies that showed more visits in the preovulatory phase of the cycle. Unfortunately, however, this information does not translate directly into pregnancy and the presence of premenstrual asthma does not necessarily suggest that asthma will worsen during pregnancy.

Epidemiologic studies done in both the US and Finland suggest that asthma exacerbations are most common between gestation weeks 17–24 [8] and symptoms worsen mostly between 29 and 32 weeks [9]. There is usually an improvement in symptoms after 36 weeks. It is possible that this improvement late in the pregnancy is related to cortisol levels at term reaching four times pre-pregnancy levels.

Of those patients who have worsening of their asthma during pregnancy, close to 60% improve in the postpartum period, whereas worsening was seen in 87% of women whose asthma had improved during pregnancy [10]. When women were followed during successive pregnancies, only 60% followed the same course in the second pregnancy as in the first. Thus, it is difficult to predict with certainty the course asthma will take in an individual pregnancy.

Effect of asthma on pregnancy

Case–control studies have shown that well-controlled pregnant asthmatics do not have a significantly higher rate of adverse outcomes than women without asthma [11,12]. Pregnancy outcomes are not as favorable in women with severe or poorly controlled disease. Of 37,000 women with asthma and 2495 exacerbations, those with exacerbations were more likely to have miscarriage or therapeutic abortions than those without [13]. Suboptimal control appears to be associated with low birthweight, intrauterine growth restriction, and cesarean section. Other adverse pregnancy outcomes thought to be associated with asthma include preterm delivery and maternal hypertension but these risks have not been shown consistently and systemic steroid use may have a confounding effect.

Pre-eclampsia has also been associated with severe asthma in some studies, but it is unclear whether it is the underlying disease or the concomitant use of systemic steroids and comorbidities that is the culprit [14].

The manner by which poorly controlled asthma affects obstetric outcomes remains unclear. While maternal hypoxia is often offered as an explanation, the majority of pregnant women with even poorly controlled asthma are unlikely to have chronic hypoxia to the degree that would explain these obstetric outcomes. A relationship between obstetric outcomes and chronic inflammatory mediators associated with poorly controlled asthma is therefore speculated although it remains unproven.

Classification of asthma severity

The National Asthma Expert Panel Report (EPR 3) [15] classifies asthma into severity according to two domains – impairment and risk. The term "mild intermittent" has been eliminated and the classification now falls into the following

four categories: intermittent, mild persistent, moderate persistent, and severe persistent. Patients within each category can be classified as well controlled, not well controlled or poorly controlled (Tables 1.1 and 1.2). These same categories should be used in evaluating pregnant women with asthma and are useful in directing appropriate management with step therapy.

The advantage of the new guidelines compared to the previous guidelines is the fact that risk is now an important feature of the disease severity classification. Need for emergency room visits, frequency of exacerbations and steroid tapers are now taken into account when assessing disease severity. Furthermore, the more recent guidelines reinforce the need to monitor quality of life by using validated measures and emphasize the need for objective measurements with spirometry as part of the initial evaluation and follow-up care.

Management

The first step in management is establishing the diagnosis of asthma. Many patients are misdiagnosed with asthma for many years before they are correctly diagnosed with asthma mimics such as chronic obstructive lung disease, sinus disease or vocal cord dysfunction. Review of medical records and

Table 1.1 Severity assessment and initial treatment

Assessing severity and initiating treatment for patients who are not currently taking long-term control medications

Components of Severity		**Classification of Asthma Severity ≥12 years of age**			
			Persistent		
		Intermittent	**Mild**	**Moderate**	**Severe**
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
	Interference with normal activity	None	Minor lmitation	Some limitation	Extremely limited
Normal FEV_1/FVC: **8–19 y 85%** **20–39 y 80%** **40–59 y 75%** **60–80 y 70%**	Lung function	• Normal FEV_1 between exacerbations • $FEV_1 > 80\%$ predicted • FEV_1/FVC normal	• $FEV_1 > 80\%$ predicted • FEV_1/FVC normal	• $FEV_1 > 60\%$ but 80% predicted • FEV_1/FVC reduced > 5%	• $FEV_1 < 60\%$ predicted • FEV_1/FVC reduced > 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note)		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Treatment (See "Stepwise Approach for Managing Asthma" for treatment steps.)		**Step 1**	**Step 2**	**Step 3** and consider short course of oral systemic corticosteroids	**Step 4 or 5**
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

***Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decision-making to meet individual patient needs.
- Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2–4 wk and spirometry. Assign severity to the most severe category in which any feature occurs.
- Currently there are inadequate date to correspond frequencies of exacerbations with deferent levels of asthma severity. In general, more frequent and intense exacerbations (eg. requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

EIB, exercise-induced bronchospasm; FEV, forced expiratory volume; FVC, forced vital capacity; ICU, intensive care unit.

Reproduced with permission from the National Asthma Education and Prevention Program [15].

Table 1.2 Control classification

Components of Control		Classification of Asthma Control (≥12 years of age)		
		Well Controlled	**Not Well Controlled**	**Very Poorly Controlled**
Impairment	Symptoms	≤2 days/week	>2 days/week	Throughout the day
	Nighttime awakenings	≤2x/month	1–3x/week	≥4x/week
	Interference with normal activity	None	Some lmitation	Extremely limited
	Short-acting β_2-agonist use for symptom control (not prevention of EIB)	≤2 days/week	> 2 days/week	Several times per day
	FEV_1 or peak flow	>80% predicted/ personal best	60–80% predicted/ personal best	<60% predicted/ personal best
	Validated questionnaires	0	1–2	3–4
	ATAQ	≤0.75*	≥1.5	N/A
	ACQ	≥20	16–19	≤15
	ACT			
	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥2/year (see notes)	
		Consider severity and interval since last exacerbation		
Risk	Progressive loss of lung function	Evaluation requires long-term follow-up care.		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment (See "Stepwise Approach for Managing Asthma" for treatment steps.)		• Maintain current step. • Regular follow-up at every 1–6 months to maintain control. • Consider step down if well controlled for at least 3 months.	• Step up 1 step. • Re-evaluate in 2–6 weeks. • For side effects, consider alternative treatment options.	• Consider short course of oral systemic corticosteroids. • Step up 1–2 steps. • Re-evaluate in 2 weeks. • For side effects, consider alternative treatment options.

*ACQ values of 0.76–1.4 are indeterminate regarding well controlled asthma.

†**Notes:**

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2–4 wk and by spirometry/or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.
- Currently there are inadequate date to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (eg. requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well controlled asthma, even in the absence of impairment levels consistent with not-well controlled asthma.
- Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain).
- Minimal important difference: 1.0 for the ATAQ: 0.5 for the ACQ; not determined for the ACT.
- **Before step up in therapy:**
  - — Review adherence to medication, inhaler technique, environmental control, and comorbid conditions.
  - — If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step.

ACQ, asthma control questionaire; ACT, asthma control test; ATAQ, asthma therapy assessment questionaire; ICU, intensive care unit.
Reproduced with permission from the National Asthma Education and Prevention Program [15].

ensuring that the diagnosis is accurate and the history is suggestive are crucial steps.

Another important step is the identification of triggers. Once those have been recognized, every effort should be made to avoid exposure to known triggers. Frequent vacuuming of carpeted areas, avoiding contact with stuffed toys, and using a mattress cover to avoid exposure to dust mites should be encouraged.

According to the US national health interview survey in 2005, 21% of women of childbearing age in the US smoke. Many of those patients are likely to be asthmatic and it is paramount to address smoking habits with every patient. All smokers should be encouraged to quit especially since smoking is the most modifiable risk factor for adverse pregnancy outcomes. Counseling regarding the ill effects of smoking on asthma and fetal health

should be done periodically. Strong statements such as: "As your clinician, I need you to know that quitting smoking is the most important thing you can do to protect your baby and your own health" help send a clear message to the pregnant smoker (see section on smoking cessation below).

In addition, pregnant asthmatic patients should be asked about sulfite (additives to prepared foods that preserve freshness) and aspirin sensitivity, rhinitis and sinusitis, GERD, exercise- or cold-induced asthma, and nocturnal asthma. Many pregnant women have GERD so that counseling about lifestyle modifications, including elevating the head of the bed, eating smaller meals, and eating earlier in the evening, can be helpful. Identification and treatment of sinus disease or nasal congestion secondary to allergic rhinitis or gestational rhinitis may also help control symptoms.

Compliance and proper use of medications is another major issue in patients with asthma as poor asthma control results in many cases from inadequate use of the drugs. Pregnancy poses an additional challenge since patients may not be compliant with their medications because of fear of fetal harm. This fear may be propagated by family members, friends, or even other healthcare providers who are less familiar with treating pregnant women. Counseling regarding the safety of the drugs should be done with all asthma patients and it is important to clarify that the benefits of asthma control far outweigh the risks of medications. Reviewing inhaler techniques with all patients should be done not only on their first visit but also periodically on follow-up visits. It should never be assumed that patients who have had asthma for many years know how to properly use their drugs. In our experience, many of those patients use their inhalers incorrectly (Box 1.1).

The National Asthma Education and Prevention Program (NAEPP) has placed substantial emphasis on patient education to help with disease monitoring. In essence, asthma patients need to be educated about their disease, the triggers, ways to avoid them, identifying signs of an attack, monitoring of peak flows and understanding the implications of different stages of obstruction suggested by peak flow meters. In our practice, a written asthma management plan is provided to every patient with asthma after proper education.

Drugs

General principles regarding drug prescription in pregnancy include:

- finding out whether the condition is self-limited and how necessary the medications are;
- evaluating the possible outcomes to the mother and fetus of the untreated condition
- assessing safety data of the drug to be administered and whether other drugs with a better safety profile and similar efficacy could be used instead
- understanding how the patient's value system and cultural beliefs affect decision making with regard to taking medications during pregnancy.

Box 1.1 Instructions for proper inhaler use

- Inhalers come as metered dose inhalers (MDI), MDI with a spacer, and dry powder inhalers. The latter two have the advantage that hand–breath co-ordination is not critical. The disadvantage of dry powder inhalers, which is not a problem with MDI, is that they do require patients to be able to take a deep, fast breath to get the medication and that an accidental exhalation will blow medication away.
- To use an MDI (e.g. albuterol or salbutamol), shake the inhaler 5–6 times. Remove the mouthpiece cover and place the spacer over the mouthpiece if a spacer is being used. If you are using a spacer, place the lips and teeth over the spacer. If a spacer is not being used, hold the inhaler mouthpiece just outside your open mouth. Breathe in slowly while giving a single squeeze to the top of the canister. Continue to inhale slowly and deeply even after the squeeze has been completed. When you have completely inhaled, hold the breath for 10 seconds. Repeat this procedure in a minute to administer a second "puff."
- To use a dry powder inhaler (e.g. Pulmicort®), there is no need shake the inhaler. Twist the cover off. "Load" the medication by twisting the base grip to the right as far as it will go and then twist it back to the left. A click should be heard, meaning the medication is loaded. Place the inhaler between your lips in a horizontal position and take a fast, deep breath through your mouth and not your nose, continuing to inhale deeply. Repeat this procedure in a minute to administer a second "puff."
- To use a dry powder disk inhaler (e.g. Advair®), there is no need to shake the inhaler. Hold the disk level in one hand. With the other hand, put the thumb in the appropriate notch and push it away from you as far as it will go to expose the mouthpiece and the lever for "loading" the medication. Move the lever as far as it will go. A click should be heard, meaning the medication is loaded. Place the mouthpiece between your lips and take a fast, deep breath through your mouth (not your nose) and continue to inhale deeply. Repeat this procedure to administer a second "puff."

In a patient with asthma, the answer to the first two questions is clear: the attacks should not be assumed to be self-limited and the disease can be life threatening. Therefore the need for therapy is obvious. Below, we will review safety data regarding all the medications used in asthma. Individual counseling should be undertaken in patients with different beliefs and cultural influences to explain the need for therapy and the downside of withholding therapy. The NAEPP published guidelines on pharmacologic management of pregnant patients with asthma in 2004 after reviewing data on fetal safety of the drugs [16].

Short-acting beta-agonists

Short-acting beta-agonists, also called rescue inhalers, are the most potent and rapidly acting bronchodilators currently available for clinical use. Beta-agonists interact with beta-receptors on the surface of a variety of cells implicated in asthma pathogenesis. Among other things, beta-agonists have the potential to relax bronchial smooth muscle and affect vascular tone and edema formation. These drugs have not been shown to affect the maternal circulation even at high doses and are thought to be safe to use in pregnancy.

Long-acting beta-agonists

Formoterol and salmeterol are available in the US. Their safety profile and toxicologic data are similar to those of short-acting beta-agonists. Animal data were suggestive of possible teratogenic effect in one animal species, later labeled as "sensitive rabbits," when salmeterol was used intravenously at very high doses. However, inhaled use of the drug results in minimal absorption. Further animal studies have not shown such effects even at doses 1600 times higher than the human dose. The use of long-acting beta-agonists is certainly justifiable in pregnancy in patients who are poorly controlled on inhaled corticosteroids alone.

Anticholinergics

Anticholinergic drugs such as ipratropium bromide lead to parasympathetic blockade and further accentuate the bronchodilating effect of beta-agonists. Anticholinergic drugs can be of use in acute exacerbations in the emergency room or hospital (and are often given in combination with beta-agonists in this setting) but have not been shown to have any benefit in long-term therapy of asthma. Although the published data about the safety of these agents in pregnancy are scarce, the systemic absorption is minimal and their use for exacerbations leading to hospital visits is readily justifiable.

Inhaled corticosteroids

Inhaled corticosteroids (ICS) should be the first alternative in patients with poorly controlled symptoms on beta-agonists. Corticosteroids have been shown to inhibit multiple cell types such as mast cells, eosinophils and basophils as well as mediator production and secretion (e.g. histamine and cytokines) involved in asthma pathogenesis. Beclomethasone and budesonide are the most studied inhaled corticosteroids in pregnancy and are thought to be safe for use. However, patients who have been well controlled on a different inhaled steroid prior to conception may be maintained on their drugs since the goal in asthma therapy is optimal control and especially since ICS should be the first-line controller medication.

Leukotriene inhibitors

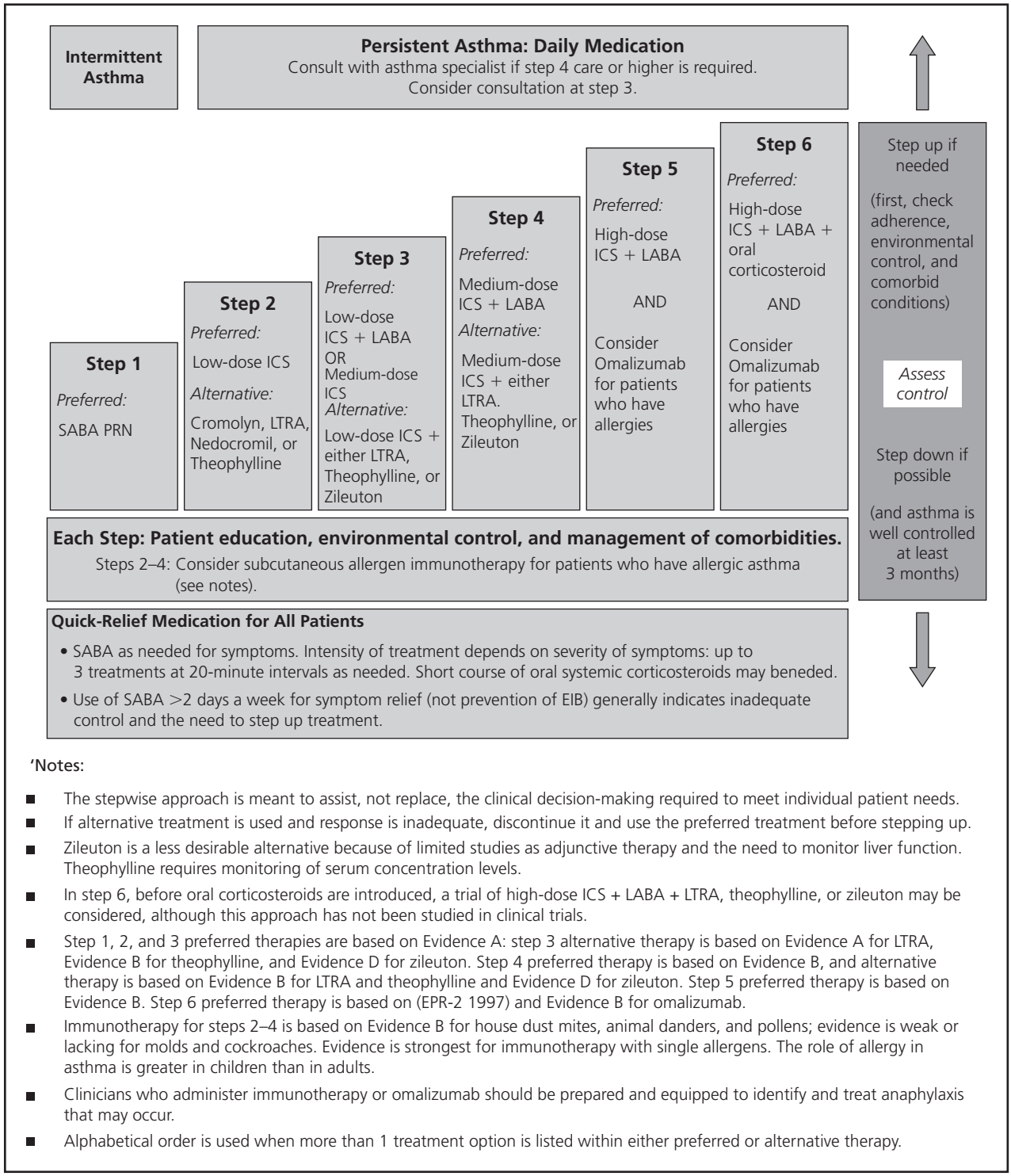
Leukotrienes are substances that induce numerous biologic activities including augmentation of neutrophil and eosinophil migration, neutrophil and monocyte aggregation as well as increasing capillary permeability and smooth muscle contraction. All these effects contribute to the inflammation, edema, bronchoconstriction, and mucus secretion seen in asthma. Leukotriene inhibitors block the physiologic effects of leukotrienes.

Animal data regarding these drugs suggest that they are likely to be safe for use in pregnancy; however, human data are lacking. Therefore, the risks and benefits need to be balanced in an individual patient. For instance, those patients who required a leukotriene inhibitor in addition to their steroid inhaler and long-acting beta-agonist for optimal symptom control would need to remain on all their drugs during the pregnancy, including leukotriene inhibitors. Patients who are on a leukotriene inhibitor without adequate inhaled steroids may be switched to steroids since more data regarding those are available in pregnancy.

Other drugs

In the most recent report from the National Institutes of Health (NIH) on asthma management in pregnancy, the NAEPP guidelines [16] suggest using low-dose inhaled corticosteroids as a preferred agent in patients with mild persistent asthma, with accepted alternatives listed alphabetically: cromolyn, leukotriene receptor antagonists or theophylline (Figure 1.2). In our experience and in many studies, use of inhaled steroids is certainly superior to the use of any of these agents in the general population. In addition, a study comparing a low-potency steroid (beclomethasone) with theophylline in pregnancy has shown comparable benefit but the steroids were much better tolerated [17]. We believe that inhaled steroids should certainly be used first especially because a superior benefit may be expected from higher potency inhaled steroids compared to beclomethasone, making them a better choice than theophylline.

Other studies have suggested that the use of systemic steroids in pregnant asthmatics increases the risk of orofacial clefts (a 2–7-fold increase in risk to 2–14 per 1000 births with use in the first trimester), pre-eclampsia, premature rupture of the membranes and the delivery of both preterm



'Notes:

- The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
- If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
- Zileuton is a less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
- In step 6, before oral corticosteroids are introduced, a trial of high-dose ICS + LABA + LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
- Step 1, 2, and 3 preferred therapies are based on Evidence A: step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR-2 1997) and Evidence B for omalizumab.
- Immunotherapy for steps 2–4 is based on Evidence B for house dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
- Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
- Alphabetical order is used when more than 1 treatment option is listed within either preferred or alternative therapy.

Figure 1.2 Step therapy for asthma. Reproduced with permission from the National Asthma Education and Prevention Program [15]. EIB, exercise induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LTRA, leukotriene receptor antagonist; PRN, as needed; SABA, short-acting beta agonist.

and low birthweight children [14], despite the fact that 87% of prednisone is metabolized by the placenta before it reaches the fetus. Systemic steroids may also contribute to the development of gestational diabetes. However, if indicated, the benefit of systemic steroids to treat inadequately controlled asthma certainly outweighs these risks.

The monoclonal antibody omalizumab blocks the binding of IgE to the IgE receptors and is now being used in moderate to severe asthmatics who are not well controlled on the usual regimen and have significant allergic triggers to their disease. Animal data do not seem to show significant teratogenicity but there have been no safety data in human studies since the initial trials have excluded pregnant patients. Postmarketing data are also limited given that the drug was only recently introduced to the market. For those reasons, the use of omalizumab cannot yet be recommended in pregnancy.

