Chapter 11
Pulmonary Disorders in Pregnancy

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Pulmonary Disorders in Pregnancy

Pregnancy is associated with some profound changes in the cardiovascular, respiratory, immune, and hematologic systems that impact the clinical presentation of respiratory disorders, their implications in pregnancy, and the decisions to treat. In addition, concerns for fetal well-being and safety of various interventions complicate the management of these disorders. In many circumstances, especially life-threatening ones, decisions are based upon a careful assessment of the risk benefit ratio rather than absolute safety of drugs and interventions. In this chapter, we review some of the common respiratory disorders that internists or obstetricians may be called upon to manage.

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Asthma

Asthma is the most common respiratory disease during pregnancy. Asthma affects 4–8 % of pregnancies in the United States and up to 12 % in the United Kingdom and Australia. Difference in prevalence around the world may be related to reporting methods, diagnostic methods, or possibly some environmental or genetic influences.

Pregnancy is a state of important physiological changes in the respiratory system. These physiological changes vary across the course of the pregnancy and are summarized in Table 11.1.

Table 11.1 Respiratory physiological changes during pregnancy

	Changes Seen
Upper respiratory tract	• Hyperemia and edema of naso- and oropharynx resulting in rhinitis of pregnancy
Thorax/diaphragm	• Diaphragm rises by 4 cm • Chest diameter increases by 2 cm • Subcostal angle widens from 68° to 104°
Minute ventilation	• ↑↑↑(40–50 %)
Tidal volume	• ↑↑↑(40 %)
Respiratory rate	• ↔ to ↑(10 %)
O$_2$ consumption	• ↑(20–30 %)
Lung Volumes (ml)	
TLC	• ↔to ↓(5 %)
ERV	• ↓(15–20 %)
RV	• ↓ (20–25 %)
FRC	• ↓ (20–30 %)
VC	• ↔
IC	• ↑(5–10 %)
IRV	• ↔
Spirometry	
FEV1 (L/min)	• ↔
FVC	• ↔
Diffusion capacity	• ↔
Arterial Blood Gases	
PaO$_2$ (mm Hg)	• 105–106 in first trimester and 101–106 by third trimester
PaCO$_2$ (mmHg)	• 28–29 in first trimester and 26–30 by third trimester
pH	• 7.43
HCO$_3$ (mEq/L)	• 17–18

TLC total lung capacity, *ERV* expiratory reserve volume, *RV* residual volume, *FRC* functional residual capacity, *VC* vital capacity, *IC* inspiratory capacity, *IRV* inspiratory reserve volume, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *PaO₂* partial arterial pressure of oxygen, *PaCO₂* partial arterial pressure of carbon dioxide

Effect of Pregnancy on Asthma

The course of asthma during pregnancy is variable. The majority of patients who improve in pregnancy tend to worsen in the postpartum period and vice versa [1]. In general, asthma improves toward the end of the pregnancy, including labor and delivery. However, the rate of asthma *exacerbations* is increased between gestational weeks 17 and 32 [1, 2]. This may in part be due to medication noncompliance during the earlier part of the pregnancy upon discovery of the pregnancy but may also have to do with other pregnancy-related factors such as esophageal reflux, nasal congestion, hormonal factors, and alterations in immunity that may result in increased susceptibility to infections. The major predictor of disease course is the severity of asthma prior to the pregnancy, but race and obesity may also play a role. African American and Hispanic women are more likely to have asthma exacerbations. Poor compliance with medications and difficulties with access to medical services may be important confounders. Additionally, obese women tend to have more severe asthma as both asthma and obesity share a common inflammatory pathway at the cellular level. Asthma also tends to behave in a similar fashion in subsequent pregnancies.