Cimetidine, ranitidine, and metoclopramide can all be used safely in pregnant women with GERD who need pharmacologic treatment. Rhinitis in the pregnant woman can be treated with nasal ipratropium and inhaled nasal steroids. See Table 1.3 for an overview of the drugs used to treat asthma in pregnancy. It is also recommended that all pregnant women receive immunization for influenza regardless of gestation and this is particularly important in asthmatics (see influenza section below).

Management of acute exacerbations

Patients presenting with an acute exacerbation should be assessed promptly. Those with a clear history of asthma and an exam suggesting an acute exacerbation should receive bronchodilators without delay. Peak flow measurements help determine the severity of the attack, guide therapy, and monitor for a response to interventions (Box 1.2). On physical exam, patients should be assessed for the use of accessory muscles since this suggests a severe exacerbation. Arterial blood gases should be obtained if patients are not improving with initial treatment or if a severe exacerbation is suspected. It is important to recognize that normal $PaCO_2$ in pregnancy is 30–35 mmHg. Therefore, a tachypneic patient with a $PaCO_2$ above that range should prompt the suspicion of impending respiratory failure.

The NAEPP guidelines published in 2004 have clear advice on the management of acute exacerbations of asthma in pregnancy and are shown in Figure 1.3. It should be noted that this is essentially unchanged from treatment in nonpregnant patients.

Fetal surveillance during pregnancy

The primary affect on the fetus from asthma, or any other pulmonary disease, is chronic hypoxia. The impact of hypoxia can manifest in several ways, including growth restriction or, more significantly, fetal death. Shortly after a woman with asthma becomes pregnant, she should have an early ultrasound to confirm her pregnancy dating. Women should be instructed to monitor fetal activity during the course of the pregnancy. A third-trimester ultrasound can be considered in a woman with well-controlled asthma who has appropriate growth in the fundal height. The NAEPP Working Group recommends serial ultrasounds starting at 32 weeks gestation in women with suboptimally controlled asthma and women with moderate-to-severe asthma [16]. If the growth is not appropriate or the woman has an acute exacerbation, fetal testing should be started. Testing may include umbilical artery Doppler flow velocity studies, nonstress testing (NST) or biophysical profiles (BPP). The frequency of such testing would depend on the severity of the patient's asthma or the degree of growth restriction.

Labor and delivery

Asthma exacerbations are rare in labor and delivery. This is thought to be related to the increase in serum cortisol that occurs during that period. Despite that, it is advisable to administer stress doses of steroids to patients who have been on prolonged systemic steroids during the pregnancy (see Chapter 47). Asthma medications should not be discontinued through labor and delivery.

Prostaglandin E2 is safe for cervical ripening, as is oxytocin. The agent 15-methyl prostaglandin F2-alpha should be avoided because it may cause severe bronchospasm. Although methylergonovine may cause dyspnea, asthma is not an absolute contraindication, and therefore it can be used when appropriate in the management of postpartum hemorrhage. Fentanyl is preferred to morphine and meperidine, which can release histamine. Epidural anesthesia is usually advised because it decreases oxygen consumption and minute ventilation. Epidural anesthesia also decreases the possibility of requiring general anesthesia if an emergency cesarean becomes indicated during labor. However, if cesarean delivery is required, a high level of sensory block may produce some degree of patient anxiety in the intraoperative period.

Several published articles in recent years have suggested that the increase in cesarean delivery rates over past years may be linked to the increasing incdence in asthma in the general population [18,19]. The "hygiene hypothesis" is put forward as a possible explanation as the establishment of GI flora in neonates born by cesarean section is delayed and this could have implications for the development of the neonatal immune system which ultimately leads to atopy and asthma. However, the existence of a relationship between asthma and mode of delivery requires further exploration in prospective studies that are controlled for confounding variables at the time of this writing.

Postpartum period

During the postpartum period, women should initially continue the same asthma medications they required during pregnancy. Close peak flow monitoring is indicated, particularly in those with poorly controlled or moderate-to-severe asthma.

Table 1.3 Drugs for treating common pulmonary conditions in pregnancy

Indication for treatment	Pregnancy			Breastfeeding		
	Use justifiable when indicated	Use may be justifiable in rare circumstances	Use almost never justifiable	Use acceptable in breastfeeding	Can be used safely in breastfeeding but may be second choice to column left	Should not be used with breastfeeding
Asthma						
Beta-agonists	–	–	–	–	–	
albuterol$_C$ (*ventolin™, Proventil™*)	Yes	–	–	Yes	–	–
formeterol $_C$ (*Foradil ™*)	Yes	–	–	–	Yes	–
flunisolide $_C$ (*Aerobid ™*)	–	–	–	–	Yes	–
fluticasone $_C$ (*Flovent™ *)	–	–	–	–	Yes	–
metaproterenol$_c$ (*Alupent™*)	Yes	–	–	Yes	–	–
montelukast $_B$ *singulair™*	–	Yes	–	–	Yes	–
omalizumab $_B$ (*Xolair™*)	–	Yes	–	–	–	–
pirbuterol $_c$ (*Maxair™)*	Yes		–	Yes	–	–
salmeterol$_c$ (*Serevent™)*	Yes		–	Yes		–
terbutaline$_c$ (*Brethaire™*)	Yes	–	–	Yes	–	–
theophylline $_C$					Yes	
triamcinolone $_C$ (*Azmacort™*)			–		Yes	–
zafirlukast$_B$ (*accolate™*)	–	Yes	–	–	Yes	–
zileuton $_B$ (*zyflo™*)	–	–	Yes	–	–	–
Inhaled steroids						
beclomethasone $_C$ (*Beclovent™ Vanceril™*)	Yes	–	–	Yes	–	–
flunisolide $_C$ (*Aerobid ™*)	Yes	–	–	–	–	–
fluticasone $_C$ (*Flovent™*)	Yes	–	–	–	–	–
triamcinolone $_C$ (*Azmacort™*)	Yes	–	–	–	–	–
budesonide $_B$ (*Pulmicort*)	Yes			Yes		
Other	*Other*					
systemic steroids $_C$	Yes			Yes		
ipatropium $_B$ (*Atrovent™*)	Yes			Yes		
cromolyn $_B$ (*Intal™*)	Yes			Yes		
theophylline $_C$	Yes					
minophylline	Yes					
Nasal congestion						
pseudoephedrine$_C$ (*Sudafed™*)	Yes	–	–	–	Yes (*if used short term*)	Yes (*if used long term*)
nasal steroids (*Beconase™$_C$, Rhinocort™$_C$, Flonase™$_C$, Nasacort™$_C$*)	nasal steroids (*Beconase™$_C$, Rhinocort™$_C$, Flonase™$_C$, Nasacort™$_C$*)	–	–	nasal steroids (*Beconase™$_C$, Rhinocort™$_C$, Flonase™$_C$*)	–	–
oxymetazoline$_C$ (*Afrin™*)	Yes	–	–	Yes	–	–
nasal ipratropium $_B$ (*Atrovent nasal™*)	Yes	–	–	Yes	–	–
Cough						
guaifenesin $_C$ (*Robitussin™ *)	Yes	–	–	Yes	–	–
dextromethorphan$_C$ (*Benylin DM™ *)	Yes	–	–	Yes	–	–
albuterol $_C$	Yes	–	–	Yes	–	–
codeine $_C$	Yes	–	–	–	Yes	–

Adapted with permission from Powrie RO. Drugs in pregnancy. Respiratory disease. Best Pract Res Clin Obstet Gynaecol 2001;15(6):913–36.

Box 1.2 Use of the peak flow meter

- Peak flow meters are inexpensive portable, hand-held devices that measure the patient's ability to push air out of her lungs and are used as a convenient standardized way for a patient and her provider to monitor the course of her asthma on a daily basis. Peak flow meters also help identify worsening asthma before the patient may be aware of an exacerbation and thereby allow early intervention.
- Patients should measure their peak flow rate around the same time each day, often first thing in the morning and early in the evening. Normal peak flow rates can be obtained in standardized charts and vary with height, gender and race. A 30-year-old white woman with a height of 5′ 5″ will typically have a peak flow rate of 400 L/min. Most experts, however, will have their patients measure themselves against their own "personal best," i.e. the best peak flow rate that they have obtained under stable conditions. Patients can be taught to consider peak flow rates within 80% of their personal best as "normal" (the "green zone"), flow rates that are within 50–80% of normal as cause for concern or caution (the "yellow zone") and flow rates less than 50% of normal as being potentially dangerous (the "red zone"). Patients should be given explicit instructions as to what they should do with results in each zone.

Most drugs used for asthma treatment can be safely used in breastfeeding women (see Table 1.3). In fact, breastfeeding should be encouraged given the many well-recognized benefits for both mother and baby. Whether breastfeeding decreases the likelihood of the development of asthma in offspring is as yet controversial but it does appear to decrease atopy. The need for medication compliance should be reinforced as some mothers will find it more difficult to tend to their own needs when they have a newborn. Women who have quit smoking during their pregnancy are at increased risk for returning to their old habit so a discussion focused on maintaining abstinence may be useful. (See smoking cessation section below.)

Smoking cessation in pregnancy

The health risks of cigarette smoking outside pregnancy are well established and include atherosclerotic cardiovascular disease, cancers of the lung, cervix, pancreas, kidneys, lower urinary tract, and upper digestive tract, as well as respiratory illness including chronic obstructive pulmonary disease and worsening of asthma. It is also associated with diseases such as osteoporosis and peptic ulcer disease. As the leading preventable cause of death worldwide, it is responsible for approximately 1 in 10 deaths in adults and costs billions of dollars in annual health-related economic losses. For the smoking pregnant woman and her fetus, the risks are more immediate and include low birthweight, spontaneous pregnancy loss, stillbirth, premature rupture of membranes, placental abruption, placenta previa, and preterm delivery.

Epidemiology

According to studies from the 1990s, between 1 in 3 and 1 in 5 women living in developed countries reported smoking during pregnancy [20]. However, the prevalence may be even higher as smoking is notoriously under-reported by gravid women, probably because of the lack of social acceptability of cigarette use in pregnancy. Smoking is particularly common in those who are socially disadvantaged and have low income but poor social support, depression, work stress, and exposure to intimate partner violence are also associated factors. Women with concern about weight gain during pregnancy may use continued smoking as a method of weight control.

Pathophysiology

Smoking is the most important modifiable risk factor for adverse pregnancy outcome. It is estimated that in a population with a high smoking prevalence, smoking cessation could prevent up to 10% of perinatal deaths, 35% of low birthweight babies, and 15% of preterm deliveries [21]. Mechanisms by which these adverse outcomes may occur include impaired oxygen delivery to the fetoplacental unit, exposure to carboxyhemoglobin, direct fetal genetic damage or other toxicities from the multiple substances present in cigarettes and cigarette smoke. In the postpartum period, cigarette smoking is associated with further risks for babies including an increased risk of neonatal death and sudden infant death syndrome, respiratory infections, asthma, otitis media, colic, childhood obesity, and possibly type 2 diabetes mellitus (Box 1.3).

Management

Antepartum

The benefit of smoking cessation both within and outside pregnancy is clear but successful abstinence is difficult.

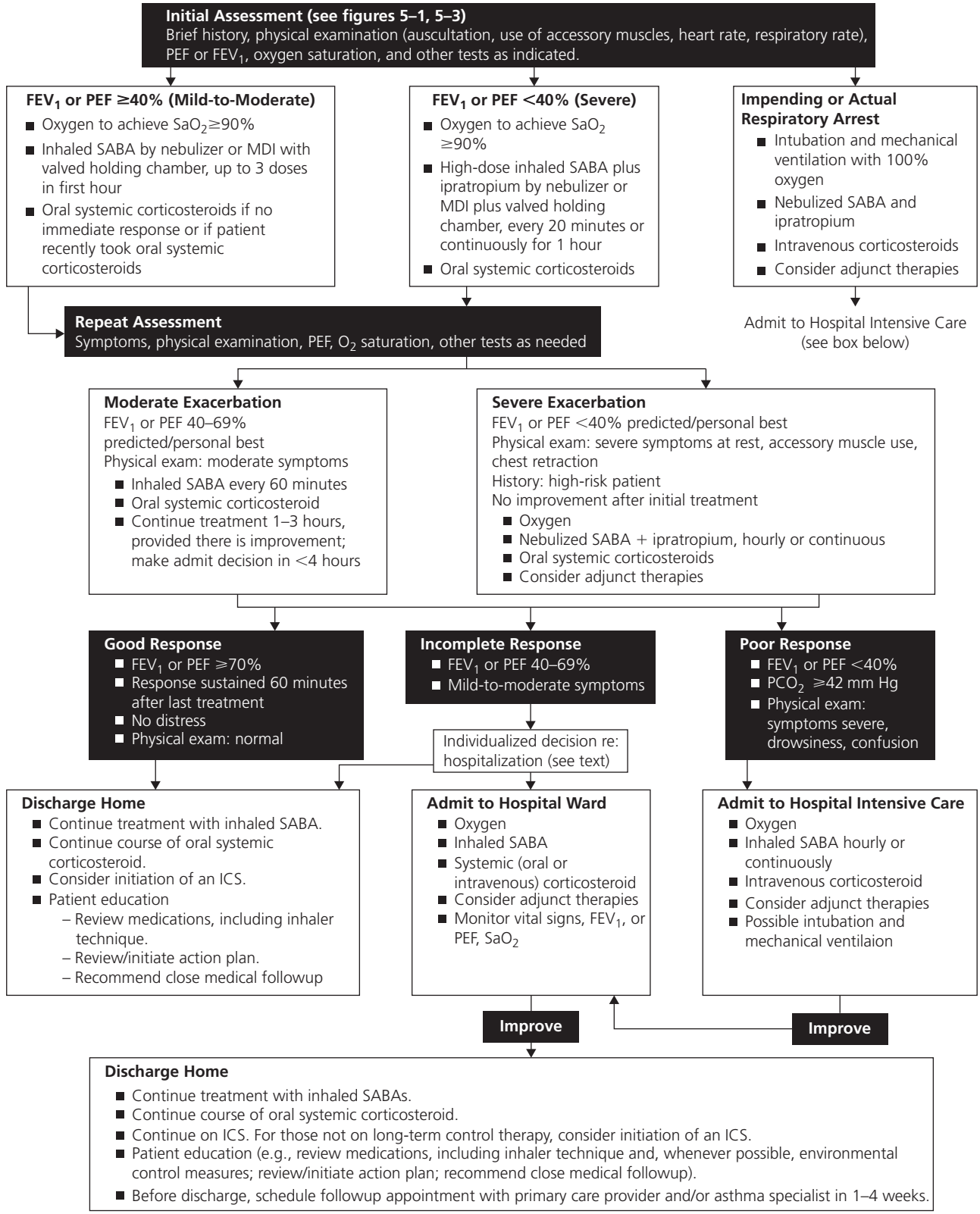


Figure 1.3 Management of asthma exacerbations: emergency department and hospital-based care. Reproduced with permission from The National Asthma Education and Prevention Program [15]. FEV_1, forced expiratory volume in 1 seconds; ICS, inhaled corticosteroid; MDI, metered dose inhaler; PCO_2, partial pressure carbon dioxide; PEF, peak expiratory flow; SABA, short-acting beta-agonist; SaO_2, oxygen saturation.

Box 1.3 Adverse pregnancy outcomes associated with smoking

- Infertility
- Low birthweight
- Spontaneous pregnancy loss
- Stillbirth
- Premature rupture of membranes
- Placental abruption
- Placenta previa
- Preterm delivery
- Possibly congenital malformations

Adverse effects on neonates and infants of mothers who smoke

- Increased risk of neonatal death and sudden infant death syndrome
- Increased respiratory infections (including otitis media)
- Increased asthma
- Increased colic
- Possible increased childhood obesity
- Possible increased type 2 diabetes mellitus

However, factors which may help motivate pregnant women include the desire to have a healthy pregnancy and newborn and the frequent contact with healthcare providers who can provide tobacco abstinence encouragement and support. Complete smoking cessation is only accomplished by approximately 20–40% of smoking pregnant women. Of those who do stop, most have already quit by their first prenatal visit. Risk factors for continued smoking include lower education status, those smoking less than 10 cigarettes per day, having a partner who smokes, and those who have other psychosocial issues. A study looking at a group of women who continued to smoke during pregnancy cited the following reasons for continued smoking: skepticism about smoking-related harms, addiction to nicotine, smoking among partners/family members, doubt about the safety of nicotine patch, and that the provider stopped asking about smoking status [22].

The 5As (Ask, Advise, Assess, Assist, Arrange) remain the cornerstone in approaching smoking pregnant women just as for nonpregnant patients (see Box 1.3, Tables 1.4 and 1.5). Inquiries about smoking status should be made on each visit and appropriate reinforcement given. If a patient is considering smoking cessation, a discussion centered on her continued need for stopping and recommendations for possible cessation strategies should be provided. Once a patient has actually stopped, continued positive reinforcement of useful strategies will be helpful for ongoing success. Additional resources for specific strategies for smoking cessation in pregnancy will be found at the following websites: www.modimes.org, www.helppregnantsmokersquit.com, and www.acog.org.

Drugs

In nonpregnant women, pharmacotherapy is strongly encouraged but because of concerns regarding drug use in pregnancy, medication is often not considered as a tool for use in smoking cessation in pregnancy. However, the considerable risks of ongoing tobacco use in a gravida unable to stop smoking without pharmacotherapy must be balanced against the risks of medication use. In particular, nicotine has known adverse fetal effects for which it has earned an US Food and Drug Administration (FDA) pregnancy safety category D ("studies have demonstrated a risk to the fetus"). However, with continued smoking, a fetus is exposed not only to nicotine but also to many other substances with adverse effects. Interestingly, several recent studies have suggested no worsened and even

Table 1.4 The 5 As for pregnant women

The 5 As	Action	Length of time spent
ASK about smoking status	Ask the pregnant woman to describe herself as one of the following: (a) I have NEVER smoked or have smoked LESS THAN 100 cigarettes in my lifetime (b) I stopped smoking BEFORE I found out I was pregnant, and I am not smoking now (c) I stopped smoking AFTER I found out I was pregnant, and I am not smoking now (d) I smoke some now, but I cut down on the number of cigarettes SINCE I found out I was pregnant (e) I smoke regularly now, about the same as BEFORE I found out I was pregnant	1 minute
ADVISE quitting	Give the patient strong, clear advice to quit smoking describing the impact of smoking and the benefits of quitting on the mother and fetus (see Table 1.5)	1 minute
ASSESS willingness to quit	Discuss whether the patient is willing to quit smoking in the next 30 days	1 minute
ASSIST in helping patient to quit	Discuss problem-solving methods and skills for cessation. Provide pregnancy-specific self-help materials. Encourage social support in the smoker's environment	3 minutes +
ARRANGE follow-up	Periodically assess smoking status and encourage cessation if continued smoking	1 minute

Adapted with permission from the National Partnership to Help Pregnant Smokers Quit: www.helppregnantsmokersquit.org.

Table 1.5 Benefits of smoking cessation in general over time

Time period	Result
Within 20 minutes	Blood pressure drops to near that of before the last cigarette. Temperature of hands and feet increases to normal
Within 12 hours	Carbon monoxide level drops to normal
Within 24 hours	The risk of myocardial infarction decreases
Within 2–3 weeks	Circulation improves and lung function increases
Within 1–9 months	Coughing, sinus congestion, fatigue, and shortness of breath decrease
Within 1 year	The excess risk of heart disease is half that of a smoker's
Within 5 years	The risk of stroke reduces to that of a nonsmoker's
Within 10 years	The risk of many cancers decreases, including lung, mouth, and throat cancer
Within 15 years:	The risk of heart disease reduces to that of a nonsmoker

Adapted with permission from the National Partnership to Help Pregnant Smokers Quit: www.helppregnantsmokersquit.org.

Box 1.4 Specific benefits of smoking cessation to tell pregnant patients

- After you stop smoking more nutrition will go to your baby to help him/her grow.
- After you stop smoking, your chances of having a healthy baby increase, and the baby is more likely to have a healthy childhood.
- After you stop smoking you will have more energy and may feel less stressed.
- After you stop smoking you'll breathe easier and you will be better able to keep up with your active, healthy baby.
- After you stop smoking, you'll reduce your risk for cancer, cardiovascular, and other diseases so you can be around a long time to be a good mother.

Adapted with permission from *You and your baby,* American Lung Association: www.lungusa.org.

improved fetal outcome associated with nicotine replacement therapy. One study looking at the rate of stillbirth in pregnant women using nicotine gum, patch or inhaler did not show an increase in stillbirth in nicotine replacement users [23]. The use of 2 mg nicotine gum in a study by Oncken *et al.* did not show increased quit rates but did show increased birthweight and a lower risk of preterm delivery as compared with placebo [24]. Ideally a pregnant woman would stop smoking without any pharmacologic aids but in the practical world, the likelihood is lower. Therefore, many would consider the benefit of nicotine replacement therapy and the higher likelihood of smoking cessation to be greater than the risk of continued smoking, especially in women who are at high risk for continued smoking.

Though bupropion is more effective for smoking cessation than nicotine replacement therapy outside pregnancy, there are limited data on its use in pregnancy for either smoking cessation or depression. Therefore, nicotine replacement is preferable for use in pregnancy. Both nicotine replacement and bupropion are acceptable for breastfeeding but nicotine replacement is preferable. Likewise, the safety of varenicline in pregnancy and lactation is even less clear and it should be avoided in pregnant and breastfeeding women until more data are available.

Post partum

Among those women who do stop smoking during pregnancy, 90% will relapse in the first postpartum year and most often within the first 6 weeks after delivery. Therefore, cessation programs should target this time period to minimize recidivism. Discussions addressing postpartum relapse should begin in the third trimester (Box 1.4). Risk factors for relapse include women with depressed mood, women who have family members or friends who are continued smokers, those with less social support, and those with less confidence in their ability to remain smoke free. Women who smoke in the postpartum period are also less likely to breastfeed.

Respiratory tract infection

Rhinitis and sinusitis

Up to 30% of women develop symptoms of rhinitis or sinusitis during pregnancy and the risk dramatically increases in smokers [25]. The effects of increased blood volume and vascular congestion on the nasal mucosa are thought to be responsible for gestational rhinitis. In addition, women with underlying allergic rhinitis or nasal polyps may develop worsening of their baseline symptoms with pregnancy.

Rhinitis may be categorized as allergic or nonallergic, both presenting with similar symptoms of rhinorrhea and nasal obstruction but with varied underlying causes. Allergic rhinitis may not be life threatening but its negative impact on quality of life of pregnant women is significant. Allergic rhinitis often co-exists with asthma and up to 40% of rhinitis patients become asthmatics [26]. Furthermore, clinically diagnosed allergic rhinitis is associated with worse asthma control. Of note, rhinitis in pregnancy may be associated with snoring.

Reassurance may be the only intervention necessary for rhinitis but women with particularly bothersome symptoms can try saline nasal spray or intranasal preparations of beclomethasone

Table 1.6 Differential diagnosis of rhinitis in pregnancy and some treatment options

Diagnosis	Clinical features	Treatment
Rhinitis medicamentosa	A condition of rebound nasal congestion brought on by extended use of topical decongestants (e.g. oxymetazoline, phenylephrine, and xylometazoline nasal sprays) that work by constricting blood vessels in the lining of the nose	Discontinue topical vasoconstrictors
Pregnancy rhinitis	Runny nose and nasal congestion presenting at any time in pregnancy caused by mucosal and vascular changes in nasopharynx	Buffered saline nose spray or nasal lavage, external nasal dilator (e.g. Breath-Rite strips)
Infectious rhinosinusitis	Usually a bacterial infection complicating the common cold with symptoms worsening after 5 days or not improving after 10 days and nasal congestion, fever and sinus pain predominating	Antibiotics (usually amoxicillin or azithromycin in penicillin-allergic patients) if no co-morbid conditions and no recent prior antibiotic use), nasal lavage, limited use of oxymetazoline nasal spray or pseudoephedrine after first trimester
Vasomotor rhinitis	Itch, sneeze, cough, nasal congestion, rhinorrhea in response to specific allergens (e.g. hay fever)	No specific therapy. Nasal ipratropium or pseudoephedrine after first trimester for limited period
Allergic rhinitis	Nasal congestion and rhinorrhea in response to nonallergenic environmental stimuli (e.g. cold, heat, alcohol, emotion, spicy food)	Intranasal cromolyn +/− nasal oxymetazoline or pseudoephedrine, topical beclomethasone or fluticasone, oral antihistamines (chlorpheniramine maleate, diphenhydramine)

and/or cromolyn [27]. First-generation antihistamines such as chlorpheniramine or diphenhydramine are reasonably used to treat allergy-related symptoms. Warning against overuse of topical decongestants which can cause rhinitis medicamentosa is important as many women may try these to avoid systemic medications. Table 1.6 outlines the differential diagnosis of rhinitis in pregnancy with recommended treatment options.

Sinusitis is increased sixfold in pregnancy as compared with nonpregnant patients. Complicating its diagnosis is the fact that 50% of pregnant women with documented purulent sinusitis do not have classic sinusitis symptoms (sinus tenderness, purulent discharge, fever). Therefore, despite the common rhinitis symptoms of pregnancy, clinicians should have a high index of suspicion for sinusitis in gravid women. The organisms causing sinusitis in pregnancy are the same as in the general population so antibiotics should be geared towards covering *Haemophilus influenzae, Mycoplasma. catarrhalis,* and *Streptococcus pneumoniae*. Assuming antibiotic resistance patterns do not dictate otherwise, reasonable antibiotic choices for use in pregnancy include amoxicillin/clauvulanate, cefuroxime axetil, and azithromycin. However, ciprofloxacin, doxycycline and tetracycline should be avoided.

Acute bronchitis

Acute bronchitis usually refers to a self-limited respiratory illness characterized by the predominance of a productive cough in a patient with no history of chronic obstructive pulmonary disease and no evidence of pneumonia. It affects approximately 5% of adults in the US annually [28].

Most cases of acute bronchitis seem to have a viral etiology; however, atypical bacteria including *Bordetella pertussis, Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are important causes [29]. The etiologic pathogen is isolated from the sputum in only a minority of patients.

During the first few days of infection, the illness is indistinguishable from other acute upper respiratory infections. However, with acute bronchitis, coughing persists for more than 5 days, and during this period the results of pulmonary function testing may become abnormal [30]. Reduction in FEV_1 or bronchial hyper-reactivity may be noted, with improvement in the following 5–6 weeks. Typically, cough persists for 3 weeks following acute bronchitis, but may last 4 weeks or more.

Differential diagnosis includes asthma, bronchiolitis, bronchiectasis or acute exacerbation of chronic bronchitis. Chronic bronchitis by definition is the presence of cough and sputum production on most days of the month for at least 3 months of the year during 2 consecutive years.

No studies have looked specifically at the course of acute bronchitis in pregnancy. One retrospective cohort study found an association between placental abruption and acute respiratory illnesses, including acute bronchitis among white women [31].

Most patients with acute cough syndromes require no more than reassurance and symptomatic treatment. A chest X-ray would only be indicated if pneumonia was suspected on clinical exam. Diagnostic testing for a particular pathogen can only be justified when the organism is treatable and a community outbreak is suspected.

Antimicrobial agents are not recommended in most cases of acute bronchitis. Multiple studies indicate that patients with acute bronchitis do not benefit from these drugs. Antimicrobial therapy may be considered in patients when a treatable pathogen is identified or in epidemic settings to limit transmission. Table 1.7 includes suggested treatment regimens for pregnant patients.

Table 1.7 Recognized causes of acute bronchitis and treatment options

Pathogen	Comments	Treatment options in pregnancy	Treatment options with lactation
Influenza virus	Precipitous onset with fever, chills, headache, cough and myalgias	Supportive treatment with acetaminophen, fluids, rest. Antiviral agents recommended for treatment of influenza have either very little or concerning pregnancy safety data (see influenza section)	Supportive treatment with acetaminophen, fluids, and rest (see influenza section)
Parainfluenza virus	Epidemic may occur in fall. Croup in a child at home suggests its presence	Supportive treatment with acetaminophen, fluids, rest	Supportive treatment with acetaminophen, fluids, rest
Respiratory syncytial virus	Outbreaks occur in winter or spring. Approximately 45% of adults exposed to an infant with bronchiolitis become infected	Supportive treatment with acetaminophen, fluids, rest	Supportive treatment with acetaminophen, fluids, rest
Coronavirus	Severe respiratory symptoms may occur	Supportive treatment with acetaminophen, fluids, rest	Supportive treatment with acetaminophen, fluids, rest
Adenovirus	Infection is clinically similar to influenza, with abrupt onset of fever	Supportive treatment with acetaminophen, fluids, rest	Supportive treatment with acetaminophen, fluids, rest
Rhinovirus	Fever is uncommon, infection is generally mild	Supportive treatment with acetaminophen, fluids, rest	Supportive treatment with acetaminophen, fluids, rest
Bordetella pertussis	Incubation period is 1–3 weeks. Post-tussive vomiting may be present. Fever is uncommon	Azithromycin for 5 days (500 mg on day 1, 250 mg days 2–5)*or* Erythromycin for 14 days (500 mg 4 times daily) *or* Trimethoprim/Sulfamethoxazole for 14 days (160/800 mg twice daily)	Acceptable for use in lactation: Erythromycin$_B$ Azithromycin$_B$ Acceptable as second choice: Trimethoprim/sulfamethoxazole$_C$
Mycoplasma pneumoniae	Gradual onset over 2–3 days of headache, fever, malaise and cough. Wheezing may occur. Dyspnea is uncommon	Azithromycin for 5 days (500 mg on day 1, 250 mg days 2–5) or no therapy*	Acceptable for use in lactation: Erythromycin$_B$ Azithromycin$_B$
Chlamydia pneumoniae	Gradual onset of cough with preceding hoarseness	Azithromycin for 5 days (500 mg on day 1, 250 mg days 2–5) or no therapy*	Acceptable for use in lactation: Erythromycin$_B$ Azithromycin$_B$

Adapted with permission from Wenzel RP, Fowler AA 3rd. Clinical practice. Acute bronchitis. N Engl J Med 2006;355(20):2125–30.

Pneumonia

Pneumonia and influenza combined are the seventh leading cause of mortality in the United States and the most common cause of death from an infectious disease [32]. The incidence of pneumonia requiring hospitalization in pregnancy is between 2.6 and 15.1 per 10,000 deliveries, a rate comparable to that seen in nonpregnant women of a similar age [33]. Although historically pneumonia has been cited as the third most frequent cause of indirect obstetric death in North America, several recent studies have reported no or rare maternal deaths, with mortality rates similar to young hospitalized nonpregnant patients [34]. Despite this, pregnancy is associated with reduction in cell-mediated immunity and this may explain the increased risk of severe pneumonia and disseminated disease from atypical pathogens such as herpes virus, influenza, varicella, and coccidioidomycosis in pregnant women. Other anatomic and physiologic changes of pregnancy that may add to the vulnerability of the lung to injury during infection include an increase in thoracic circumference, elevation of the diaphragm (resulting in interference with clearance of secretions), decreased functional residual capacity, and increased oxygen consumption. This section will discuss the various types of pneumonia (Table 1.8).

Bacterial and atypical pneumonia

Although rigorous investigation into specific causes of pneumonia in pregnancy is lacking, the etiology is likely similar to the nonpregnant population, with *Streptococcus pneumoniae* being the most commonly isolated organism. Other causes of pneumonia include *Staphylococcus aureus, Haemophilus influenzae, Legionella* spp, *Mycoplasma pneumoniae, Chlamydia* and viruses. Among patients requiring admission to intensive care units, *Pseudomonas aeruginosa* and Enterobacteriaceae also play an important role. However, even with extensive diagnostic testing, the etiologic agent cannot be identified in at least 50% of cases.

Clinical presentation

Signs and symptoms of pneumonia in pregnancy are similar to those in nonpregnant individuals. Symptoms usually include cough, sputum production, chills, rigors, dyspnea and pleuritic

Table 1.8 Types of pneumonia and their treatment

Type of pneumonia	Recommended antibiotics acceptable for use in pregnancy	Lactation	Other comments
Community-acquired pneumonia Organisms: *S. pneumoniae* Respiratory viruses *M. pneumoniae* *H. influenza* *C. pneumoniae* *Legionella* Unknown	Ceftriaxone (2 g IV daily) or cefotaxime or ampicillin/sulbactam (3 g IV q 6 h) PLUS macrolide (azithromycin, erythromycin) If concern for MRSA, add vancomycin (15 mg/kg q 12 h)	All these agents can be used safely in breastfeeding mothers	Avoid tetracycline and doxycycline in pregnant or breastfeeding mothers Antipneumococcal fluoroquinolone may be used in nonpregnant patients but generally avoided in pregnancy or breastfeeding mothers
Hospital-acquired pneumonia/healthcare-associated pneumonia/ventilator-associated pneumonia Organisms: Aerobic gram-negatives (*P. aeruginosa, E.coli, Klebsiella pneumoniae, Acinetobacter* sp.) Gram-positive cocci *(Staph. aureus,* esp. methicillin resistant (MRSA) Oropharyngeal commensals (viridans group strep, coagulase-negative staph, *Neisseria* sp, *Corynebacterium* sp) Multidrug-resistant organisms (MDR) (as per local patterns)	Ceftriaxone (2 g IV daily) or ampicillin/sulbactam (3 g IV q 6h) If concern for MDR: Ceftazidime (2 g IV q 8 h) or cefepime (2 g IV q 8 h) or imipenem 500 mg q 6 h) or piperacillin/tazobactam (4.5 g q 6 h) or aztreonam (2 g q 6–8 h) PLUS Gentamycin or tobramycin PLUS Vancomycin (15 mg/kg q 12 h)	All these agents can be used safely in breastfeeding mothers	Antipneumococcal fluoroquinolone may be used in nonpregnant patients but generally avoided in pregnancy or breastfeeding mothers Avoid tetracycline and doxycycline in pregnant or breastfeeding mothers
Aspiration pneumonia Organisms: Oropharyngeal commensals (viridans group strep, coagulase-negative staph, *Neisseria* sp, *Corynebacterium* sp)	Clindamycin or penicillin	All these agents can be used safely in breastfeeding mothers	
Varicella pneumonia	Acyclovir IV 10 mg/kg q 8 h	Can be used safely in breastfeeding	

chest pain, although nonrespiratory symptoms such as vomiting, abdominal pain and fever may also occur. Physical exam may reveal fever, tachypnea, hypoxia, abnormal breath sounds, including a pleural friction rub, egophony (consolidation causing the patient's spoken "a" to sound like an "e" on auscultation) or tactile fremitus (consolidation causing the spoken words "99" to cause a palpable vibration on the chest wall). Hemodynamic instability may be present in cases of severe illness. Mothers who develop pneumonia are more likely to have co-existing medical problems including asthma, drug abuse, anemia and HIV infection. The use of corticosteroids for enhancement of fetal lung maturity and tocolytic agents has also been associated with antepartum pneumonia [35].

Diagnosis

Information obtained from the history or physical examination cannot rule in or rule out the diagnosis of pneumonia with adequate accuracy. Therefore, to confirm the diagnosis and to assess severity of illness and presence of complications such as pleural effusion or multilobar disease, a chest radiograph should be performed in all patients suspected to have pneumonia. Laboratory data should include a complete blood count, serum chemistries for hepatic, renal and glucose evaluation, assessment of oxygenation and two sets of blood cultures; however, blood cultures may be positive only 7–15% of the time. The American Thoracic Society (ATS) does not recommend routine performance of sputum culture and gram stain. However, if a drug-resistant pathogen or an organism not covered by usual empiric therapy is suspected, sputum culture should be obtained. HIV status should be reviewed for all pregnant women with pneumonia and testing should be offered if it has not previously been done. Testing for *Pneumocystis jiroveci* infection should occur in all HIV-positive women who present with pneumonia.

The differential diagnosis for a pregnant woman presenting with symptoms of pneumonia is varied. Pulmonary embolism can present identically to an acute pneumonia with dyspnea, cough, chest pain, low-grade fever and chest X-ray infiltrates and remains the leading direct cause of maternal mortality in the US and the UK. Aspiration chemical pneumonitis, amniotic fluid embolism and pulmonary edema related to sepsis, tocolysis or pre-eclampsia can also present in a similar fashion. Other infectious illnesses, including cholecystitis, appendicitis and pyelonephritis, should also be considered.

Management

Preconception counseling

Pneumonia does not generally prompt preconception counseling because it is an acute infectious illness. There are a few issues worth consideration, however. Women who are HIV infected with low CD4 cell counts should continue prophylaxis for *Pneumocystis jiroveci* (see Chapter 18). Immunizations to prevent pneumonia and its complications are also indicated. The Centers for Disease Control and the American College of Obstetricians and Gynecologists advise that women should routinely receive influenza vaccination (see section on influenza below). Women with diabetes mellitus, asthma, chronic cardiac or pulmonary disease, chronic hypertension or immune compromise disease should receive the pneumococcal vaccine. It is also recommended post splenectomy and in women with functional hyposplenism, such as with sickle cell disease, and for women living in prisons or long-term care facilities. All nonpregnant women of childbearing age who are not immune to varicella should be vaccinated but it is a live vaccine and should not be given during pregnancy.

Potential maternal and fetal complications

Pregnancy increases the risk of maternal complications from pneumonia, including the need for mechanical ventilation. Respiratory failure due to pneumonia is the third leading indication for intubation in pregnancy [36]. Other maternal complications include pulmonary edema, bacteremia, empyema and pneumothorax. Pregnancies complicated by acute respiratory illnesses, including viral and bacterial pneumonia, have been shown to be associated with placental abruption [31]. Increased rates of preterm labor and delivery before 34 weeks of gestation have also been described [37], resulting in significantly lower average birthweight at delivery. The neonatal mortality rate due to antepartum pneumonia ranges from 1.9% to 12%, with most mortality attributable to complications of preterm birth [38]. Although most cases of pneumonia in pregnancy are caused by organisms which do not affect the fetus except through their effects on maternal status, some organisms, such as varicella, may present specific risks to the fetus. The fetus may also be at risk from maternal conditions which predispose to pneumonia, such as anemia or HIV infection.

Treatment

Although several guidelines to assess severity and need for hospitalization have been developed for pneumonia in the nonpregnant population, discriminatory features that identify those pregnant women who can be successfully managed as outpatients have not been determined. Pregnant women with pneumonia should generally be admitted for initial therapy, fetal evaluation and to ensure adequate oxygenation (oxygen saturation $\geq$95% or $pO_2 \geq$70 mmHg).

Several recommendations for the empiric treatment of community-acquired pneumonia exist. These support the use of a macrolide (erythromycin in any form except estolate ester, or azithromycin) in conjunction with a beta-lactam (cefotaxime, ceftriaxone or ampicillin-sulbactam) for most inpatients with pneumonia. Although levofloxacin and doxycycline are often recommended in the treatment of pneumonia in the nonpregnant population, these drugs should be avoided in pregnancy. Clarithromycin has shown adverse effects in animal trials at doses equivalent to 2–17 times the maximum recommended human dose. It is therefore best avoided in pregnancy, with use limited to those cases where no alternative therapy is appropriate. Monotherapy with high-dose amoxicillin (3–4 g a day) is supported in some European recommendations for nonpregnant patients, but ATS guidelines suggest addition of azithromycin for adequate coverage of *H. influenzae* (see Table 1.8).

With appropriate antibiotic therapy, some improvement in the patient's clinical course should be seen within 72 hours. Patients initially treated with intravenous antibiotics can be switched to oral agents (erythromycin/azithromycin with cefprozil or cefpodoxime) once the patient is afebrile for 24–48 hours. Continuation of therapy for a total of 10–14 days is recommended for all agents except azithromycin which can be given for only a 5-day course because of its extended half-life. Clinicians should ensure that a follow-up chest X-ray is done to confirm that there is no other underlying pathology complicating the pneumonia.

Aspiration pneumonia

Due to significant progress in modern obstetric and anesthetic management, acute aspiration pneumonitis has become a very uncommon cause of pneumonia in pregnancy. Although aspiration usually occurs in association with a difficult intubation or during the postanesthetic period when the gag reflex may be depressed, it may also develop *de novo* in pregnant women. Gastric juice in the lungs leads to intense pulmonary inflammation over 8–24 hours. The patient becomes tachypneic, hypoxic and febrile and the chest X-ray can show a complete "white out." Despite this rapidly deteriorating course, the picture resolves without antibiotics within 48–72 hours unless bacterial superinfection intervenes.

Bacterial aspiration pneumonia usually has a more insidious onset. Clinical manifestations typically begin 48–72 hours after aspiration, with persistent fever, sputum and leukocytosis. In this syndrome, chest X-ray findings are typically localized to the basilar segments (if the patient aspirated while upright) or to the posterior segment of the upper lobe or the superior segment of the lower lobe (if the patient aspirated while supine). The bacterial infection is generally polymicrobial with mouth anaerobes predominating and antibiotic treatment with penicillin or clindamycin is recommended.

Viral pneumonia

Varicella and influenza are the most common pathogens associated with viral pneumonia in pregnancy; however, cases with pneumonia resulting from rubella, hantavirus and SARS have also been reported in pregnancy. Viral pneumonia is often complicated by acute respiratory failure, secondary bacterial infections and acute respiratory distress syndrome (ARDS). This chapter will cover influenza, severe acute respiratory syndrome (SARS), and varicella pneumonia.