Effect of Asthma on Pregnancy

While well-controlled asthma does not appear to have adverse consequences during pregnancy, poorly controlled asthma may negatively impact some maternal and fetal outcomes.
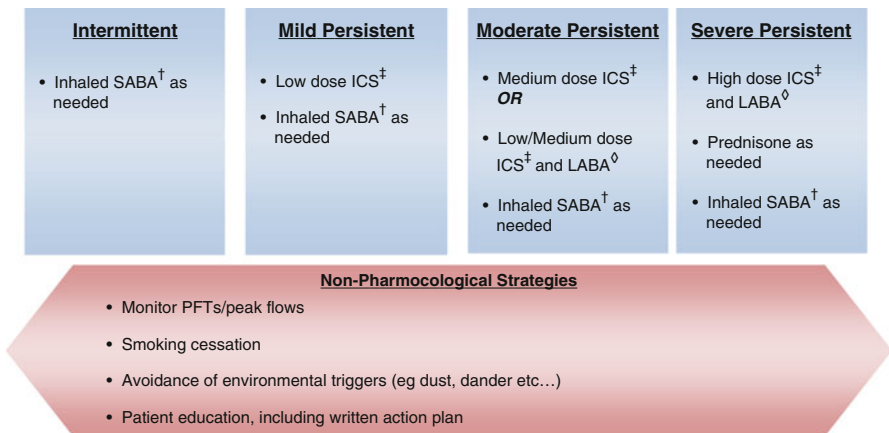
In the largest study performed to date on over 37,000 women with asthma and over 280,000 controls, asthmatic women were more likely to have pregnancies complicated by miscarriage, antepartum and postpartum hemorrhage, anemia, and depression [3]. However, the risk of other negative outcomes such as gestational hypertensive disorders and stillbirths was not significant in this study. In other large studies, a small, but statistically significant risk of perinatal mortality, preeclampsia, and preterm deliveries have been reported [4, 5]. A more recent retrospective cohort study performed in 12 clinical centers in the United States has shown increased risk of preeclampsia, gestational diabetes, and all preterm births [6]. Secondary analysis of a recent randomized controlled trial showed that women with perception of good asthma control had a reduced risk of planned cesarean deliveries, asthma exacerbations, and preterm birth [7]. In the same study, women with increased anxiety had a higher risk of exacerbations. There is some evidence suggesting that poorly controlled asthma also confers an increased risk of small for gestational age, and low birth weight [8]. Growth restriction may, however, be confounded by smoking. Babies born to severe asthmatics are possibly more likely to have congenital anomalies [5].

Management/Treatment

General Principles and Management

The treatment of asthma involves assessment and management from preconception to the postpartum period. Please refer to Table 11.3 and Figure 11.1 for a general overview of the classification and management of chronic asthma.

There are four general components of asthma care, irrespective of gestational age. These are (1) monitoring of respiratory status, (2) avoidance of possible triggers, (3) patient education, and (4) pharmacological treatment. Patients should get a baseline spirometry and be instructed in how to follow their peak expiratory flow rate (PEFR) at home. Ideally, this should be done twice a day in patients with persistent disease. Since pregnancy does not affect flow rates, reductions in these numbers usually indicate a worsening degree of airflow obstruction and should prompt quick medical evaluation. Second, it is critical that patients avoid their known triggers to asthma including tobacco, dust, extreme temperatures, and allergens such as pollen and pet dander. Third, patients need to be educated about their disease. Pregnancy constitutes a perfect window to educate women given the multiple contacts with providers increased motivation due to concerns for fetal well-being. Trigger control from washing bed sheets to vacuuming to rodent control are important strategies to review, especially since in most circumstances, women are more likely to be exposed to these triggers. Important topics that need to be reviewed also include inhaler technique, early recognition of symptoms of worsening asthma, an action plan for acute asthma exacerbations, as well as an overview of how poorly

Intermittent	**Mild Persistent**	**Moderate Persistent**	**Severe Persistent**
• Inhaled SABA[†] as needed	• Low dose ICS[‡] • Inhaled SABA[†] as needed	• Medium dose ICS[‡] **OR** • Low/Medium dose ICS[‡] and LABA[◊] • Inhaled SABA[†] as needed	• High dose ICS[‡] and LABA[◊] • Prednisone as needed • Inhaled SABA[†] as needed

Non-Pharmocological Strategies

• Monitor PFTs/peak flows

• Smoking cessation

• Avoidance of environmental triggers (eg dust, dander etc…)