Influenza in pregnancy (see also Chapter 17)

Outbreaks or epidemics of influenza generally occur in the fall and winter but can occur year round in the tropics. The viruses causing influenza are of two types, A and B. The A virus is further classified by the hemagglutinin (H) and neuramidase (N) surface antigens and antibodies against these antigens decrease the likelihood of infection. However, antibodies to one subtype do not necessarily confer immunity to another or a variant of a subtype, such as occurs with antigenic drift. This is an important consideration in determining the influenza strains against which the annual vaccines are targeted. A major change in the antigens resulting in essentially a novel influenza virus, termed antigenic shift, has the potential to cause pandemics.

Children have the highest rate of influenza infection but anyone in the general population may become infected. Between the years 1990 and 1999, the average annual number of deaths related to influenza infection in the US was 36,000 [39]. Those who are at the greatest risk for serious infection or death include people $\geq$65 years old, children $<$2 years old, those with chronic cardiac and pulmonary disorders, those with chronic metabolic conditions (such as diabetes mellitus), those with chronic medical conditions (such as renal insufficiency, hemoglobinopathies, and immunodeficiencies such as HIV), as well as pregnant women. Complications of influenza include severe primary viral infection as well as secondary bacterial infections causing pneumonia, sinusitis, and otitis media. Further complications are secondary to decompensation of underlying diseases, particularly cardiopulmonary disease.

The influenza virus is spread via respiratory droplets from person to person. The incubation period is approximately 1–4 days and virus may be shed from several days before obvious infection to 5–10 days after. Symptoms include the abrupt onset of fever, headache, myalgia and respiratory symptoms such as cough and sore throat. Uncomplicated infection resolves after 3–7 days but some patients may have persistent malaise for more than 2 weeks.

Influenza is a relatively common infection in pregnancy. One study in 2000 found that of 1659 pregnant women in the United Kingdom, 11% had serologic evidence of a new influenza infection during the pregnancy [40]. Influenza is also associated with increased morbidity and mortality in pregnant women. The mortality for all infected pregnant women in the 1918 flu epidemic was 27% but when women were infected in the last month of pregnancy, the mortality was over 60%. Of the pregnant women who developed pneumonia, over 50% died as compared with 30% of nonpregnant patients who developed pneumonia. During the 1957 Asian flu epidemic in New York City, over half the young women who died with pneumonia were pregnant. Since that time, improved healthcare with wider immunization practices (and possibly the specific antigenic strains of influenza circulating) have been associated with lower mortality rates. Despite this, pregnant women with influenza are still at increased risk for serious complications requiring hospitalization [41]. Neuzil *et al.* estimated from their data in 1998 that in the average flu season, 25 out of 10,000 pregnant women in the third trimester will require hospitalization for influenza-related morbidity [42]. Pregnant women with influenza and associated co-morbidities such as asthma, diabetes, cardiac disease, cigarette smoking or other high-risk medical diseases are at increased risk for hospitalization with influenza. The likelihood of requiring hospitalization also increases with each trimester. Physiologic changes in pregnancy which may explain the increase of influenza complications in gravid women include changes in immune function, predisposition to the development of pulmonary edema, higher baseline oxygen consumption and a higher cardiac output.

It appears that the effects of influenza on the fetus are primarily related to the severity of maternal illness. Though there are reports of increased congenital anomalies, stillbirths, and prematurity with pandemics, a Tennessee Medicaid population study conducted from 1985 to 1993 did not reveal an increase in adverse perinatal outcomes with respiratory hospitalizations during the influenza season [43]. A few cases of the influenza virus infecting the placenta and fetus have been reported but others have found no increase in obstetric complications, congenital malformations or other evidence of transplacental transmission.

The management of pregnant women with influenza rests primarily on supportive care and aggressive treatment of superinfection. Fevers should be controlled with acetaminophen and adequate hydration provided. Pneumonia, sinusitis, and otitis media require appropriate antibiotics. These patients should be followed closely for any deterioration as those with worsening shortness of breath, hypoxia or abnormal chest exams are at risk for requiring mechanical ventilation. Amantadine and rimantadine are not effective against influenza B and there is emerging resistance in influenza A such that they have not been recommended for use in the United States in recent years. Both agents are teratogenic and embryotoxic in rodents so their use is not recommended in pregnancy anyway. There is only limited information about the neuramidase inhibitors zanamivir and oseltamivir in pregnancy. Use of these agents requires careful consideration of the potential benefits against their unknown risks.

Table 1.9 Use of antiviral drugs for influenza in pregnancy

Antivirals	Use in pregnancy	Use in breastfeeding
Adamantanes: amantadine, rimantadine	Teratogenic and embryotoxic in rodents	Amantadine not reviewed by American Academy of Pediatrics (AAP) but may suppress milk production Rimantadine not reviewed by AAP but concentrated in rodent milk. It is used in pediatric patients over 1 year old, however
Neuramidase inhibitors: zanamivir, oseltamivir	The potential benefits of use in pregnancy must be weighed against the unknown risks. However, during the early 2009 H1N1 epidemic, the use of these agents in pregnant women was recommended by the US CDC Zanamivir crosses the placenta in rats and rabbits. Congenital abnormalities were not found in rats and rabbits exposed to zanamivir *in utero* In rats, dose-dependent minor skeletal changes were noted in the offspring of mothers given oseltamivir	Zanamivir and oseltamivir are not reviewed by AAP but given limited efficacy should probably not be used routinely in breastfeeding patients. However, during the early 2009 H1N1 epidemic, the use of these agents in pregnant women was recommended by the US CDC

Prevention of influenza infection is unequivocally the most important measure in the fight against influenza. Hygiene, such as handwashing measures, is recommended but cannot replace immunization. In one study of more than 2000 pregnant women immunized for influenza, no adverse fetal effects were associated with the vaccination [44]. Further, immunization of pregnant mothers in Bangladesh against influenza reduced influenza illness by 63% in infants up to 6 months of age and reduced by one-third all febrile respiratory illness in both mothers and infants [45]. Universal vaccination of pregnant (regardless of trimester) and breastfeeding women is recommended by the American College of Obstetricians and Gynecologists (ACOG) and the Centers for Disease Control and Prevention (CDC) [46].

Severe acute respiratory syndrome (see also Chapter 17)

Severe acute respiratory syndrome is a new viral illness that was first described in 2002. Prior to its containment in July 2003, the global outbreak of SARS affected more than 8000 people and caused more than 800 deaths worldwide. SARS is caused by a novel coronavirus and results in an atypical pneumonia which can rapidly progress to respiratory failure. Symptoms usually develop 2–7 days after exposure and include fever, chills, malaise, myalgia and headache. A nonproductive cough, dyspnea and diarrhea develop over 3–7 days and respiratory failure may develop in up to 20%. Patients are most infectious in the second week of illness. Laboratory abnormalities include lymphopenia, thrombocytopenia, prolonged partial thrombin time (PTT) and electrolyte abnormalities. Chest radiograph findings include generalized, patchy, interstitial infiltrates. Diagnosis can be confirmed by viral culture, polymerase chain reaction (PCR), ELISA and immunofluorescence assay. Since the clinical presentation of SARS is nonspecific, the differential diagnosis is wide and includes influenza virus, parainfluenza viruses, respiratory syncytial virus, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella* spp. and *Chlamydia* spp.

Although there were reports of pregnant women with SARS from several countries, the number of reported cases is too small to permit any definitive conclusions as to whether SARS was more or less severe among pregnant women as compared with nonpregnant women. The largest case series which included 12 pregnant patients with SARS showed high rates of morbidity and mortality [47], with a case fatality rate of 25%. Among the seven women who were infected in the first trimester, four had spontaneous abortions, and two had induced abortions. Of the five women who were infected later in pregnancy, three underwent preterm cesarean delivery (26–32 weeks of gestation) for worsening maternal hypoxemia; two of the three women who underwent cesarean delivery subsequently died. No cases of vertical transmission have been reported. Treatment with ribavirin, oseltamivir, steroids or combination steroids and antiviral medications has demonstrated reduction in mortality in the nonpregnant population [48]. However, ribavirin is teratogenic in animals and its use in pregnancy for this indication is evolving.

Varicella pneumonia (see also Chapter 17)

Although primary varicella infection is a childhood illness, 5–10% of cases occur after age 15 years. Acute VZV infection affects 5–7 of 10,000 pregnancies [49]. Ten to 20% of women with primary varicella infection in pregnancy can develop fulminant pneumonia. Before the availability of antiviral therapy, maternal mortality in cases of VZV pneumonia was as high as 40%. With the advent of antiviral agents, the mortality has decreased but still remains substantial. Risk factors for varicella pneumonia include later gestational age, history of or current smoking and skin involvement with >100 vesicles. Signs and symptoms of pneumonia may become manifest approximately 3–5 days after onset of rash and include dyspnea, tachypnea, cough with blood-tinged sputum, malaise and pleurisy. Chest X-ray may reveal a diffuse interstitial

nodular pattern ("ground-glass" appearance) or focal infiltrates. Mechanical ventilation may be required in up to half the patients. Treatment is parenteral acyclovir.

Management of maternal exposure to varicella during pregnancy is based on maternal immune status to varicella. Previous known varicella infection, previous vaccination or presence of serum IgG against varicella confers immunity and there is no risk from exposure. If exposure to varicella occurs in a gravid woman without immunity, VZ IG should be administered within 96 hours in an attempt to prevent maternal infection. The ability to prevent congenital varicella syndrome with VZ IG is unknown. Oral acyclovir (800 mg five times a day) is recommended for pregnant women with primary varicella infection to prevent serious complications such as pneumonia, but is most effective if given within 24 hours of development of rash. Parenteral acyclovir (10 mg/kg every 8 hours) should also be given to all varicella nonimmune patients who develop respiratory symptoms within 10 days of exposure to varicella.

Fungal pneumonia

Pneumonia caused by fungal organisms is rare in pregnancy. Histoplasmosis and blastomycosis (most commonly acquired in the Ohio or Mississippi River valleys in the southeast US but found throughout the world) have been most commonly associated with fungal pneumonia in pregnancy and cause a mild, self-limiting illness. Cryptococcosis (found worldwide in soil contaminated with bird droppings) also may present in pregnancy, though meningitis is more common than pneumonia. Coccidioidomycosis pneumonia (most commonly acquired in the desert south west of the US) has been associated with disseminated disease, particularly with infection in the third trimester. Disseminated fungal infection in a gravid woman is associated with increased risk of preterm delivery, perinatal and maternal mortality.

Fungal pneumonia may present with slow onset of cough and dyspnea or an acute onset of pleuritic chest pain and hypoxemia. Chest X-rays tend to show nodular disease with adenopathy. Diagnosis may be confirmed by sputum gram stain and culture for fungal organisms or by detection of serum fungal antigens. Severe pneumonia or disseminated disease is treated with amphotericin B. Ketoconazole or itraconazole is an option, although safety data for long-term use in pregnancy are limited and some concerning data exist for ketoconazole that suggest it may be teratogenic.

Pneumocystis jiroveci pneumonia

Pneumocystis jiroveci pneumonia (PJP) is the most common cause of AIDS-related death among pregnant patients. Symptoms include dry cough, tachypnea and dyspnea. Chest radiographs demonstrate diffuse interstitial infiltrates. In most cases, the diagnosis can be made by histologic staining of sputum, although bronchoscopy may be necessary in some cases. In a review of 22 cases of PJP in pregnancy, high rates of respiratory failure, maternal and fetal mortality were found [50]. However, these numbers may not necessarily reflect the true incidence of complications, because none of the patients in this series were on antiretroviral therapy and the diagnosis of HIV/AIDS was made only after the PJP was detected. Treatment is with trimethoprim-sulfamethoxazole (TMP/SMX) or pentamidine. For patients without hypoxemia (PaO_2 >70 mmHg), oral TMP/SMX 2 double-strength tablets or intravenous 15 mg/kg/day of TMP component every 8 hours for 21 days is recommended. For severe cases, oral or intravenous steroids are initiated before addition of TMP/SMX. HIV-infected patients with CD4 counts less than 200/μL, a history of oropharyngeal candidiasis or an AIDS-defining illness should receive prophylaxis with TMP/SMX, one double-strength tablet daily (see Chapter 18).

Tuberculosis in pregnancy

Tuberculosis (TB) is an age-old disease that is still very relevant to the worldwide community, causing 8 million new cases and 2 million deaths annually. Pregnant women are not spared its effects. Of all the TB deaths in women, 80% occur during the childbearing years. Because of its significant impact on pregnant women and their children, TB is targeted in Millennium Development Goals 4 and 5 to reduce childhood mortality and improve maternal health [51] (Box 1.5). In developed nations TB appears to be decreasing in incidence overall but even in the US, inner-city dwellers and immigrants from countries with a high prevalence represent significant populations with untreated TB. Women from these populations may seek healthcare only in the context of pregnancy

Box 1.5 Millennium Development Goals

Goal 4 – Reduce child mortality

Certain diseases . . . (including) TB . . . when they occur in pregnancy can lead to underweight and premature babies whose chances of survival are diminished. It follows, then, that treating these diseases in pregnant women will also help reduce under-five mortality.

Goal 5 – Improve maternal health

Target 6: Reduce by three-quarters, between 1990 and 2015, the maternal mortality ratio. Certain diseases . . . possibly including TB . . . when experienced during pregnancy, can be especially hard-hitting, and contribute to maternal mortality.

such that pregnancy presents a public health opportunity to identify and treat infected individuals.

Pathophysiology

Tuberculosis is caused by the acid-fast tubercle bacillus, *Mycobacterium tuberculosis*. It is spread via respiratory droplets from person to person. The inhaled organism is ingested by macrophages and disseminated tuberculosis occurs if the organism is not contained in the local lymph nodes. Granulomas develop secondary to the host's immune response to the mycobacterium. The infected primary lesion may heal and those individuals will not go on to have subsequent evidence of disease. Others may develop reactivation TB years later, particularly in circumstances of physiologic stress or depressed immunity (such as with HIV infection).

Clinical manifestations

Primary infection with TB is typically asymptomatic unless it disseminates. Reactivation TB presents with low-grade fevers, weight loss, and drenching night sweats. Respiratory symptoms may not be prominent even with pulmonary TB but cough and hemoptysis can occur. Symptoms of extrapulmonary TB are referable to the organ system involved.

Diagnosis

The diagnosis of a TB infection is established when the organism is identified in sputum, urine, body tissue or body fluid. Acid-fast bacilli may be seen on stained slides initially but culture can take up to 4–8 weeks to grow on classic culture media. Ideally, 2–3 sputum specimens obtained at least 8 hours apart (with at least one being an early morning specimen) should be sent for evaluation. If patients are unable to produce sputum, a nebulizer of hypertonic saline may be helpful in inducing some. Auramine-rhodamine or auramine O fluorescence staining (ideally used in combination with confirmatory nucleic acid amplification testing or NAAT) is more sensitive and now more commonly used than the classic Ziehl–Neelson stain but definitive diagnosis or exclusion of tuberculosis still requires culture. Positive cultures are typically subjected to confirmatory (DNA/RNA probe or high-pressure liquid chromatography or biochemical methods) and drug susceptibility testing. A rapid detection assay under development, called the microscopic-observation drug-susceptibility (MODS) assay, offers a combined rapid (7 days) tentative detection method and drug susceptibility testing for *M. tuberculosis* in resource-limited settings.

Chest X-ray findings suggestive of tuberculosis include multinodular infiltrates of the upper lobes and superior segments of the lower lobes. Cavitary lesions may also develop. The classic Gohn complex represents a healed primary lesion with a calcified hilar node and calcified peripheral nodule. However, it is important to be aware that up to 10% of patients with early culture-positive tuberculosis will have normal chest radiographs.

Screening

The CDC and the ATS recommend targeted testing for TB to identify persons with either latent tuberculosis or TB disease who would benefit from treatment [52]. They do not recommend screening for those who are not at high risk for TB exposure and since pregnancy itself does not represent a risk for exposure, pregnant women should be screened as in non-pregnant patients. Indications for tuberculin testing in and out of pregnancy are listed in Box 1.6. The common practice of universal tuberculin testing of pregnant women in hospital-based prenatal clinics is best justified in settings with a large proportion of socio-economically disadvantaged women, immigrants from high-risk areas or women with recent or active substance abuse or malnutrition.

Screening recommendations are established with the Mantoux tuberculin skin test and consist of an intradermal injection of 0.1 mL of purified protein derivative (PPD) containing 5 tuberculin units just beneath the skin surface on the forearm. A trained healthcare worker measures the area of induration (NOT erythema) in millimeters 48–72 hours later to determine the test result. The classification of a positive result depends on the presence of known risk factors (Box 1.7). For instance, a woman who has recently immigrated from a high-risk area has a positive Mantoux or PPD if the area of induration measures 10 mm or more. However, a woman with HIV has a positive test if the area of induration is 5 mm or more. Pregnancy does not impact on the interpretation of the test.

The QuantiFERON-TB Gold test was approved by the US FDA in 2005 for use in diagnosing both TB infection and latent TB infection. The test measures the white blood cell response to two synthetic peptides representing *M. tuberculosis* proteins. Though it is designed to be used in the same circumstances as the Mantoux test, there are limited data on its use in immunocompromised persons as well as in pregnancy. Therefore, until more data are available in these populations, the Mantoux test is preferable. Advantages to the QuantiFERON-TB Gold test are that it only requires a single blood draw, results are available within 24 hours and are not affected by prior BCG vaccination or subject to reader bias, and it is not affected by boost responses. Disadvantages are the need to collect, transport, and process blood samples in a specific manner within 12 hours and the uncertainties about its use in certain populations, as noted.

Course in pregnancy

Before antituberculous drugs were available, the outcome of pregnancy complicated by tuberculosis was poor for both

Box 1.6 Who should receive tuberculin testing outside pregnancy?

Patients who should have annual tuberculin testing

- Persons with HIV infection.
- Presence of a medical condition that increases the risk of active TB (diabetes, end-stage renal disease, alcoholism, solid organ transplant recipients, rapid weight loss or chronic malnutrition, anticipated long-term therapy with glucocorticoids or other immunosuppressive medications, hemodialysis, gastrectomy, jejunoileal bypass, silicosis, hematologic or reticuloendothelial malignancies).
- Ongoing potential close contact with cases of active TB including laboratory personnel handling potentially infected specimens, prison guards, healthcare workers in high-risk settings.
- New immigrants from areas where TB is common (Asia, Africa, Latin America, Eastern Europe, Russia).
- Residents of long-term care facilities (nursing homes, mental and correctional institutions).
- Medically underserved, low-income populations (including migrant farm workers, injection drug users and homeless persons).
- Children exposed to adults in high-risk categories.

Patients who should have a single tuberculin test

- Close exposure to a case of TB.
- Individuals born in Latin America, Asia or Africa or other locations with a high prevalence of TB who have relocated to a low-incidence country in the past 5 years.
- Individuals returning from work in a refugee, relief or healthcare setting in a TB-endemic area.
- Patients with an incidentally discovered fibrotic lung lesion on a CXR.

Adapted with permission from *Core curriculum on tuberculosis: what the clinician should know*. Department of Health and Human Services, Centers for Disease Control and Prevention, 2000. www.cdc.gov/tb

Box 1.7 Classification of tuberculin reactivity

≥ 5 mm induration is positive	≥ 10 mm induration is positive	≥ 15 mm induration is positive
HIV–positive patient Recent contact with person with TB	Recent immigration from high-prevalence area	Person with no known risk factors for TB*
Patient with changes on CXR consistent with TB	Injection drug users	
Patient with organ transplant and other immunosuppressed conditions	Residents and employees of high-risk congregate settings Laboratory personnel in mycobacteriology labs Persons with clinical conditions that place them at high risk[†] Children less than 4 years old or older children exposed to adults in high-risk categories	

*Skin testing programs should only be done among high-risk groups.
[†]High-risk conditions include: substance abuse, diabetes mellitus, silicosis, prolonged corticosteroid therapy, other immunosuppressive therapy, cancer of the head and neck, hematologic and reticuloendothelial disease (e.g. leukemia, Hodgkin's disease), end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndromes, low bodyweight (10% or more below ideal bodyweight).

Adapted with permission from *Core curriculum on tuberculosis: what the clinician should know*. Department of Health and Human Services, Centers for Disease Control and Prevention, 2000. www.cdc.gov/tb

mother and fetus and it appeared that there was a tendency for worsening in the postpartum period. In the early 20th century it was even recommended that pregnant women with TB terminate their pregnancies. However, it now appears that the course of tuberculosis is not affected by pregnancy but rather is more related to other risk factors, such as HIV and immune status. Interestingly, active tuberculosis may be more likely to be asymptomatic in pregnancy [53].

Treated tuberculosis in pregnancy does not appear to be associated with adverse maternal or fetal outcome. Untreated and extrapulmonary disease (with the exception of TB lymphadenitis), however, is associated with low birthweight, intrauterine growth restriction, and lower APGAR scores [54]. Extrapulmonary TB has a high prevalence in pregnancy of up to 50%. Reports of extrapulmonary TB in pregnancy include tuberculous peritonitis associated with a temporary Addisonian state, colonic tuberculosis, pericardial tuberculosis, renal tuberculosis, and tuberculous meningitis. The more common presentation for TB in pregnancy is positive screening by PPD or a suspicious chest X-ray done for other reasons such as cough, purulent sputum, hemoptysis, fever, weight loss, night sweats or chest pain.

Tuberculosis only rarely affects the fetus by transplacental passage but cases of fetal infection have been well documented. Infection may occur via the fetus swallowing infected amniotic fluid or be blood borne via the umbilical vein. Granulomas have been identified in the placenta and the bacillus itself has been found in the decidua, amnion, and chorionic villi. This occurs primarily with endometrial or miliary TB. Pulmonary and lymphadenitis TB generally pose little risk to the fetus assuming oxygenation and maternal well-being is not seriously jeopardized. More commonly, a neonate becomes infected after birth from exposure to an infected mother or family member. Therefore aggressive identification of an infected mother is important. Isolation of a neonate from the mother is only required if the mother is "smear positive" (mycobacteria identified on staining of sputum). Because modern antituberculous agents render the sputum sterile within 2 weeks and markedly reduce the number of organisms within 24 hours, this should not occur frequently. The neonate will require appropriate treatment if the mother is found to have positive sputum.

Management

Pregnancy

Untreated active TB is a greater risk to the fetus than treatment itself. The main fetal concern is the effect of the antituberculous drugs. In general, the recommended initial drug regimen for pregnant women with TB is at least isoniazid (INH), rifampin (RIF), and ethambutol (EMB) (Table 1.10). Pyrazinamide (PZA) is recommended by the World Health Organization [55] and the International Unit Against Tuberculosis and Lung Disease as a fourth agent [56]. Though INH, RIF, and EMB cross the placenta, teratogenic effects have not been demonstrated. An increased incidence of hepatic toxicity of INH appears to be associated with pregnancy and the first 6 postpartum months so that baseline and monthly liver tests are recommended. In particular, Hispanic and black women seem to be especially prone. Pyridoxine (50 mg) should also be administered to pregnant women taking INH to minimize the risk of neuropathy as they have increased nutritional needs. While there is no disagreement that PZA is necessary when there is concern about drug resistance or co-infection with HIV, some reserve its use for such indications as there are limited data about its effects in pregnancy. However, since multidrug resistance and co-infection with HIV are increasingly common, data about its use are accumulating and it is being recommended more often for initial use in the US.

The emergence of drug-resistant tuberculosis is problematic as some second-line agents such as the quinolones have known risks while others have an as yet unestablished safety profile in pregnancy. Treatment of these pregnant patients requires careful consideration by a multidisciplinary team including an expert in multidrug-resistant TB.

Latent TB infection (LTBI) requires treatment to decrease the likelihood of developing active TB in the future. Isoniazid is considered the safest, most effective drug of choice for use in pregnancy [57]. In general, it is recommended that treatment not be delayed until after delivery as this is associated with fewer recurrences [58]. It is unclear whether this is related to the higher noncompliance rate post partum (which has been shown to be up to 80%) and results in reduced effectiveness of isoniazid from 93–98% to 50% [59]. Certainly if the decision is made to treat LTBI post partum, every effort should be made to ensure compliance. Complicating the treatment of women antepartum is the reluctance of women to take medications during pregnancy, particularly when they otherwise feel well and medication is needed for a prolonged period. If there is a language barrier or transportation issues with obtaining medication for directly observed therapy, success is even more difficult.

Post partum (Box 1.8)

Women should not be discouraged from breastfeeding when taking isoniazid, rifampin, ethambutol or pyrazinamide. These agents do pass into the breast milk but only to a small degree and levels are inadequate to provide any treatment or protection from TB.

Acute respiratory distress syndrome and acute lung injury in pregnancy

Acute respiratory distress syndrome, previously known as adult respiratory distress syndrome, was first described as a

Table 1.10 Antituberculous medication

Medication/dose	Pregnancy data	Adverse effects	Breastfeeding	Other comments
Isoniazid (INH) 5 mg/kg up to a maximum of 300 mg daily Dispensed in the US as 50, 100 and 300 mg tablets and 50 m/5 mL syrup	FDA pregnancy classification C Considerable reassuring pregnancy safety data make this an excellent choice in pregnancy	Hepatotoxicity (risk increased in pregnant and Hispanic patients – recommend screening baseline liver function tests and checking monthly during pregnancy) Peripheral neuritis (risk obviated somewhat by supplementation with pyridoxine 25–50 mg PO daily) Other: GI upset, seizures, rash, and multiple drug interactions	AAP deems compatible with breastfeeding Thomas Hale classifies as L3*	Consider supplementation with vitamin K 10 mg PO daily from 36 weeks gestation on to decrease the risk of postpartum hemorrhage and hemorrhagic disease of the newborn
Rifampin 10 mg/kg up to a maximum of 600 mg daily Dispensed in the US as 150 and 300 mg tablets	FDA pregnancy classification C No evidence of adverse fetal effects	Hepatitis, nausea, fever, anemia, headache, diarrhea, orange secretions, pseudomembranous colitis, multiple drug interactions, flu-like symptoms at high doses, purpura	AAP deems compatible with breastfeeding Thomas Hale classifies as L3*	Consider supplementation with vitamin K 10 mg PO daily from 36 weeks gestation on to decrease the risk of postpartum hemorrhage and hemorrhagic disease of the newborn
Ethambutol 15–25 mg/kg up to a maximum of 2500 mg daily Dispensed in the US as 100 and 400 mg tablets	FDA pregnancy classification B	Optic neuritis in 1% of patients Other: peripheral neuropathy, rash, dizziness, confusion, nausea, vomiting	AAP deems compatible with breastfeeding Thomas Hale classifies as L2*	Screen patient monthly for optic neuritis by asking about blurred vision or scotomata and performing visual acuity and color discrimination testing
Pyrazinamide (PZA) 15–30 mg/kg PO daily up to a maximum of 3000 mg daily	FDA pregnancy classification C Published human data are limited despite broad international experience	Thrombocytopenia, hepatotoxicity, interstitial nephritis, nausea and vomiting, rashes, arthralgia	Not reviewed by the AAP Thomas Hale classifies as L3* No reported neonatal adverse effects	When possible, best to be started after the first trimester
Streptomycin Dose varies	FDA pregnancy classification D Reports of fetal ototoxicity	Deafness, anemia, renal toxicity	AAP deems compatible with breastfeeding Thomas Hale classifies as L3* No neonatal concerns via milk but observe for changes in GI flora	Use in pregnancy to be avoided unless no alternatives identified

AAP, American Academy of Pediatrics.
The Food and Drug Administration (FDA) classifies the safety of medications during pregnancy as category A, B, C, D and X. This classification system is reviewed in Chapter 30
*Thomas Hale in his classic breastfeeding reference *Medications and mothers' milk* (Pharmasoft, 2008), classifies medication safety in breastfeeding as follows: L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; L5, contraindicated. See Chapter 31 for details.

clinical entity in 1967. It is characterized by an acute onset of noncardiogenic pulmonary edema resulting in severely impaired oxygenation. The current definition of ARDS was proposed in 1994 in the American-European Consensus Conference [60]. The panel recognized that severity of lung injury varies: patients with less severe hypoxia are considered to have acute lung injury (ALI) and patients with more severe hypoxia are considered to have ARDS. This definition characterizes the illness as having acute onset, bilateral chest infiltrates, pulmonary artery wedge pressure of less than 18 mmHg or absence of clinical evidence of left atrial hypertension, and PaO_2/FiO_2 ratio of 200–300 for ALI and ≥200 for ARDS.

The frequency of ARDS in the general population is estimated at 1.5 per 100,000 per year, with a fatality rate of 35–50%. Although no studies clearly elucidate the frequency of ARDS in the obstetric population, the incidence is felt to be similar to the general population. Noncardiogenic pulmonary edema or ALI, on the other hand, is known to occur more frequently in pregnant women, with an estimated

Box 1.8 Management of TB-infected mother and newborn baby

1. Mother with latent TB infection (LBTI + PPD, normal CXR and physical exam, no pulmonary symptoms, negative sputum culture)
   a. No respiratory precautions necessary
   b. Mother and baby do not need separation
   c. Begin or continue treatment for LTBI in women at high risk for progression to active disease and encourage breastfeeding
   d. Contact appropriate agency to evaluate family and contacts, if not already done
   e. Depending on findings for contacts, neonate may or may not need future skin testing
2. Mother has contagious (active pulmonary) TB (+PPD, + sputum smear or culture)
   a. Separate mother and neonate
   b. Respiratory precautions in negative pressure ventilation room
   c. Begin multidrug therapy
   d. Mother can pump breast milk until she is not contagious and can breastfeed
   e. Contact appropriate agency to evaluate family and contacts
   f. Contact pediatrician/neonatologist for neonate evaluation for TB
   g. Neonate can be reunited with mother once she is noncontagious (negative sputum smear or culture). It generally takes 2 weeks with therapy to be noncontagious as long as the TB organism is not resistant to therapy and the mother is compliant with therapy
3. Mother with +PPD and suspicion for active TB but incomplete evaluation
   a. Separate mother and baby until evaluation (CXR, sputum smear and culture) is complete
   b. Place mother on respiratory precautions in negative pressure ventilation room (wearing proper respirator when patient is not in room) until she is determined to not be contagious with 2–3 negative sputums
   c. Mother can pump breast milk for infant

Box 1.9 Causes of ARDS unique to/more common in pregnancy

1. Tocolytic (beta sympathomimetic) induced pulmonary edema
2. Pre-eclampsia
3. Acute fatty liver of pregnancy
4. Septic abortion
5. Amniotic fluid embolism
6. Placental abruption
7. Obstetric hemorrhage
8. Chorioamnionitis
9. Endometritis
10. Pyelonephritis
11. Gastric aspiration

incidence of 80–500 cases per 100,000, and is responsible for 25% of transfers of obstetric patients to intensive care units. Both the normal decrease in serum oncotic pressure that occurs in pregnancy due to a physiologic dilutional hypoalbuminemia and changes in maternal endothelium may explain this pregnancy-related propensity to pulmonary edema.

Causes of ARDS

Eighty-five percent of all ARDS cases result from one of the following four causes, with sepsis being the most common:

- sepsis from pulmonary or nonpulmonary sources
- major trauma
- multiple transfusions
- aspiration of gastric contents.

In the obstetric patient, several causes unique to pregnancy have to be considered. These are listed in Box 1.9. In all cases, the presence of excessive crystalloid administration, anemia and/or multiple gestations can significantly increase the risk that a particular precipitating factor will lead to pulmonary edema.

Pathophysiology

Acute respiratory distress syndrome results from inflammation-induced injury to the alveolar–capillary barrier. In the acute or exudative phase, this leads to flooding of the alveoli with high-protein fluid and subsequent surfactant abnormalities which lead to alveolar collapse and consolidation. Some cases resolve from this phase, which typically lasts 4–7 days, while others progress to fibrosing alveolitis with persistent hypoxemia, increased alveolar dead space, and a further decrease in pulmonary compliance. Pulmonary hypertension, owing to obliteration of the pulmonary–capillary bed, may be severe and may lead to right ventricular failure. After 1–2 weeks, those

cases that progressed may begin to resolve with clearance of pulmonary edema and inflammatory cells and reconstitution of the alveolar–capillary barrier.

Prognosis

Most studies of ALI and ARDS report high case fatality rates, though recent reports suggest that mortality from this disease may be decreasing. In most patients who survive, pulmonary function returns to near-normal levels within 6–12 months, despite the severe injury to the lung. Residual impairment of pulmonary mechanics may include mild restriction, obstruction, impairment of the diffusing capacity for carbon monoxide or gas exchange abnormalities with exercise, but these abnormalities are usually asymptomatic. Persistent pulmonary function disability is more likely in patients who required prolonged mechanical ventilation.

Clinical features

Patients with noncardiogenic pulmonary edema resulting in ALI or ARDS experience acute hypoxemic respiratory failure with evidence of dyspnea, orthopnea, tachypnea and tachycardia. Arterial hypoxemia that is refractory to treatment with supplemental oxygen is a characteristic feature of ARDS. The chest may initially be clear to auscultation, but eventually diffuse crackles and/or wheezing develop. Arterial blood gases in patients with pulmonary edema typically show an initial decrease in both PaO_2 and $PaCO_2$. As the condition worsens, PaO_2 will decrease further but $PaCO_2$ may increase if the patient is no longer able to maintain adequate ventilation. The chest radiograph is usually significant for bilateral diffuse alveolar and interstitial infiltrates. As patients move into the resolution phase, there is gradual improvement in oxygenation and most radiographic abnormalities resolve completely.

Fetal considerations

The effect of maternal ARDS on neonatal outcomes is not well studied, but high rates of fetal death, spontaneous preterm labor and fetal heart rate abnormalities are reported. In one series of 13 patients with ARDS [61] who reached gestational age compatible with viability, the perinatal death rate was 23%. Catanzarite *et al*. [62] reported 10 cases of ARDS in mothers with living fetuses at the time of intubation. Six infants were delivered for fetal heart rate (FHR) abnormalities while four were delivered for maternal reasons. One perinatal death and at least three cases of perinatal asphyxia occurred in the six infants who were delivered for FHR abnormality.

Differential diagnosis

It is important to consider pulmonary edema in the differential diagnosis of ARDS. Pulmonary edema can occur due to cardiac causes such as peripartum cardiomyopathy, ischemic heart disease or occult valvular heart disease and fluid overload. It can also occur in pregnancy due to noncardiogenic causes such as infection, pre-eclampsia or beta-sympathomimetic tocolysis. Unsuspected cardiac abnormalities are not unusual in cases of pulmonary edema even in the setting of pre-eclampsia or tocolytic therapy. Other conditions such as interstitial pneumonia, acute eosinophilic pneumonia, acute bronchiolitis obliterans pneumonia, acute hypersensitivity pneumonitis and diffuse alveolar hemorrhage may have a clinical and radiologic picture similar to ARDS.

Diagnosis

The usual investigations for acute respiratory compromise are summarized in Box 1.10. A chest X-ray is an important initial evaluation but often further investigation is necessary. To clarify possible cardiac causes, a cardiac echo should be considered in any patient with pulmonary edema. An inquiry should be made into any history suggestive of aspiration such as an episode of choking occurring in the setting of altered mental status. A review of the patient's risk factors for thromboembolic disease should also occur and if the onset of the patient's dyspnea was acute and the chest X-ray is not typical for pulmonary edema, a computed tomography (CT) angiogram or

Box 1.10 Usual investigations for acute respiratory compromise

Diagnostic tests indicated in the obstetric patient with ALI

1. Complete blood count (CBC) with differential white blood cell count: Rule out anemia as a contributing factor and look for bandemia suggesting infection
2. Creatinine and blood urea nitrogen (BUN): Rule out renal failure
3. PTT, Fibrinogen and fibrinogen degradation products (FDP): Look for evidence of amniotic fluid embolism
4. AST, uric acid and urine protein creatinine ratio (in addition to above mentioned CBC and Creatinine): Look for evidence of preeclampsia
5. Blood and urine cultures in all patients with fever or bandemia
6. Urine drug screen: Look for evidence of cocaine or narcotics as a cause
7. Echocardiogram: Rule out underlying cardiac cause for pulmonary edema or evidence of cardiac compromise in preeclampsia

ventilation/perfusion scan should be considered. A review of the patient's history for any recent transfusions or drug use should also be carried out. Presence of fever, a history of any infectious exposures (particularly influenza and varicella) and any infectious prodrome may suggest the need for empiric antibiotics.

Management

Pulmonary edema in pregnancy is a medical emergency. Its treatment is summarized in Box 1.11. The first and immediate goal is to maintain adequate maternal oxygenation ($PaO_2 \geq 70$ mmHg equivalent to oxygen saturation 95%) through the use of oxygen supplementation to avoid hypoxia in the fetus. Mechanical ventilation may be needed in severe cases to ensure adequate oxygenation.

For tocolytic-induced pulmonary edema, management consists of immediate discontinuation of tocolytic therapy, initiation of IV loop diuretic and administration of supplemental oxygen. Invasive hemodynamic monitoring is rarely necessary for tocolytic-induced pulmonary edema.

When pulmonary edema is suspected to be related to pre-eclampsia, initial management consists of oxygen supplementation, fluid restriction, and blood pressure control while plans are made for delivery. Judicious use of intravenous furosemide is recommended since many pre-eclamptic patients are relatively volume contracted intravascularly despite having massive amounts of peripheral edema and pulmonary edema. Excessive diuresis of a pre-eclamptic patient can impair maternal renal perfusion, cardiac output, and uteroplacental perfusion, leading to fetal compromise. It is our experience that most patients with pulmonary edema in pregnancy will respond favorably to doses of furosemide as low as 10 mg IV, especially if renal function is normal. Despite the need for careful fluid restriction and gentle diuresis, there is little evidence that central hemodynamic monitoring in these patients improves outcomes and the vast majority of these women can be successfully managed without central or pulmonary artery catherization.

Pulmonary edema in some cases of pre-eclampsia may be cardiogenic. A stiff left ventricle with significant diastolic dysfunction working against a high systemic vascular resistance may contribute. In others, pre-eclampsia-related vasospasm and endothelial effects may induce a transiently stunned myocardium that manifests as ventricular systolic dysfunction. In these cases afterload reduction is appropriate and hydralazine or nitroprusside (or angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in postpartum patients) may be used.

Whether delivery has a positive impact on maternal condition in patients with ARDS is unclear. While there are numerous case reports in which the fetus remained undelivered despite maternal respiratory failure and intubation, most case series in the literature suggest that mothers with ARDS in the third trimester rarely stay pregnant for more than a few days. In general, patients with ARDS secondary to chorio-amnionitis, placental abruption, amniotic fluid embolism and pre-eclampsia need immediate delivery, while those with pyelonephritis or varicella pneumonia can often recover without delivery. The high rates of adverse fetal outcomes do support expeditious delivery for maternal ARDS after 28 weeks gestation.

Box 1.11 Treatment of pulmonary edema

Salient features in management of ARDS in pregnancy

1. Supplemental oxygen to maintain maternal oxygen saturation above 95%
2. Consider intubation for $PaO_2 < 70$ mmHg or $PaCO_2 > 45$ mmHg on 100% oxygen
3. Look for precipitating causes listed in textbox 1 in addition to sepsis, massive transfusion, aspiration of gastric contents or trauma
4. Appropriate diagnostic testing as listed in textbox 2
5. Immediate discontinuation of tocolytic therapy where applicable
6. Fluid restriction
7. IV furosemide 10–20 mg
8. IV antibiotics if infection suspected
9. Echocardiogram to rule out cardiac cause for pulmonary edema
10. Consider afterload reduction with sodium nitroprusside or hydralazine if patient pregnant and angiotensin converting enzyme inhibitors or angiotensin-receptor blockers (ARBs) in the postpartum patient

Ventilatory support in pregnancy

Causes of respiratory failure in the pregnant patient include pre-eclampsia, amniotic fluid embolism, massive obstetric hemorrhage/transfusion, and peripartum cardiomyopathy in addition to all the other causes of respiratory failure that occur outside pregnancy such as pneumonia, aspiration, asthma and ARDS. As discussed earlier in this chapter, $PaCO_2$ is decreased and PaO_2 increased in normal pregnancy. General measures to consider for patients requiring assisted ventilation include noninvasive ventilation (NIV) and endotracheal intubation with ventilation.

Noninvasive ventilation

Noninvasive ventilation refers to ventilation delivered to a patient without the need for endotracheal intubation.

It is often used in nonpregnant patients with acute hypoxic respiratory failure. Its use requires that the patient is able to co-operate, clear secretions and protect her airway and is not appropriate in the setting of other organ failure or when a need for prolonged ventilation is expected. The following are general comments about the typical management of noninvasive ventilation but the reader is cautioned that there are many variables to be considered and its use is best undertaken by individuals with specialized training and ongoing experience with noninvasive ventilation.

Positive pressure ventilation is usually delivered by a full facemask in acute settings but nasal masks and plugs can be used. Ventilation can be assisted through several modalities similar to those used for invasive ventilation. Biphasic positive airway pressure (BiPAP) is a modality unique to NIV and involves both pressure support for inspiration and positive airway pressure during expiration. Patients are typically in a bed or chair at a 30° angle. The mask is selected and fit to allow one or two fingers to fit under the strap. The mask is then connected to the ventilator with the appropriate settings for the modality. Continuous positive airway pressure (CPAP) is typically started at 3–5 cmH_2O and increased in steps of 3–5 cmH_2O as needed and tolerated to 10–15 cmH_2O. BiPAP is typically started at an inspiratory pressure of 8–12 cmH_2O and an expiratory pressure of 3–5 cmH_2O. The inspiratory pressure is gradually increased by 1–2 cmH_2O to alleviate dyspnea and achieve adequate oxygenation. Occasional monitoring of blood gases is important for maximizing the success of therapy. Adjusting the patient's mask straps, checking for air leaks and encouraging and reassuring the patient are also important aspects of successful implementation of NIV.