• Patient education, including written action plan

[†] Short Acting Beta-2 Agonist. Albuterol is the most studied during pregnancy

[‡] Inhaled Corticosteroids. Budesonide is the most studied during pregnancy

[◊] Long Acting Beta-2 Agonist. Salmeterol is the most studies during pregnancy

Fig. 11.1 Management of chronic asthma during pregnancy

controlled asthma can affect the pregnancy. Patients should also be provided with the opportunity to express their concerns and ask questions. In a multi-institutional prospective study, lower forced expiratory volume in 1 s (FEV1), but not asthma symptom frequency, was shown to be associated with adverse perinatal outcomes [9]. These data may be a reflection of the effect of asthma severity or poor asthma control on perinatal outcomes and emphasize the possibility of discrepancies between symptom-based assessment and more objective measurement of lung function in pregnant women with asthma. Finally, women with asthma need to receive the appropriate pharmacological treatment to achieve disease control. Population-based data do show that well-controlled asthmatics without exacerbations have better outcomes than women with exacerbations, but for obvious reasons, there are no randomized controlled trials evaluating this particular question. Although most clinical practices use symptom-based, guideline-directed assessments to decide on medication use, recent data from a randomized controlled trial suggest lower rates of exacerbation, improved quality of life, and reduced neonatal hospitalization when management decisions were based on measurements of exhaled nitric oxide in pregnancy [10]. It is likely that this improvement in outcomes is due to improved control, rather than the method of assessment itself.

Table 11.2 provides an overview of the asthma medications that are used in pregnancy. As in the nonpregnant population, the choice of pharmacological agent depends on disease severity. A frank discussion with the expectant mother and her partner should occur to encourage them to voice their concerns regarding asthma treatment in pregnancy. Most women are told to stop their inhalers at the time of pregnancy diagnosis because of FDA category listing. For that reason, a good amount of time should be spent on counseling about the use of asthma drugs in pregnancy. Explaining to women that asthma control is key to the health of the pregnancy and their baby is an important part of counseling and may have to be done repeatedly during the course of pregnancy. In general, most asthma medications are justifiable in pregnancy, and some have adequate safety data. As noted in Table 11.2, many of the drug choices are category C according to the FDA classification; however, these drugs are used routinely in the care of pregnant women with asthma. In addition, although leukotriene inhibitors are listed as category B, safety data are less reassuring than other drugs classified as category C. Omalizumab is classified as category B by the FDA despite the fact that all of the initial trials have excluded pregnant women. These safety data are based on animal studies which are limited by the fact that teratogenicity may be species specific. In addition, although prednisone may be associated with a small risk of cleft palate when administered in early pregnancy, the benefit of this drug in an acute exacerbation of asthma by far outweighs the small risk of malformation. Table 11.3 reviews the classification of asthma severity, which includes not only symptoms but also peak flow meter measurements.

Other coexisting diseases may worsen asthma and may have to be treated in order to achieve optimal control. The most common of these disorders are allergic rhinitis, gastroesophageal reflux disease (GERD), sleep apnea, and psychiatric illnesses. Allergic rhinitis occurs in 80–90 % of nonpregnant asthmatics and worsens asthma symptoms.

Table 11.2 Overview of medications used in the treatment of asthma during pregnancy

Category	Best studied example	Risk category	Comment
Short-acting ßeta 2-agonist	Albuterol	C	No clear risk of teratogenic effect on fetus. Specific birth defects have been reported but are not the same. These findings may be due to chance. Benefit outweighs risk
Long-acting ßeta 2-agonist	Salmeterol	C	No clear risk of teratogenic effect on fetus. Benefit outweighs risk. Slightly more data available in salmeterol than formoterol
Inhaled corticosteroids	Budesonide	B	Human experience reassuring. Infants should be monitored for hypoaldosteronism. Some recent data suggestive of increased risk of metabolic dysfunction in the offspring
Anticholinergics	Ipratropium	B	Typically not used as primary agent but helpful in the treatment of acute exacerbations. Not expected to increase the risk of congenital malformations
Methylxanthines	Theophylline	C	No human reports of teratogenicity. Requires monitoring levels due to increased clearance in the third trimester and significant drug interactions
Cromoglycates	Cromolyn sodium	B	Not expected to increase the risk of congenital malformations. Human data reassuring
Leukotriene modifiers	Montelukast	B	Safety data are limited in pregnancy. However, although congenital limb defects, no syndrome of malformations has been identified in relation to montelukast
Systemic steroids	Prednisone/ methylprednisolone	C/D	Increased risk of growth abnormalities in animals, likely increased risk of cleft palates during first trimester exposures. Risk outweighs the risk in severe asthma
Epinephrine	Terbutaline	B	Unlikely to increase the risk of birth defects
Immunotherapies	Omalizumab	B	Limited human data. Risk benefit ratio needs to be considered. Pregnancy registry available