The use of NIV has not been well studied in an obstetric population. Because of the airway edema and the risk of aspiration in pregnancy, NIV may be a suboptimal mode of ventilation. However, given the lack of reports of adverse events in the literature concerning the risk of aspiration, short trials of NIV may be attempted in pregnancy prior to endotracheal intubation, especially in patients who may not require assisted ventilation for prolonged periods of time. If there are contraindications to NIV or if noninvasive measures fail to provide adequate oxygenation and ventilation, endotracheal intubation must be performed.

Endotracheal intubation

Indications for airway intubation in pregnancy are unchanged compared to the nonpregnant state:

- inadequate oxygenation using less invasive methods (often a $PaO_2 < 70$ on 100% oxygen by nonrebreather mask or NIV)
- airway protection in patients with altered levels of consciousness, inability to clear their secretions or impending airway obstruction
- hyperventilation in the setting of increased intracranial pressure.

The possible need for intubation should always be considered early in patients with acute respiratory difficulties and an anesthesiologist should be notified early to assess a patient's airway. The failure rate for intubations is one in 280 compared to one in 2330 in the general surgical population, with a potential higher risk for cardiac arrest and aspiration [63].

A number of factors may contribute to the difficulties with endotracheal intubation in pregnancy, including anatomic changes such as weight, increased breast size and airway edema. Airway edema may be further exaggerated in patients with a prolonged second stage of labor, excessive intravenous fluids and, particularly, in patients with pre-eclampsia. Morbid obesity also increases the risk of failed intubation and gastric aspiration during procedures requiring general anesthesia. Intubation is further complicated by the fact that pregnant women are more predisposed to aspiration and their lower oxygen reserve leads to a tendency to experience more rapid arterial oxygen desaturation and carbon dioxide retention. Therefore, preoxygenation with 100% oxygen with minimal manual ventilation (to avoid the risk of aspiration) is necessary in this patient population.

Because of the increased risk of serious morbidity and mortality associated with airway intubation in pregnancy, it is important that intubation is performed by the provider with the most extensive experience available. Box 1.12 lists the main points for successful intubation in pregnancy.

Mechanical ventilation

Indications for mechanical ventilation are the same as those listed above as indications for endotracheal intubation and are unchanged in pregnancy. These include status asthmaticus, ARDS, pneumonia and shock but also include situations that are specific to the pregnant population such as amniotic fluid embolism. The following are general comments about the typical use of mechanical ventilation but the reader is cautioned that given the many variables that should be considered in individual patients, clinicians with specialized training and experience with mechanical ventilation should be involved when caring for pregnant women requiring mechanical ventilation.

Mechanical ventilation can be performed in a wide range of modalities including assist control (A/C) and pressure support (PSV), and synchronized intermittent mandatory ventilation (SIMV). Choices among these modalities are often based more on institutional preferences and familiarity rather than distinct advantages of one over the other. Mechanical ventilation is a complicated and potentially dangerous intervention and is best undertaken by individuals who routinely manage ventilated patients. For many patients the initial settings might include:

- the amount of air delivered with each breath (tidal volume) of 6–8 mL per kg of ideal body weight
- a rate of 12–16 breaths per minute

Box 1.12 Key points in airway intubation of the pregnant woman

- Assess airway even in urgent intubations
- Position patient in the left lateral decubitus or left-sided tilt to avoid hypotension from compression of inferior vena cava by gravid uterus
- Avoid aspiration (e.g. do not feed patients who may require emergency intubation, have suction ready). Smaller endotracheal tube size may be necessary
- Use a lower dose of sedatives/anesthetics
- Preoxygenate patient prior to attempting intubation but use minimal manual ventilation when possible to decrease risk of aspiration
- Keep each attempt at intubation brief and separated by brief periods of bag-mask ventilation. Hypoxemia and hypercapnia develop rapidly during periods of apnea in pregnancy due to a physiologic decrease in end-respiratory volumes and increased oxygen consumption
- Be prepared for "next step" if intubation fails by having alternative equipment for the difficult airway readily available (all obstetric centers should have an easily accessible standardized "difficult airway cart" or the equivalent)
- Intubation should be performed by the most experienced provider available
- Obtain a measure of end-tidal CO_2 and CXR to verify correct endotracheal tube placement after intubation. Auscultation is not a reliable method of affirming appropriate placement

• a peak end-expiratory pressure (PEEP, used to keep alveoli open between breaths) of 5–10 cmH_2O
• the lowest fraction of inspired oxygen (FiO_2) to achieve the desired level of oxygenation.

Patients with ARDS, ALI or severe obstructive physiology are managed using the smaller tidal volumes of 6 mL per kg of ideal body weight to avoid ventilator-associated lung injury from alveolar distension.

Mechanical ventilation in pregnancy is managed in a similar manner as in nonpregnant patients but is complicated by the fact that the ventilator parameters need to consider not only maternal hemodynamics and oxygen requirements but also fetal well-being. In the nonpregnant patient, institution of positive pressure ventilation may lead to an increase in intrathoracic pressure and a drop in venous return, leading to a reduction in cardiac output and hypotension. Therefore, careful attention should be paid to the intravascular volume status when a patient is placed on positive pressure mechanical ventilation. All of the above is true for the nonpregnant population, but a reduction in venous return in pregnancy may be even more pronounced in late gestation as the uterine size may impair venous return. Placing the pregnant patient in the left lateral decubitus position or tilting her to the left with a wedge under her right hip may displace the uterus off the inferior vena cava, thereby improving venous flow.

Maintaining fetal oxygenation is clearly a significant concern in mothers with acute respiratory failure requiring mechanical ventilation. Data from chronically hypoxic high-altitude residents suggest that growth restriction and pre-eclampsia are potential complications. It is important to recognize that data on the fetal effects of short periods of desaturations in humans are lacking. Fetal oxygenation is more dependent on PaO_2 than it is on oxygen saturations and therefore, more frequent blood gases would be required in the pregnant patient. Although human data on this issue are lacking and most of the evidence is extrapolated from animal models, it would be reasonable to keep maternal PaO_2 above 70 mmHg to avoid fetal compromise. However, it should be noted that supranormal maternal PaO_2 does not carry any benefit since the maternal–fetal gradient of O_2 increases substantially as maternal PaO_2 increases. Continuous fetal monitoring should be initiated when there is an acute change in maternal respiratory status, especially upon initiation of mechanical ventilation. Once the pregnant gravida is appropriately oxygenated, intermittent monitoring (3–4 times/day) may be performed.

Managing mechanical ventilation in the pregnant patient should also consider the adverse effects of hypercapnia and hypocapnia on the fetus and the uteroplacental circulation. A gradient of 10 mmHg exists between the mother and the fetus (the fetus being 10 mm higher). Fetal hypercapnia may be associated with fetal acidosis, an increase in intracranial pressure and levels above 70 mmHg may adversely affect the uterine and placental circulation. In addition, hypercapnia in the first 72 hours of life may lead to retinopathy of prematurity. On the other hand, maternal hypocapnia is not harmless either, as it may lead to uterine artery vasoconstriction. In addition, $PaCO_2$ changes may lead to a “shift” in the oxygen hemoglobin dissociation curve. Increases in $PaCO_2$ will shift this curve to the right, meaning an elevated $PaCO_2$ is associated with a decrease in affinity of hemoglobin for oxygen (decreasing oxygen uptake by blood but facilitating

the delivery of oxygen by blood to tissue). Decreases in $PaCO_2$ will shift this curve to the left, meaning a decrease in $PaCO_2$ is associated with an increase in affinity of hemoglobin for oxygen (increasing oxygen uptake by blood but potentially decreasing the delivery of oxygen by blood to tissue). When possible, the maternal $PaCO_2$ in ventilated patients should likely be kept in the range 28–32 mmHg seen in healthy pregnancies.

These goals can represent a challenge when caring for pregnant patients with ARDS. As mentioned above, when ventilating a patient with ARDS, the preponderance of evidence suggests clear mortality and other clinical benefits to using the low tidal volume method [64]. However, the low tidal volume method is frequently associated with hypercapnia (called permissive hypercapnia) and respiratory acidosis, which may be problematic for the fetus. Although bicarbonate infusions have been used to correct acidemia in the nonpregnant patient subjected to permissive hypercapnia, it is not clear whether the rate of transfer of bicarbonate is adequate to protect the fetus from the deleterious effects of maternal hypercapnia. Decisions regarding where to strike the best balance between the risk of maternal ventilator-related lung damage and the desire to maintain normal blood gases during pregnancy need to be individualized but should be guided by the principle that fetal well-being is first and foremost dependent on maternal well-being.

Amniotic fluid embolism

First described in 1941 by Steiner & Lushbaugh [65], amniotic fluid embolism (AFE) has potentially devastating consequences. It is rare, with an estimated incidence of 1.25 (England) to 7.7 (US) per 100,000 births and a case fatality rate of 22%. It remains one of the leading causes of maternal mortality in the developed world, accounting for 6.4% of maternal deaths in Wales [66,67]. Patients who survive may suffer some degree of hypoxic encephalopathy.

Oft-cited risk factors include advanced maternal age, eclampsia, fetal distress, grand multiparity, cesarean or operative delivery, placenta previa, placental abruption, medical induction of labor, and tumultuous or precipitate labor. However, evidence to support any of these as definitive risk factors for AFE is inconclusive.

A classic clinical presentation is the sudden onset of acute respiratory distress associated with hemodynamic collapse (due to cardiac dysfunction that may be complicated by arrhythmias) and disseminated intravascular coagulation (DIC) occurring at the time of labor and delivery and often resulting in death. Cases have been reported in the first trimester, with amniocentesis, and up to 48 hours post partum. Nonspecific symptoms such as nausea, vomiting, chills, and agitation may presage the sudden cardiovascular collapse.

How the amniotic fluid gains access to the maternal vasculature to initiate this cascade of events is unclear but it has been conjectured that the site of entry involves the placenta or cervical tears. Steiner & Lushbaugh suggested that forceful uterine contractions against membranes that may remain partially intact over the cervical os and/or particularly against an applied fetal head could then force amniotic fluid into the maternal circulation. However, cases of AFE have been reported to occur at the time of amniocentesis. At autopsy, fetal material including squamous cells, vernix or fat globules, and lanugo hairs have been found in the maternal pulmonary vasculature. However, the presence of these factors is frequent in the maternal circulation even in patients who have not suffered a clinical picture consistent with AFE. Thus, it has been suggested that AFE may actually represent an anaphylactoid reaction to pregnancy, with a mechanism unrelated to physical presence of fetal materials in the maternal circulation. Gross findings at autopsy have been dilation of the right heart with right-sided vascular congestion, suggesting acute obstruction of the pulmonary vasculature, but also consistent with acute, severe right ventricular failure. Further complicating the clinical picture is hemorrhage and DIC. It has been postulated that ABO incompatibility between the fetal and maternal blood groups could also contribute to the severity of this clinical picture.

Treatment is supportive, with early ventilatory and hemodynamic support. Patients often require extensive blood product support. Although the condition is rare enough that there is no clearly proven course of action to take in caring for these patients, all of the following are commonly recommended:

- cardiac rhythm, pulse oximeter and blood pressure monitoring
- consideration of pulmonary artery catheterization
- intubation and mechanical ventilation
- consideration of fluid, norepinephrine and/or dopamine to maintain blood pressure
- delivery of the fetus if this has not already occurred.

Those patients who do survive often follow a course more consistent with anaphylaxis or pulmonary edema and do not tend to run a protracted course as is seen with ARDS.

Pulmonary hypertension

Pulmonary hypertension (PAH) is a life-threatening disease characterized by elevated pulmonary arterial pressures. Previously described as primary or secondary, pulmonary hypertension now has a clinical classification with five distinct categories, listed in Box 1.13. This section will deal with pulmonary arterial hypertension (Group 1) in pregnancy.

Pulmonary hypertension is defined as pulmonary artery pressure greater than 25 mmHg at rest or 30 mmHg with exercise, when measured by right heart catheterization, in the presence of normal pulmonary capillary wedge pressure. PAH occurs more commonly in women in their third or fourth

Box 1.13 Revised clinical classification of pulmonary hypertension (Venice 2003)

1. Pulmonary arterial hypertension (PAH)
   - 1.1 Idiopathic (IPAH)
   - 1.2 Familial (FPAH)
   - 1.3 Associated with (APAH):
     - 1.3.1 Collagen vascular disease
     - 1.3.2 Congenital systemic-to-pulmonary shunts
     - 1.3.3 Portal hypertension
     - 1.3.4 HIV infections
     - 1.3.5 Drugs and toxins
     - 1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorderes, splenectomy)
   - 1.4 Associated with significant venous or capillary involvement
     - 1.4.1 Pulmonary veno-occlusive disease (PVOD)
     - 1.4.2 Pulmonary capillary hemangiomatosis (PCH)
   - 1.5 Persistant pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
   - 1.1 Left-sided atrial or ventricular heart disease
   - 1.2 Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Sleep-disordered breathing
   - 3.4 Alveolar hypoventilation disorders
   - 3.5 Chronic exposure to high altitude
   - 3.6 Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   - 4.1 Thromboembolic obstruction of proximal pulmonary arteries
   - 4.2 Thromboembolic obstruction of distal pulmonary arteries
   - 4.3 Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous
   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

decade. It is a progressive disease which is usually fatal. There are numerous causes of PAH including idiopathic PAH (both sporadic and familial), collagen vascular disease, left-to-right intracardiac shunts, anorectic drugs, stimulants (e.g. cocaine, methamphetamine), HIV, and portal hypertension. The presence of medial hypertrophy, intimal fibrosis or fibrinoid necrosis, arteritis and plexiform lesions in the pulmonary vasculature may be evident on histology.

Due to an inability to increase cardiac output with exercise, most patients with PAH initially experience exertional dyspnea, lethargy, and fatigue. As the PAH progresses and right ventricular failure develops, exertional chest pain, exertional syncope, and peripheral edema may develop. Passive hepatic congestion may cause anorexia and abdominal pain in the right upper quadrant. Cough and hemoptysis occur less often. The initial physical finding is usually increased intensity of the pulmonic component of the second heart sound, which may even become palpable. Signs of right heart failure such as elevated jugular venous pressure, third heart sound, hepatomegaly, a pulsatile liver, peripheral edema, and ascites may occur as PAH worsens and RV failure occurs. Patients with idiopathic PAH (IPAH) have a survival of only 3 years without treatment and less than 1 year if the pulmonary hypertension is severe.

Treatment may include any of the following, depending on the type of PAH that the patient has: diuretics, home oxygen, anticoagulation, digoxin, exercise, and advanced therapy with calcium channel blockers (typically nifedipine and helpful in only a small proportion of patients), prostanoids (e.g. epoprostenol, trepostinil, iloprost), endothelin

receptor antagonists (e.g. ambrisentan, bosentan) or phosphodiesterase-5 inhibitors (e.g. sildenafil). Creation of a right-to-left shunt with an atrial septostomy and lung transplantation are options for patients unresponsive to these medical options.

Pregnancy is poorly tolerated in women with significant PAH. In a normal pregnancy, the pulmonary vascular resistance decreases. However, in pregnant women with PAH, the increase in cardiac output coupled with an inability to decrease pulmonary vascular resistance can lead to increased pulmonary artery pressure. In addition, the hypercoagulable state in pregnancy predisposes these women to thromboses in the pulmonary vascular bed which may further worsen pulmonary hypertension.

Maternal mortality in PAH is as high as 30% [68]. In a review of published reports, most of the deaths occurred in the third trimester, with the highest risk in the first 10 days post partum. In view of the high maternal mortality, preconception counseling is of vital importance. Such counseling should emphasize the reduced life expectancy of the patient herself, as well as the significant risk of mortality with pregnancy and poorer fetal outcomes. If a woman does become pregnant and chooses not to proceed with pregnancy, it should be understood that some women with significant pulmonary hypertension may also have difficulty tolerating some termination of pregnancy procedures.

Management of pregnant women with PAH requires close monitoring. Limited data suggest that pregnant patients with pulmonary hypertension who are admitted to hospital early have a better prognosis. Heparin use throughout the pregnancy is recommended because these patients are at increased risk for venous thromboembolism as well as for *in situ* thrombosis. Given the life-threatening nature of this condition, use of any agent effective for treating PAH in nonpregnant patients seems justifiable even in the absence of extensive pregnancy data. Other measures that should be considered in pregnant patients with PAH include work-up and treatment of obstructive sleep apnea (see below) to limit nocturnal arterial oxygen desaturations that may worsen pulmonary artery pressures further.

In patients with PAH, labor and delivery are best performed in a controlled setting with a multidisciplinary team including an obstetrician, maternal-fetal medicine specialist, a pulmonologist and/or a cardiologist experienced in the care of PAH, obstetric anesthesiologist and obstetric internist. Full resuscitation facilities and access to an intensive care unit should be readily available. Some experts recommend right heart catheterization in the intrapartum and postpartum period. Early epidural anesthesia is advisable to control oxygen consumption and minimize the catecholamine surge. Slow administration of the epidural to minimize hypotension is preferred. Supplemental oxygen should be administered. Vasodilator therapy with epoprostenol or nitric oxide should be considered during labor and delivery. Fluid overload should be strictly avoided during labor and in the postpartum period. However, early and aggressive management of postpartum hemorrhage and hypotension is also essential. Patients with severe pulmonary hypertension are encouraged to use nonestrogen-containing contraceptive methods.

Obstructive sleep apnea

Obstructive sleep apnea (OSA) is defined as a combination of disturbed sleep with more than five episodes of apnea/hypopnea per hour at night and daytime symptoms of sleepiness, poor concentration or fatigue. Snoring is a prominent feature of the disease. It is a common condition affecting 9–12% of women and is more common with age, obesity and in African Americans. Untreated OSA can lead to hypertension, pulmonary hypertension, arrhythmias and right-sided heart failure caused by the effects of chronic intermittent hypoxia during the night. Cases suggestive of sleep apnea are confirmed using a sleep study (polysomnography). Treatment includes weight loss, avoidance of alcohol, and the use of positive pressure airway devices or surgery.

The significance of OSA in pregnancy is as yet unclear but there are case reports and reasons for concern. Physiologically, the increased minute ventilation of pregnancy, increased upper airway dilator muscle activity, and decreased REM sleep could potentially decrease the likelihood of OSA. However, other competing factors favoring the development of OSA include increased mucosal edema and hyperemia, decreased oropharyngeal junction (even smaller in pre-eclamptics) and decreased functional residual capacity. Snoring, a marker for OSA, is common in pregnancy, occurring in up to 44% of pregnant women [69]. Further, there is evidence suggesting an association between adverse pregnancy outcomes and OSA. In a case series of 502 women, snoring was found to be an independent risk factor for hypertension and pre-eclampsia even when adjusted for age and weight [70]. Snoring has also been found to be associated with fetal growth restriction [71]. Sleep-disordered breathing, including arterial oxygen desaturations, occurs more in patients with pre-eclampsia than in controls. Interestingly, both pre-eclampsia and OSA are associated with increased inflammatory markers, endothelial dysfunction, obesity and hypertension.

While the prevalence and significance of OSA are not known, screening should be considered in pregnant women in the appropriate setting such as obesity, excessive weight gain, hypertension, snoring, excessive daytime somnolence, and headaches. Once diagnosed in pregnancy, OSA should be treated with CPAP. There are available data in small numbers of patients to suggest that OSA may improve in the postpartum period, even in patients on no therapy. The experience of these authors supports these findings. However, some women will continue to require longer term treatment, suggesting that their sleep apnea was not recognized prior to pregnancy.

Cystic fibrosis

Over the past three decades, the survival of patients with cystic fibrosis (CF) has dramatically improved, resulting in more women with CF reaching reproductive age. Currently about 140 pregnancies in CF women are reported annually to the US Cystic Fibrosis Foundation Registry, with approximately 100 resulting in livebirths.

Pathophysiology

Cystic fibrosis is an autosomal recessive disorder that results from a defect in the CF transmembrane conductance regulator (CFTR) gene. Abnormal production or function of the CFTR protein leads to a dysfunctional chloride channel and subsequent impaired sodium and water transfer across glands in many organ systems. Glandular secretions become thick and tenacious, predisposing to organ failure. While any organ with a significant exocrine component may be affected, most clinically significant disease arises in the lungs, gastrointestinal tract and pancreas. Sweat chloride remains the primary diagnostic test for this disorder and is abnormal if >60 mmol/L.