Management of the allergic rhinitis with drugs such as steroidal nasal sprays often improves asthma symptoms. Women who are pregnant can also develop a different form of rhinitis, called rhinitis of pregnancy. This typically occurs in the latter part of pregnancy and resolves completely within 2 weeks after delivery.

The prevalence of GERD among nonpregnant asthmatics varies between 30 and 90 %. In pregnant women with asthma, this number is likely higher given that

Table 11.3 Classification of asthma severity[a]

	Intermittent	Persistent		
		Mild	Moderate	Severe
Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
Nighttime awakenings	≤2×/month	3–4×/month	>1×/week but not nightly	Often 7×/week
Short-acting beta$_2$-agonist use	≤2 days/week	>2 days/week but not daily and not more than 1× on any day	Daily	Several times per day
Interference with normal activity	None	Minor limitation	Some limitation	Significant limitation
Peak Flow/ Pulmonary function tests	• Normal FEV$_1$ • 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 decreased by 5 %	• FEV$_1$<60 % predicted • FEV$_1$/FVC decreased by>5 %

FEV1 forced expiratory volume in 1 s, *FVC* forced vital capacity
[a]http://www.nhlbi.nih.gov

GERD has been reported to be present in nearly 75 % of all pregnant women [11]. GERD can worsen bronchoconstriction via increased vagal tone, heightened bronchial reactivity, and microaspiration of gastric contents into the upper airway. Patients who have symptoms of GERD benefit from treatment. Although proton pump inhibitors are not expected to increase the risk of congenital malformation in experimental animal studies and limited human pregnancy exposures, ranitidine constitutes a safer first choice. Finally, asthma and psychiatric comorbidities may coexist. Stress and mental illness can worsen asthma in the pregnant women and may also complicate compliance.

During labor, the general management of asthma is not significantly different than above. Most patients with asthma do not require a labor and delivery plan. However, patients with more severe disease or those who suffered an exacerbation close to term would require a detailed plan. Stress dosing with steroids during labor can be considered in patients who have been on prolonged periods of systemic steroids during the pregnancy. Patients with active symptoms or more severe asthma may benefit from regional anesthesia. Epidural anesthesia reduces minute volume and oxygen consumption and may help prevent hyperinflation in patients with active symptoms and reduce oxygen consumption. If general anesthesia is to be considered, then ketamine and halogenated anesthetics are preferred. It is safe to use oxytocin and prostaglandin E2. However, ergotamine and ergot derivatives, 15-methyl prostaglandin F2 alpha, morphine, and meperidine should be avoided in pregnant women with asthma as they may be associated with an increased risk of bronchospasm.

Treatment of Acute Asthma Exacerbations

An overview of the management of acute asthma exacerbations in the pregnant woman is detailed in Fig. 11.2. More detailed information can be found in National Heart Lung and Blood Institute guidelines on asthma and pregnancy published in 2004. The treatment is similar to nonpregnant women with a few key differences that need to be highlighted. The first is to remember that during pregnancy, the normal $PaCO_2$ is lower than in the nonpregnant state. Therefore, a normal or high $PaCO_2$ heralds worsening respiratory failure and should be acted upon quickly. Second, hypoxia during asthma exacerbations can lead to fetal distress and decelerations. Therefore, immediate bronchodilators and supplemental oxygen should be administered. Finally, it should be noted that while the indications for airway intubation are the same in the pregnant asthmatic as the nonpregnant asthmatic, intubation during pregnancy, especially in the third trimester, can be more difficult. This is due to increased airway edema, low FRC and oxygen reserve, and a more profound response to sedatives from decreased venous return. Hence, the most experienced member of the team should perform the intubation and be familiar with difficult airway management procedures. Airway intubation is discussed in more detail in the critical care Chap. 2.

Pneumonia in Pregnancy

Bacterial Pneumonia

Pneumonia is one of the leading causes of non-obstetric maternal deaths in the United States [12]. There are several categories of pneumonia based on the likely spectrum of pathogens: community-acquired pneumonia (CAP), healthcare-associated pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia as well as pneumonia in the immune-compromised host. As pregnant women are usually young and healthy, CAP predominates.

Microbiology and Epidemiology

The overall rate of CAP in pregnant women is 0.5–1/1,000 pregnancies depending on the population being studied [13–15]. The risk of pneumonia is notably increased in gravidas with comorbid conditions such as asthma, anemia, and human immunodeficiency virus [16]. Tobacco and substance abuse have also been independently associated with an increased risk for pneumonia. Influenza increases the risk for development of bacterial pneumonia by denuding the respiratory epithelium and predisposing the host to infection.
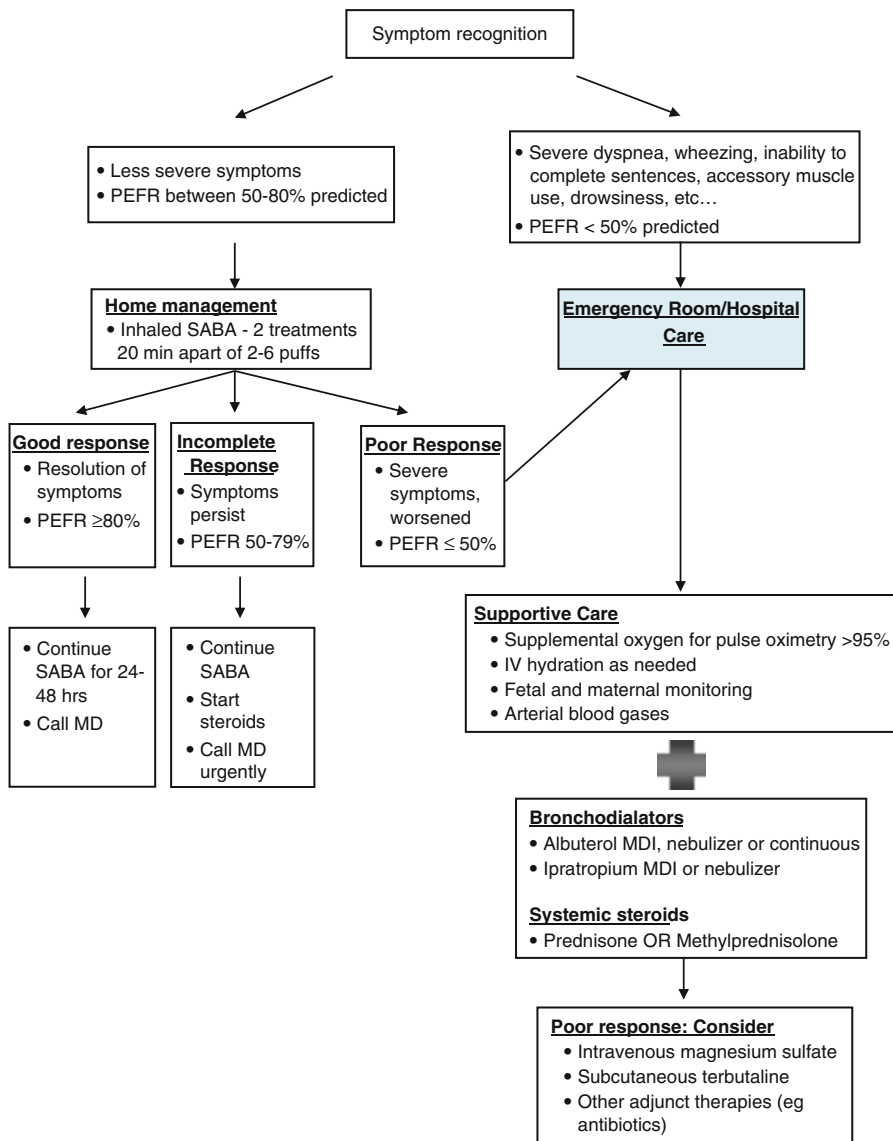
Fig. 11.2 Management of acute asthma exacerbation during pregnancy. Simplified from http://www.nhlbi.nih.gov/health/prof/lung/asthma/astpreg/astpreg_qr.pdf