In the respiratory system, bacterial colonization and recurrent airway infections result in permanent dilation of bronchi (bronchiectasis) and an obstructive physiology. Respiratory failure is the leading cause of death in the vast majority of patients with CF. Pancreatic insufficiency is another common manifestation of CF. Both the male and female reproductive tracts are affected by mutations in CFTR, leading to infertility. Life expectancy for patients with CF has risen steadily since the middle of the last century and the median predicted survival now sits at 35 years of age.

Treatment of CF is reviewed in Box 1.14 and applies equally to both nonpregnant and pregnant patients (see below). Lung transplantation is offered to patients with progressive or severe pulmonary functional impairment (e.g. FEV_1 <30% of predicted, hypoxemia, hypercapnia) or major life-threatening pulmonary complications (e.g. recurrent massive hemoptysis).

Pregnancy

Obstructive azoospermia is the most common cause of infertility in men; however, nonobstructive causes including reduced spermatogenesis, reduced semen volume and low semen pH have also been recognized. Unlike men with CF, women with CF usually have anatomically normal reproductive tracts but infertility remains a significant problem in up to 20% of patients. Amenorrhea (likely caused by patients being anovulatory due to being underweight) and tenacious cervical mucus are two contributing factors.

With improved survival and health outcomes in women with CF, the number of pregnancies in these women has also increased. Although earlier reports of pregnancy in CF were discouraging, recent publications have attested to the safety of pregnancy in CF women with good lung function.

Box 1.14 Management of cystic fibrosis

1. Respiratory
   a. Antibiotics for treatment and prevention of bacterial infection and colonization
   b. Clearance of thick pulmonary secretions using chest PT, postural drainage, mucolytics (DNase I)
   c. Treatment of bronchospasm and airway inflammation with beta-agonists and steroids
2. Gastrointestinal
   a. Ensure adequate calorie intake
   b. Pancreatic enzyme supplementation
   c. Supplementation of fat-soluble vitamins A, D, E and K
3. Metabolic
   a. Treatment of CF-related diabetes mellitus and impaired glucose tolerance

Long-term survival is not negatively affected by pregnancy in women with CF. In a cohort study of 680 women with CF, followed between 1985 and 1997, 10-year survival rate was higher for women who had been pregnant when compared to never-pregnant controls [72]. Pregnancy was not harmful even in those patients whose FEV_1 was <40% predicted at baseline or those with insulin-dependent diabetes, pancreatic insufficiency or *Pseudomonas aeruginosa* colonization. However, whether the women with CF who became pregnant were somehow healthier than those who did not is not clear.

Cystic fibrosis patients have more outpatient visits and hospitalizations during pregnancy than their baseline and when compared with never-pregnant CF women. Pregnant women may also need more intravenous antibiotics and supplemental nutrition

Pulmonary function may decline in pregnancy but significant irreversible loss of lung function does not occur. CF patients have a tendency to develop gallstones; this risk likely increases somewhat during pregnancy. Pancreatic dysfunction in CF is associated with decreased insulin production which has also been noted in pregnancy. Furthermore, pregnancy in CF is also associated with decreased insulin sensitivity, increased protein turnover and less response to insulin's anticatabolic effect. These changes predispose pregnant CF women to early development of diabetes and poor weight gain. CF patients have higher caloric requirements at baseline secondary to increased work of breathing, poor intestinal absorption and increased metabolic rate related to the inflammatory effects of the disease. Those metabolic demands rise even further during pregnancy.

The ACOG Committee on Genetics recommends that prenatal and preconception carrier screening for CF should be available to all couples regardless of race or ethnicity [73]. All children of a mother with CF will be obligate CF carriers. If the biologic father is of European descent, approximately 2% of children born to a CF mother would be expected to have the disease. Paternal screening for CF should be recommended prior to conception. For postconception diagnosis of CF in the fetus, amniocentesis with genetic analysis can be performed.

The offspring of women with CF may be at increased risk for prematurity and low birthweight [74]. However, other studies have shown a median gestational age of over 40 weeks and a median birthweight of 3.2 kg. Neither the rate of abortions nor that of congenital anomalies is increased in CF women. The overall perinatal mortality rate (7.9–11%) seems to be increased and is directly related to the severity of CF [75] but reports of perinatal mortality vary significantly among available registries. The difference in these reports of neonatal outcomes, including mortality, is likely explained by variations in the access to care and the application of standard of care to these patients. Severity of the disease at the time of conception likely plays an important role in predicting outcomes as well. Risk factors for poor obstetric outcome include severe pulmonary dysfunction, pulmonary hypertension, hypoxemia and poor maternal nutrition. In addition, the likelihood of suffering the loss of the affected parent prior to achieving adulthood is high for children born to CF women [76].

Management

Clinical management of CF involves a multidisciplinary team with medical, nursing, nutrition, physical therapy, social work and sometimes psychotherapy staff. Box 1.14 lists salient features in CF management. Special considerations may apply additionally during pregnancy.

Routine management of CF should be continued throughout gestation as needed. As with any medical issue in pregnancy, the safest possible therapeutic agent should be chosen.

Chest physical therapy should be continued aggressively. Antibiotics, including quinolones, should be used when necessary. Parenteral therapy with aminoglycosides is considered safe in pregnancy. Inhaled tobramycin and colistin have little systemic absorption and can also be safely used. Inhaled beta-agonists and inhaled steroids can be used to improve respiratory function during pregnancy. Short-term use of oral or parenteral steroids may be necessary in some patients. Chronic inhalation therapy with DNAse-I has been shown to reduce the viscosity of sputum and improve lung function. Limited data are available on its use in pregnancy. However, given that systemic absorption from inhaled therapy is minimal, cautious use may be justified under certain circumstances. Supplemental oxygen may be necessary if there is evidence of hypoxia, particularly in late gestation. Nutritional supplementation may be necessary if normal weight gain is not sustained. Regular assessment of fetal growth should be undertaken and if the growth rate slows then more intensive surveillance for fetal well-being and timely delivery are indicated. The mother may need admission for nutritional supplementation and supplemental oxygen. Maternal weight gain and nutritional status should be monitored closely throughout gestation with greater calorie and protein intake than recommended for normal pregnancy. The 1998 CF Foundation Consortium recommends that all pregnant CF patients have an oral glucose tolerance test (OGTT) to screen for diabetes before pregnancy and at the end of each trimester or until diabetes develops [77]. In patients with pre-existing diabetes, insulin requirements may increase.

Delivery and postpartum issues

Vaginal delivery with optimal pain control and supplemental oxygenation is recommended for all women with CF, with cesarean section being reserved for obstetric indications. Mothers who have CF should be closely monitored for disease exacerbation in the postpartum period, especially because decreased adherence to a medical regimen is common in new mothers. Successful breastfeeding in CF mothers is possible. Breast milk from women who have CF has normal sodium and protein levels, with lipid levels sufficient for the nursing needs of the infant.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterized by an irreversible or partially reversible airway obstruction with mucus hypersecretion and ciliary dysfunction on pathologic examination. Though COPD is the fourth leading cause of mortality in the USA and Europe, it is not common during the childbearing years unless there are significant predisposing factors present. The most common risk factor for COPD is cigarette smoking. Other risk factors include chronic exposure to certain environmental factors, airway hyper-responsiveness, recurrent childhood infections and genetic predisposition such as alpha-1 antitrypsin deficiency. Women are more predisposed to developing COPD than men, because of their smaller airway size and an apparently greater susceptibility to smoking [78].

A Th1-dominated response is prominent in COPD and leads to interferon-gamma and tumor necrosis factor (TNF) production. TNF is thought to be responsible for systemic manifestations such as cachexia and peripheral muscle wasting.

The main manifestation of COPD in women is dyspnea on exertion that worsens with disease progression. Sputum production is more common in men. Systemic manifestations of the disease include cachexia and peripheral muscle

wasting. COPD may also predispose to osteoporosis and cardiovascular disease. Signs on physical examination include tachypnea, a prolonged expiratory phase, wheezing and rhonchi. Signs of right-sided heart failure may be seen in patients with more advanced disease. COPD is usually diagnosed later in women, and after more prominent symptoms than it is in men. This is in part secondary to physician bias against the diagnosis of the disease in women.

Pulmonary function tests usually help establish the diagnosis. According to the GOLD criteria [79], a postbronchodilator $FEV_1/FVC < 70$ is diagnostic of COPD.

Pregnancy

Chronic obstructive lung disease is rare in women of childbearing age. One case report [80] described a woman with bullous emphysema secondary to alpha-1 antitrypsin deficiency who delivered a healthy baby despite a spontaneous pneumothorax that required a chest tube at 21 weeks of gestation. A pregnant patient was treated at our institution for two episodes of spontaneous pneumothoraces that were secondary to extensive bullous emphysema. The patient had a chest tube placed on both occasions and delivered a healthy baby. No information was available at the time of her pregnancy regarding her lung function.

It is not known whether pregnancy may affect the course of COPD since the reported cases are minimal and the disease is rare in the childbearing years. Patients should continue to use their prescribed inhaled medications and their treatment in pregnancy should not be different from the treatment outside pregnancy. Smoking should be strongly discouraged and clear directions given to help with quitting. Ipratropium has no reported teratogenic effects in pregnant rats and rabbits and has no reported cases of teratogenicity in humans. Ipratropium is preferred to tiotropium as the latter is less well studied in pregnancy. Both short-acting and long-acting beta-agonists are thought to be safe in pregnancy. Oxygen home therapy is given to nonpregnant COPD patients with a $PaO_2 \leq 59$ mmHg or a oxygen saturation of $\leq 88\%$ but should be considered in pregnancy if there is a $PaO_2 \leq 70$ mmHg or oxygen saturation of $\leq 95\%$ at sea level.

Kyphoscoliosis

Kyphoscoliosis is a spinal deformity characterized by abnormal curvature of the spine. It is uncommon, with reported incidence in pregnancy varying from 0.02% to 0.7%. The primary concern with kyphoscoliosis is that there may be cardiopulmonary compromise due to the mechanical restriction caused by the spinal deformity and this may be further exacerbated by pregnancy-related respiratory changes. However, with aggressive treatment of kyphoscoliosis early in life, marked restriction of pulmonary function can be prevented and current literature suggests that most women with kyphoscoliosis experience normal pregnancy and delivery. In a cohort study, most women who had prior surgical or brace treatments for scoliosis experienced normal pregnancies, with rates of cesarean section and back pain similar to the general population [81]. As in cystic fibrosis, the limiting factors are hypoxemia, pulmonary hypertension and mechanical issues. In patients with severe kyphoscoliosis and hypoventilation, noninvasive ventilatory support can be an option. Epidural or spinal anesthesia may be technically challenging because of the spinal deformity and may lead to an incomplete or unilateral block. These patients are more likely to require cesarean section, because of associated abnormalities of the bony pelvis and abnormal presentation of the fetus. Patients with achondroplasia and other chondrodystrophies may have similar though less severe respiratory and pelvic problems.

Erythema nodosum

Eyrthema nodosum (EN) [82] is a rare disorder, characterized by the presence of inflammatory, tender, nodular lesions, usually located on the anterior aspects of the lower extremities. It is seen most often in women of reproductive age. The process may be associated with a wide variety of diseases, including infections, rheumatologic and autoimmune diseases, inflammatory bowel disease, medications, pregnancy, and malignancies.

Box 1.15 lists some of the conditions associated with EN. Most patients with EN have either an antecedent streptococcal infection or no identifiable cause. Although its pathogenesis is unclear, it is presumed to be a delayed hypersensitivity reaction to antigens associated with the various conditions mentioned above.

The typical eruption is quite characteristic and consists of a sudden onset of symmetric, tender, erythematous, warm nodules and raised plaques usually located on the shins, ankles and knees. Lesions are usually bilateral and may rarely extend to the thighs, anterior aspect of arms and even the face. Within a few days, the nodules evolve into bruise-like lesions which resolve without scarring over 6–8 weeks. Ulceration is never seen with EN.

Diagnosis is mostly clinical, with biopsy reserved for atypical cases and in areas where tuberculosis is endemic. Recommended diagnostic testing is aimed at trying to establish probable cause and includes complete blood count (CBC) with differential, liver function tests, creatinine and urinalysis, antistreptolysin-O titer at diagnosis and 2–4 weeks later (to assess for antecedent streptococcal infection), plain chest radiograph (to assess for hilar adenopathy or other evidence of pulmonary sarcoidosis, tuberculosis or fungal infection) and skin testing for tuberculosis.

Erythema nodosum is self-limited and treatment should be directed at the underlying disorder, if identified. Nonsteroidal

Box 1.15 Conditions associated with EN

- Bacterial infections
  - Streptococcal infections
  - Tuberculosis
  - Syphilis
  - Mycoplasma and Chlamydia infections
- Viral infections
  - CMV
  - Hepatitis B and C
  - HIV
- Fungal infections
- Parasitic infections
- Medications
  - Oral contraceptives
  - Certain antibiotics (including amoxicillin, sulfamethoxazole, nitrofurantoin)
- Malignancy
- Pregnancy
- Sarcoidosis
- Inflammatory bowel disease
- Behçet's disease
- Chronic active hepatitis
- Rheumatoid arthritis
- Reiter's syndrome
- SLE
- Wegener's granulomatosis

anti-inflammatory drugs and potassium iodide, which are used for symptomatic relief in the nonpregnant population, are best avoided in pregnancy. Oral steroids, starting at 40 mg/day and tapered over a few days, may be an option but should be used with caution, keeping in mind the possibility that an underlying neoplastic, inflammatory or infectious condition may be masked.

Sarcoidosis

Sarcoidosis is a multisystem disease of unclear etiology that is characterized by the presence of noncaseating granulomas in the affected organs, which mainly include lungs, lymph nodes, eyes and skin. It can affect individuals between the ages of 20 and 40 years and therefore women of childbearing age represent a group at risk for the disease. The prevalence of the disease is estimated to be 10–20 per 100,000 with a lifetime incidence of 0.85% among whites and 2.4% among blacks in the US.

Sarcoidosis most commonly affects the lung, and cough, dyspnea, and chest pain are common manifestations. However, most cases are detected incidentally on routine chest radiographs before symptoms of sarcoidosis develop. Chest X-ray findings can vary and may be normal or show evidence of hilar lymphadenopathy and/or reticular opacities. Pulmonary function tests may show restrictive or obstructive disease with variable degrees of reduction in the diffusion capacity.

Other common manifestations of sarcoidosis include hypercalciuria and hypercalcemia rashes (erythema nodosum, skin nodules, and maculopapular eruptions), lymphadenopathy, inflammation of the eye (iridocyclitis, chorioretinitis, and keratoconjunctivitis) and hepatic infiltration. Less commonly, sarcoidosis can affect the spleen, neurologic system, bone marrow, heart, kidney, bones, joints, salivary glands, the ear, nose and throat, and muscles.

Although reproductive organs may be affected by the disease, there is no evidence that sarcoidosis affects fertility. No data suggest that patients with sarcoidosis have a higher risk of maternal, fetal or neonatal complications.

There is no single standard way to monitor patients with sarcoidosis. Frequency and type of evaluation will be determined by severity of disease, organs affected and whether treatment has been initiated. Typically patients should have a review of symptoms, physical examination, spirometry and a diffusing capacity (DLCO, a measurement of gas exchange that is very sensitive to the presence of interstitial lung disease) every 3–4 months and a CBC, creatinine, calcium, liver function tests, EKG and ophthalmologic exam yearly or more often if symptomatic or previous abnormalities of these tests have been identified.

Systemic steroids are the mainstay of treatment for sarcoidosis but their use is generally reserved for those with significant symptoms such as ocular disease or pulmonary compromise. It is not clear if steroids affect the long-term course of the disease in more mild cases. A variety of agents are used to treat the minority of cases unresponsive to steroids and include chloroquine, hydroxychloroquine, methotrexate, azathioprine, cyclophosphamide, cyclosoporine and infliximab.

Pregnancy usually has no effect on the course of the disease, but it may result in a temporary improvement. Women with a normal chest radiograph or those without active disease tend to remain stable during pregnancy and the postpartum period. Active disease that is present before pregnancy may show partial or complete resolution during pregnancy, but may relapse 3–6 months post partum.

Pregnancy in a woman with sarcoidosis does not merit a change in frequency of monitoring, which should be dictated by the patient's clinical status. Indications for steroid therapy are unchanged in pregnancy although potential complications of hyperglycemia and infections should be watched for. Stress-dose steroids should be considered at the time of labor in women who have required daily doses of 5 mg or more of prednisone for 3 or more weeks in the year preceding delivery (see Chapter 47). Pre-existing hypoxia, severe restrictive lung disease and secondary pulmonary hypertension increase the risk of maternal and fetal complications.

Management of labor and delivery should be directed by obstetric indications, with general goals aimed at decreasing pain and oxygen consumption. Maternal hypercalcemia can lead to neonatal hypocalcemic tetany and seizures, therefore calcium levels should perhaps be monitored more closely in pregnancy – we would typically do so once a trimester. Fortunately, the hypercalcemia in sarcoidosis is rarely severe and is not likely to lead to neonatal complications. Vitamin supplements with calcium and vitamin D may exacerbate hypercalcemia and should probably be avoided in pregnant patients with sarcoidosis.

Wegener's granulomatosis

Wegener's granulomatosis (WG) is a rare form of systemic vasculitis in which necrotizing granulomatous lesions affect the upper respiratory tract (particularly the nose – causing perforation of the septum), lungs and kidneys. It presents with nasal symptoms, hemoptysis, general malaise or renal failure often accompanied by systemic symptoms of night sweats, fever, weight loss and anorexia. Up to a third of patients will also have cranial or peripheral neuropathies. Diagnosis is confirmed by blood testing for circulating antineutrophil cytoplasmic antibodies (ANCA, both c-ANCA (cytoplasmic) and p-ANCA (plasma)) and biopsy of affected tissue. Patients with WG are at an increased risk of venous thromboembolism that may be as high as 7 per 100 person-years. Untreated, WG is rapidly fatal, with up to 90% of patients dying within 2 years. Treatment with a combination of cyclophosphamide and glucocorticoids, however, has improved survival to 80%, with 75% of patients achieving complete remission. Once remission has been achieved (usually in 3–6 months), patients are typically placed on azathioprine or methotrexate for maintenance therapy. Cyclophosphamide is discontinued and steroid therapy tapered and stopped.

Patients with WG are typically followed on the basis of their symptoms, laboratory parameters (including serial creatinine, BUN, microscopic urine examination, quantification of urinary protein, liver function tests, complete blood count and chest X-ray) and their titer of ANCA. The frequency of testing will depend on symptoms, disease activity and treatment.

The condition is now being diagnosed more frequently in or before pregnancy as less severe cases are recognized and treated earlier with prednisone and cyclophosphamide. There is insufficient experience to comment whether the course of WG is affected by pregnancy. On balance, most reports suggest that pregnancy is associated with exacerbation of the disease but this may just represent selective reporting. It is not likely that the course of WG has direct effects on the fetus aside from the risks associated with maternal organ dysfunction and treatment.

While prednisone may be used throughout pregnancy (see Chapter 47), cyclophosphamide is potentially teratogenic; normal and malformed offspring have been reported following first-trimester use. Patients who have WG should therefore ideally wait until they are in remission so that cyclophosphamide can be stopped before pregnancy and introduction of maintenance therapy with azathioprine has been accomplished. Patients should be informed, however, that cyclophosphamide may affect their subsequent fertility by causing premature ovarian failure. Patients who have conceived while taking cyclophosphamide should be offered the option of termination because of the risks of both the disease and its treatment. The use of azathioprine in pregnancy is discussed in Chapters 8 and 10 but its use in pregnancy is readily justifiable for the treatment of WG. Methotrexate use in pregnancy is contraindicated, however.

For patients who present with new-onset or a relapse of WG in pregnancy, cyclophosphamide has been used in the latter half of pregnancy with good outcomes. Although transient leukopenia and intrauterine growth restriction have been reported (and there is always the concern about the potential for alkylating agents to induce leukemia), the very serious nature of this disease makes its use in pregnancy for this indication readily justifiable.

Monitoring of patients with Wegener's disease should not be significantly altered in pregnancy from what is described above. Establishment of "baseline" values prior to 20 weeks may be helpful if features of pre-eclampsia arise later in the pregnancy.

Pulmonary lymphangioleiomyomatosis

Pulmonary lymphangioleiomyomatosis (LAM) is a rare disease that primarily affects women, particularly in their childbearing years. It is characterized by non-neoplastic proliferation of atypical smooth muscle cells in the lung parenchyma and cyst formation. It presents similarly to asthma or COPD rather than as an interstitial lung disease. It results in progressive loss of lung function and eventually death. It may occur sporadically or in association with tuberous sclerosis. A variety of intra- and extrathoracic complications have been associated with pulmonary LAM, including spontaneous pneumothorax, chylothorax and chyloperitoneum (chylous lymphatic fluid and free fatty acids in the pleural or abdominal space). Renal angiomyolipomas and meningiomas also occur frequently. Patients present with breathlessness or with symptoms from pneumothorax or chylothorax. In general, the diagnosis should be strongly suspected in any young woman who presents with emphysema, recurrent pneumothorax or a chylous pleural effusion.

Chest radiology may be normal initially or show interstitial thickening, pneumothorax or pleural effusion. High-resolution CT (HRCT) scanning may be necessary to show the typical small cystic changes. Lung function tests show air flow obstruction and characteristically low gas transfer

factor. HRCT can often confirm the diagnosis, and tissue confirmation may not always be necessary, especially if a diagnosis of tuberous sclerosis has already been established.

Early reports suggested that most patients died within 10 years of diagnosis. More recent studies, possibly in patients diagnosed earlier in the course of the disease, are more optimistic. Taylor *et al*. [83] found that 78% of patients were alive 8 years after diagnosis. Evidence from case series of close to 70 patients suggest that the risk of complications is higher during pregnancy than at any other time in a woman's life. In another series that described six out of 50 patients who became pregnant and continued their pregnancies, five had very complicated pregnancies with recurrent pneumothoraces and three lung surgeries were required during the pregnancies. Hormonal manipulation and oophorectomy have been used as treatment with limited or no benefit. Lung transplantation may improve survival and overall quality of life, but disease-related complications are frequent.

Pre-pregnancy counseling and decisions about termination of pregnancy can only be based on a frank discussion of the uncertainty about the natural history of this condition. Women contemplating pregnancy should be made aware of their own mortality with or without the pregnancy so that they can make a more informed decision that would include the possibility of the patient not being alive through the adolescent years of their children's lives.

Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with a progressive and typically fatal outcome, often within 3 years of diagnosis. IPF is a disease of the elderly, with most cases occurring in the sixth or seventh decades of life, making its presentation in a woman of childbearing age extremely unlikely. Very few case reports of pregnancy in a woman with IPF exist in the literature. Consequently little is known about its course during pregnancy or its effects on pregnancy outcomes. A woman with IPF contemplating pregnancy must be advised to consider her own prognosis for survival outside pregnancy. Patients with severe disease may be unable to tolerate the increased oxygen demands of pregnancy. IPF has been treated with steroids and immunomodulatory agents with limited response. Decisions to continue therapy during pregnancy will need to be individualized. Single lung transplant has demonstrated improved survival in these patients and successful pregnancy after lung transplant has been reported.

Churg–Strauss syndrome

Churg–Strauss syndrome (CSS, also known as allergic granulomatous and angiitis) is a rare allergic granulomatosis characterized by asthma, allergic rhinitis, and systemic vasculitis. Manifestations can include eosinophilia, rash, pericarditis, cardiovascular disease, glomerulonephritis, peripheral neuropathies and an eosinophilic gastroenteritis. It is often misdiagnosed as steroid-dependent asthma with other clinical features becoming apparent with attempts at steroid tapering. Diagnosis is made with biopsy of affected tissue. Treatment is with systemic steroids which have greatly improved prognosis in this previously frequently fatal condition.

The literature on CSS in pregnancy is very limited. Although single case reports suggest that Churg–Strauss improves in pregnancy [84], it may also become more obvious in pregnancy because of efforts to withdraw steroid therapy by patients or their physicians.

Lung cancer

Lung cancer in pregnancy is rare. However, with delayed childbearing and increasing incidence of smoking among reproductive age women, its incidence can be expected to rise. Because of the paucity of data in the literature, no specific recommendations with regard to screening and management in pregnancy can be made. In general, when malignancy is suspected in a pregnant woman, diagnostic radiologic testing should not be withheld for fear of fetal radiation exposure, which is usually minimal for most diagnostic tests for lung cancer. Staging involves a thorough history and physical exam, CBC, liver function tests, bone enzymes, a chest X-ray and a CT scan of the chest to determine resectability but may also necessitate additional imaging procedures.

Treatment can be carried out in pregnancy in many cases, but the management depends upon gestational age at diagnosis, clinical staging and histologic type of cancer and whether the tumor is operable (see Chapter 22 for a complete discussion of treatment of the more common causes of cancer in pregnancy). Based upon the few case reports in the literature, prognosis for lung cancer diagnosed in pregnancy is poor. In the largest case series of 19 patients of lung cancer during pregnancy [85], the maternal mortality was 68% within 9 months of diagnosis, but the neonatal outcome of all cases was favorable. Data remain insufficient to opine whether pregnancy affects the natural history of lung cancer.

Pneumothorax and pneumomediastinum

Pneumothorax and pneumediastinum refer to the presence of air in the pleural space or mediastinum respectively. Both these conditions occur infrequently in pregnancy, but probably more commonly than in the nonpregnant state. They most commonly occur in susceptible individuals due to the expulsive efforts of labor [86,87]. However, pneumomediastinum in particular may occur at other times such as in

association with bronchial asthma or following vomiting. Pneumothorax may occur in association with other chest conditions, such as emphysema, pulmonary tuberculosis or cystic fibrosis. In most cases of pneumomediastinum, which is more common in pregnancy than pneumothorax, a false passage is created between the airways and the mediastinal tissues. The condition usually, although not invariably, follows a strenuous labor. Air tracks through the mediastinum to the neck or pericardium (pneumopericardium), and there may be subcutaneous emphysema over the thorax or even the whole body. This produces a characteristic crackling sound and sensation on palpation, which does not occur in any other condition. In addition, there may be a crunching noise (Hamman's sign) synchronous with the heartbeat at the left sternal edge due to air. Although most cases of pneumomediastinum in pregnancy will be due to the mechanism just described, the differential diagnosis includes the much more serious esophageal rupture in patients who have undergone trauma, instrumentation or severe retching/vomiting (Boerhaave syndrome). These patients usually have severe chest and abdominal pain and proceed to manifestations of sepsis and septic shock in a short time frame. CT scan of the chest is usually diagnostic.

In pneumothorax there is a false passage between the airways and the pleural cavity. Pneumothorax accompanies about one-third of the cases of pneumomediastinum that occur in pregnancy but may also occur independently [88]. In both conditions, the patient complains of sudden-onset chest pain and breathlessness, and the diagnosis is confirmed by chest radiography. In tension pneumothorax the patient will become cyanosed and hypotensive due to the reduction in venous return. A similar variant of pneumomediastinum, "malignant mediastinum," also occurs but is much rarer.

Pneumomediastinum normally clears spontaneously and the treatment is therefore usually conservative, with oxygen and analgesics. Malignant mediastinum requires urgent relief either by multiple incisions over the subcutaneous tissue where air is trapped or by splitting the sternum. Pneumothorax should be drained via an underwater seal if the lung is more than 25% collapsed. Tension pneumothorax requires immediate relief by a large-bore needle inserted through the chest wall overlying the pneumothorax. If pneumothorax or pneumomediastinum has occurred in pregnancy, an operative vaginal delivery should be considered to minimize the chance of recurrence, caused by raised intrapulmonary pressure due to maternal straining.

Pleural effusion

Pleural effusions can be caused by a variety of conditions as listed in Table 1.11 along with some characteristic findings on pleural fluid analysis. Physiologic changes of pregnancy, including an increased blood volume and decreased colloid osmotic pressure, may promote transudation of fluid into the pleural space. Benign small postpartum pleural effusions have been noted on chest radiographs and ultrasound studies after normal vaginal delivery [89,90] with an incidence of about 25%. In addition, pre-eclampsia and other conditions associated with pulmonary edema in pregnancy may result in pleural effusion.

Signs and symptoms vary according to underlying condition but mainly include dyspnea, cough and pleuritic chest pain. Hypoxia may be present, particularly when the effusion is very large or when the underlying cause involves lung parenchyma or the pulmonary vasculature. Decreased breath sounds, dullness to percussion, decreased tactile and vocal fremitus may be noted on physical exam.

Diagnostic approach is largely guided by findings on history and physical exam and conditions being considered in the differential. While chest radiographs can usually confirm presence of fluid in the pleural space, ultrasound or CT scan may sometimes be necessary to further characterize the effusion and to narrow the differential. A diagnostic thoracocentesis should always be considered for an unexplained pleural fluid collection but especially in the presence of fever, hemoptysis, and weight loss or when hemothorax or empyema is suspected.

Management usually involves treatment of the underlying condition. Rarely, a therapeutic thoracocentesis may be necessary, particularly in case of a large (e.g. TB) or rapidly accumulating (e.g. malignancy) effusion. Presence of blood, pus or chylous effusion warrants placement of a thoracostomy tube. While performing these procedures in pregnancy, it is important to remember that the diaphragm is about 4–5 cm elevated and a higher approach may be needed than in non-pregnant patients and that ultrasound guidance may be desirable.

Anesthetic considerations

Many factors should be considered when administering anesthesia to the parturient with pulmonary disease. Early recognition and assessment of respiratory conditions, both as independent entities as well as complications of other primary conditions, are essential and facilitate disease assessment and optimization, early planning of anesthetic care, and joint discussion with the patient and parent team. Therefore early anesthetic referral during pregnancy should be performed as part of interdisciplinary care.

Labor and delivery

During labor and delivery, pain causes hyperventilation, increased respiratory work and increased oxygen consumption which combine to increase the risk of acute respiratory deterioration. Thus, it is extremely important to provide effective analgesia. This is best achieved using regional anesthesia.

Table 1.11 Some causes of pleural effusion and some characteristic findings on pleural fluid analysis

Etiology	Findings on pleural fluid analysis
Exudative pleural effusions*	
Parapneumonic: a sterile effusion occurring in proximity to an infectious pneumonitis	pH >7.2, glucose >40 mg/dL (2.2 mmol/L) Gram stain and culture negative
Empyema: an infected pleural effusion	Appearance of frank pus, pH <7.3, glucose <40 mg/dL (2.2 mmol/L) Positive gram stain and/or culture
Pulmonary embolism	Bloody appearance (blood may also be caused by malignancy)
Pancreatitis	Elevated amylase (pleural fluid level greater than serum level)
Tuberculosis	Positive stain for acid-fast bacilli (AFB) Glucose <60 mg/dL (3.3 mmol/L)
Esophageal rupture	pH <6.0 Elevated amylase (pleural fluid level greater than serum level)
Malignancy: metastatic or primary mesothelioma	Abnormal cytology Glucose <60 mg/dL Elevated amylase (pleural fluid level greater than serum level)
Chylothorax	High triglycerides (>110 mg/dL or 1.24 mmol/L)
Rheumatoid arthritis	Glucose <60 mg/dL
Ovarian hyperstimulation syndrome (OHSS)	Usually happens in the context of ascites, but OHSS has been reported as an isolated cause of pleural effusion in pregnancy
Transudative pleural effusions*	
Congestive heart failure	Underlying diagnosis usually apparent from other systemic manifestations
Cirrhosis	Underlying diagnosis usually apparent from other systemic manifestations
Nephrotic syndrome	Underlying diagnosis usually apparent from other systemic manifestations
Exudative or transudative pleural effusions*	
Idiopathic	Diagnosis may not be apparent in up to 25% of patients after initial evaluation

Pleural fluid is typically sent for cell count, pH, protein, LDH, glucose, cholesterol, gram stain, culture and cytology. In some circumstances, an amylase, triglyceride should be sent.

*Transudative effusions are caused by disturbances in hydrostatic pressure or oncotic pressure (e.g. congestive heart failure, cirrhosis or nephritic syndrome). Exudative effusions are caused by damage of the pleural membranes and/or vasculature (e.g. cancer, infection, collagen vascular disease). Transudates have none of (and exudates have one of) the following characteristics: (1) pleural fluid protein to serum protein ratio of >0.5; (2) a pleural fluid LDH to serum LDH ratio of >0.6 (or a pleural fluid LDH that is greater than two-thirds the upper limit of normal for the serum level). A pleural fluid cholesterol >45 mg/dL (1.17 mmol/L) is also suggestive, but not diagnostic, of an exudate.

Both epidural analgesia and paracervical block have been shown to reduce oxygen consumption, tidal volume and minute ventilation in labor [91,92]. However, in modern practice, carefully titrated epidural and combined spinal-epidural analgesia are the modalities most commonly used. In addition, placement of an epidural catheter provides the option of rapid extension of the block and avoidance of general anesthesia in the event that cesarean delivery is required. Ideally, epidural analgesia should be commenced early in labor and maintained through the first and second stages.

The main adverse effect of epidural anesthesia is the possibility of diminished respiratory muscle function, especially if a dense or high (thoracic) block occurs [93]. This potentially may reduce breathing effort as well as the ability to cough. The risk is minimized by the use of incremental doses of low concentrations of local anesthetic (e.g. bupivacaine or ropivacaine). Addition of small doses of a lipophilic opioid (e.g. fentanyl or sufentanil) enhances analgesia without additional motor block. Provided that extensive block is avoided, epidural analgesia using low concentrations of local anesthetic has been shown not to decrease spirometric values in healthy patients during labor and may even improve them slightly [94]. However, all patients should be closely monitored and supplementary oxygen should be administered according to clinical assessment.

Systemic methods of analgesia (e.g. opioids, nitrous oxide) are not as effective as regional anesthesia but may be considered in patients in whom regional anesthesia is contraindicated. However, opioids reduce respiratory drive and cause sedation which may increase the risks of respiratory failure and pulmonary aspiration in some patients. Some opioids (e.g. morphine) stimulate histamine release which theoretically may induce or exacerbate bronchospasm in asthmatics and other susceptible patients, thus fentanyl may be a preferred systemic opioid. Nitrous oxide should be avoided in patients with pulmonary bullae or pneumothorax because of its propensity to expand air-filled cavities.

Cesarean delivery

Regional anesthesia has a number of advantages for cesarean delivery. Importantly, it avoids the risks of airway manipulation

which include pulmonary aspiration and hypoxia secondary to difficult or failed tracheal intubation (see previous section in this chapter on ventilatory assistance in pregnancy). Furthermore, airway manipulation and light general anesthesia may stimulate bronchospasm, particularly in asthmatic patients. Epidural anesthesia, spinal anesthesia or combined spinal-epidural anesthesia can be used, the choice depending on the clinical urgency and the preferences and experience of the attending anesthesiologist.

However, because a more dense and more extensive block is required for cesarean delivery compared with vaginal delivery, the potential for motor block to adversely affect respiratory function is greater when regional anesthesia is administered for cesarean delivery compared with labor. Studies of the effect of spinal anesthesia on spirometric pulmonary function during cesarean delivery in normal parturients have shown that most parameters are decreased, including FVC, FEV_1, peak expiratory flow rate (PEFR) and forced expiratory flow (FEF) [95,96]. These changes were shown to be greatest when the abdomen was open [95] and lasted for several hours after induction of anesthesia [96]. The effects of spinal anesthesia on respiratory function are even greater in obese parturients [97]. Studies of epidural anesthesia have shown small or no differences in respiratory function [98]. Peak expiratory pressure (PEP) was shown to be better preserved with the use of bupivacaine 0.5% versus lidocaine 2% with epinephrine [99]. Although the respiratory changes associated with regional anesthesia usually are not clinically important in normal parturients, patients with severe respiratory disease who have diminished reserve may become compromised intraoperatively. Therefore the decision to use regional anesthesia in these patients should be individualized with this consideration in mind.

General anesthesia is required in patients in whom regional anesthesia is contraindicated or in patients with poor respiratory function who are considered unable to tolerate regional anesthesia. In these patients, general anesthesia with mechanical ventilation facilitates adequate gas exchange which may be particularly important in patients with acute deterioration, for example from exhaustion or sepsis. Additionally, endotracheal intubation ensures a secure and protected airway for these patients. However, it is known that regional anesthesia is associated with a lower risk of postoperative pulmonary complications in nonpregnant patients with chronic stable lung undergoing abdominal surgery. Although it is not known whether similar benefits exist for pregnant patients with lung disease undergoing cesarean deliveries, it is likely that regional anesthesia when possible is generally preferable in this setting as well.

Agents chosen for general anesthesia should be those least likely to provoke bronchospasm. In this respect, ketamine is a useful induction agent because of its bronchodilating properties,

Table 1.12 Summary of general recommendations for management of pregnant patients with pulmonary disease

Recommendation	Comments
Assess baseline pulmonary status and confirm diagnosis (ideally done both during pre-pregnancy counseling and at first antenatal visit)	1. Perform indicted genetic testing such as paternal testing for cystic fibrosis 2. Document baseline signs and symptoms. Document baseline respiratory rate and physical exam. Obtain baseline CBC 3. Check oxygen saturation at rest and with ambulation 4. The goal of oxygen saturation for fetal well-being in pregnancy is ≥95% or $pO_2 \geq 70$ mmHg. Provide supplemental oxygen to obtain this if necessary 5. Obtain baseline blood gas if abnormal oxygenation or there is concern about possible CO_2 retention 6. Obtain pulmonary function tests (including DLCO if patient has interstitial lung disease) if not recently done 7. Review previous testing such as CXR, chest CT, etc. 8. Consider echocardiogram if there is concern about secondary pulmonary hypertension or if history not typical for pulmonary disease, or concern for concomitant heart disease 9. Consider cardiopulmonary stress testing if there is doubt about the patient's pulmonary reserve for meeting pregnancy needs
Assess and optimize disease control and review medication use for pregnancy	Review the need for medication in light of underlying disease and adjust as necessary. Address effect of the untreated disease as well as the effect of the medicine on the unborn fetus
Reassess pulmonary status at each visit	1. Assess for any changes in signs and symptoms and investigate as indicated 2. Address respiratory rate and any other changes in physical exam and investigate as indicated 3. Check oxygen saturation at rest, and with ambulation, if indicated 4. Evaluate the need for repeat testing, such as repeat pulmonary function testing or repeat imaging as indicated

(*Continued on p. 44*)

Table 1.12 (Continued)

Recommendation	Comments
Make labor and delivery plan as end of pregnancy nears. (This often requires involvement of anesthesia, obstetric medicine, pulmonary, labor and delivery room nursing, respiratory therapy, in collaboration with maternal-fetal medicine and/or generalist obstetrician)	1. Determine mode and timing of delivery 2. Determine appropriate anesthesia 3. Determine whether second stage should be assisted 4. Determine appropriate maternal monitoring during labor such as continuous pulse oximetry and cardiac monitoring 5. Determine which staff need to be available 6. Determine appropriate management of medication during labor and delivery and make arrangements if special medication should be administered or readily available. (Does the patient need stress-dose steroids? Are there specific medications that should be avoided?) 7. Determine reassuring fetal status prior to beginning an induction of labor 8. Determine when continuous fetal monitoring will be initiated 9. Determine best setting for patient to recover postpartum (such as routine postpartum floor or respiratory care unit, etc.)
Immediate postpartum management	1. Reassess pulmonary status by signs and symptoms, physical exam, and objective findings such as pulse oximetry, peak flow meter 2. Take special note of volume status, given postpartum volume shifts 3. Reassess medication needs (including any special management of pain medication). 4. Consider and discuss safety of medication with lactation
Longer term postpartum management	1. Clarify medications to be taken at discharge 2. Determine whether further testing is indicated postpartum, such as repeat PFT, CT scans, etc. 3. Confirm follow-up appointments with appropriate providers (such as obstetric medicine, pulmonary, obstetrics)

BPP, fetal biophysical profile; CBC, complete blood count; CT, computed tomography; CXR, chest X-ray; DLCO, diffusion lung capacity for carbon dioxide; NST, fetal non stress test; PFT, pulmonary function test.

although both propofol and sodium pentothal are acceptable general anesthetic induction agents. Muscle relaxants with minimal histamine-releasing properties should be used (e.g. rocuronium, vecuronium or cisatracurium). Volatile anesthetics all promote bronchodilation but there is no evidence to support choice of any particular agent. Unnecessary light anesthesia should be avoided and inspired gases should be humidified.

Gas exchange should be closely monitored intraoperatively. Use of pulse oximetry and capnography is standard and in selected patients insertion of an arterial catheter should be considered for repeated blood gas analysis. Intraoperative spirometry is standard and display of continuous flow-volume and pressure-volume loops is particularly useful for monitoring changes in respiratory resistance and compliance [99].

Postpartum care

Postpartum or postoperative care in a high-dependency or intensive care unit should be considered and in some patients postoperative ventilation may be required. Adequate analgesia after cesarean section is important and can be effectively provided using epidural or intrathecal opioids without the risks of decreasing respiratory drive that may be seen with systemic opioids.

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Useful resources

American Lung Association – www.lungusa.org
1800-LUNG-USA, Freedom from Smoking – www.ffsonline.org
March of Dimes – www.marchofdimes.com
National Partnership for Smoke-free Families
American Legacy Foundation
www.smokefree.gov
1800quitnow.cancer.gov
Toll Free Quit Line: 800-QUITNOW
www.helppregnantsmokersquit.org
American Academy of Allergy, Asthma, and Immunology – www.aaaai.org
American Thoracic Society – www.thoracic.org
American Association for Respiratory Care – www.aarc.org/links/links.asp
American College of Chest Physicians – www.chestnet.org/about/links/index.php