In adults, the causative agents for CAP are identified in 40–60 % of cases when advanced testing techniques are utilized [17, 18]. The yield is much lower, in the range of 10–25 %, with regular testing. Though specific studies in pregnant women are lacking, the likely pathogens are not considered to be significantly different

from those in the general population. *Streptococcus pneumoniae* is the most common single pathogen isolated in 30–50 % followed by *Haemophilus influenzae* and *Mycoplasma pneumonia* [19]. Pregnant women may be more likely to contract viral infections and tend to have more severe disease than the nonpregnant population. Therefore, the estimates above may be somewhat different in pregnancy.

Effect of Pregnancy on the Disease

Gingival hyperplasia in pregnancy may promote changes in oral flora and promote growth of anaerobic bacteria. Aspiration risk and heartburn [11] may be increased in pregnancy, especially when undergoing sedative procedures or general anesthesia. Whether these changes and increased gastroesophageal reflux disorders are associated with increased risk of pneumonia is not clear. Immune alterations in pregnancy that promote maternal tolerance to the fetus may impair optimal function of host defense mechanisms and increase the risk of infections. Pregnant women have decreased lung capacity and decreased ERV and RV resulting in a reduction in functional residual capacity. A state of compensated respiratory alkalosis is established by increasing minute ventilation. This is largely secondary to an increase in tidal volume and to a lesser extent an increase in respiratory rate. Healthy gravid subjects have increased cardiac output and decreased oncotic pressure which peaks in the third trimester that promotes transudation of fluid into the pulmonary interstitium. These changes diminish oxygen reserve, increase the risk of development of pulmonary edema with fluid resuscitation, and predispose to respiratory failure and predispose women to more severe disease.

Effect of Disease on the Pregnancy

Pneumonia may be complicated by hypoxia, respiratory failure, or death, and preterm delivery appears to be the most common obstetric complication associated with maternal pneumonia. While intrauterine infection is known to cause preterm delivery, a causal relationship between pneumonia in pregnancy and preterm delivery is not well established. It is possible that higher levels of cytokines and other mediators such as TNF-α and prostaglandin F2 reported in bacterial infections may lead to preterm delivery and low birth weight. Other reported complications include placental abruption, preeclampsia and eclampsia, and low Apgar scores [20–22]. It is unclear, however, whether these complications are related to the actual infection or to other host factors.

Differential Diagnosis

Common causes for respiratory distress in pregnancy include infection such as urinary tract infection, pulmonary edema, asthma, aspiration, and pulmonary embolus.

Diagnostic Evaluation

The clinical spectra of pneumonia caused by different pathogens overlap considerably. Thorough history and examination along with microscopic examination of respiratory secretions may narrow the differential diagnosis and identify the offending pathogen. Urine pneumococcal and legionella antigen may also aid in guiding antibiotic therapy and should be considered for patients requiring admission. During influenza seasons, respiratory viral panel should be sent. Though blood cultures are usually negative and of low yield, they may add value in the patient requiring admission to the intensive care unit (ICU). Arterial blood gas should be done for all patients with hypoxia or those requiring admission to the ICU and interpreted according to pregnant status.

Chest X-ray should be performed in patients suspected of having pneumonia and helps confirm the diagnosis or show evidence of a complicated pneumonia such as lung abscess or pleural effusion. Computed tomography scan is unlikely to add value in the management of pneumonia, unless empyema is suspected. Ultrasound guidance likely reduces the risk of complications with thoracentesis in pregnancy given the cranial displacement of the diaphragm in pregnancy. Bronchoscopy though rarely needed can be performed safely in pregnancy and should not be withheld when indicated.

Management/Treatment

Supportive Treatment

General supportive measures are similar in patients with various types of pneumonia. For patients with a viable fetus who require admission, the obstetric team should be consulted for fetal monitoring as well as timing of delivery in the event of fetal distress. Hypoxia, acidosis, and fever should not be tolerated as they are independently associated with poor fetal outcomes. Oxygen should be supplemented for goal saturations > 95 % or PaO_2 above 70. Fever should be treated aggressively for a goal temp of less than 38 °C.

In cases of severe pneumonia associated with respiratory failure, early intubation should be considered. Intubations in pregnancy have a higher failure rate than the general surgical population (see Chap. 2 on airway intubation). Attempts to maintain CO_2 within an acceptable range may be challenging in the event of acute respiratory distress syndrome (ARDS) and the use of lung protective strategies. Low tidal volume ventilation strategy with a target tidal volume of 6 ml/kg is recommended for ARDS [23]. Though pregnant women were excluded in the acute respiratory distress network studies on lung protective strategies, low tidal volume ventilation should be attempted, initially with a higher respiratory rate to maintain ventilation given the survival benefit observed in the nonpregnant population. However, higher tidal volumes may be required to correct acidosis that may compromise the fetus, in

such instances attempts should still be made to keep the plateau pressure below 30 cm of water as barotrauma is thought to contribute significantly to lung injury. $PaCO_2$ levels need to be watched closely, and given the 10 mmHg gradient between fetal and maternal, maternal $PaCO_2$ should be kept at 55 mmHg or lower. Use of bicarbonate to correct the PH has been suggested in the nonpregnant population though clinical studies to support this approach are limited. It is thought that the transfer of bicarbonate across the placenta is slow and may not be adequate to correct fetal acidosis. While the decision to admit patients to the ICU is complex and should be individualized, clinicians should have a lower threshold when evaluating pregnant mothers.

Antibiotic Therapy

Antibiotic therapy should be initiated empirically while awaiting confirmatory tests that may aid in narrowing the antimicrobial coverage. In influenza season, antiviral (usually oseltamivir) should be started empirically as well. Decisions about antibiotic choice should address the most likely pathogen, adverse effect on the mother, and should also weigh the risk of the specific drug to the fetus against the risk of inappropriately treated disease. An optimal drug would be one with maximal efficacy against the known pathogen and no risk to the fetus. However, such drugs are scarce, and in most circumstances, a drug with more benefit than risk can be selected. Other than concern for fetal safety, preferred antibiotics are not different from those in nonpregnant women, but dosing should take into account increased hepatic and renal clearance and increased volume of distribution. There is a theoretical concern that aminoglycosides and vancomycin may be associated with hearing and kidney dysfunction in the offspring, but this possibility has not been confirmed clinically. Penicillins, clindamycins, and most macrolides except clarithromycin have a good safety profile. Fluoroquinolones are usually avoided in pregnancy due to a theoretical risk of arthropathy in the offspring. However, some experts argue that this issue is not clinically significant in humans. Tetracyclines should be avoided as they may cause permanent dental discoloration.

Varicella Pneumonia

Varicella (chicken pox) is caused by *Varicella zoster* virus (VZV). Varicella is predominantly a childhood illness that is usually self-limited and rarely results in severe disease. In adults, however, it is much more likely to be severe. VZV is not only likely to have increased morbidity and mortality in pregnancy but may also be associated with congenital abnormalities and poor fetal outcomes. Varicella pneumonia is among the most severe maternal complication of VZV infection [24–27].

Viral particles are shed from varicella-associated vesicles and get airborne. Inhalation or contact with the conjunctiva results into contraction of the infection

with entry of the virus through the respiratory mucosa. Crusting over of the last crop of vesicles usually marks the end of the contagious period. Patients are known to be infectious 2–3 days prior to development of the vesicular rash; for this reason, an alternative viral shedding site such as the respiratory tract is believed to exist [28].

Epidemiology

Varicella is highly contagious with seasonal variation in incidence, being most prevalent in the winter and spring. It has a very high clinical attack rate of 65–86 % following exposure to susceptible individuals [29]. Following a primary infection with varicella, lifelong immunity is usually established in the majority of subjects; in a few people, however, second attacks of varicella may occur [30].

While varicella follows a benign course in children, adults have up to 25 times increased risk of severe disease [31]. Pregnant women are at a uniquely increased risk for infection. In the United States, the incidence of primary varicella averages 0.7–3 cases/1,000 pregnancies. Varicella pneumonia complicates 10–20 % of all cases, and 40 % of mothers with pneumonia require mechanical ventilation [32, 33]. Maternal mortality from Varicella pneumonia used to be high at 20–45 % before the introduction of antiviral therapy but is currently estimated at less than 3–14 % [34, 35].

Effect of Pregnancy on the Disease

Changes in physiology and immunity associated with pregnancy may increase the risk of infection and severe outcomes in the pregnant women. In an effort to promote maternal tolerance to fetal antigens, pregnancy is associated with a shift from Th1 to Th2 lymphocyte responses and associated cytokines at the maternal fetal interface. Macrophage and lymphocyte-secreted Th2 cytokines stimulate B lymphocytes promoting a humoral response while suppressing cytotoxic lymphocytes. While pregnancy may not necessarily be an immune-suppressed state in the real sense, immunity against VZV infection is primarily cell mediated, and a systemic shift away from cell-mediated immunity may increase susceptibility to intracellular viral pathogens, parasites, and bacteria.

Effect of Disease on the Pregnancy

Primary varicella (chicken pox) is associated with several adverse effects in pregnancy such as preterm delivery and low birth weight. In one study involving 106 pregnant women with varicella compared to a similar number of noninfected controls, 14.3 % of pregnant women with chicken pox had a preterm delivery as compared to 5.6 % of controls [36]. Low birth weight and intrauterine growth restriction have been described. Nearly 1–2 % of cases of maternal primary VZV infection result in congenital varicella syndrome (CVS), which is associated with a mortality

of up to 30 % in the first few months of life and severe disability in survivors. Primary VZV infection prior to the 20th week of pregnancy is associated with the highest risk for CVS [24, 36].

Clinical features of CVS include skin lesions in a dermatomal distribution that may lead to eventual scarring in up to 70 % of cases, muscle and limb hypoplasia in up to 72 % of cases, chorioretinitis and cataracts in up to 52 % of cases, and abnormalities of gastrointestinal, genitourinary, and cardiovascular system in 7–24 % of cases [37, 38]. Neurological abnormalities such as mental retardation, microcephaly, and hydrocephalus occur in 48–62 % of cases resulting in learning difficulties and developmental delays [39]. The pathobiology of CVS is thought to be in utero reactivation similar to that of herpes zoster with a shortened latency period that is likely due to immature fetal cell-mediated immunity.

While up to 25 % of babies born to mothers with primary VZV infection have serologic evidence of infection, there is no serologic evidence of infection in babies born to mothers with herpes zoster. Similarly, infants do not appear to be at risk of infection if maternal zoster occurs near delivery [40]. Unless disseminated, herpes zoster is thus not associated with a significant increase in adverse fetal outcomes [37, 41]. Peripartum varicella infection places the infant at risk for neonatal varicella, which is associated with mortality rate as high as 20 %.

Diagnosis

Following a 2- to 3-week incubation period, fever, headache, malaise, anorexia, and other constitutional symptoms precede the occurrence of the rash by 2–3 days. The rash is typically vesicular, generalized, and intensely pruritic. Varicella pneumonia can develop anywhere from day 1 to day 6 after the onset of the rash.

Late onset of respiratory symptoms with recurrence of fevers is suggestive of bacterial coinfection rather than primary viral pneumonia. Skin superinfection with staphylococcal bacteremia and neurological involvement with encephalitis may occur. A thorough history and skin exam may strongly suggest the diagnosis of varicella. Chest radiograph pattern in varicella pneumonia is nonspecific and may be normal or show unilateral or patchy areas of consolidation or nodular opacities. CT findings include multicentric hemorrhage and necrosis centered around the airways and small nodular opacities surrounded by ground glass which may coalesce to form consolidations. Healed and calcified pulmonary nodules may persist [42]. Skin lesion (rather than bronchoscopic) sampling offers a high yield and should be attempted first. The base of newly erupted vesicles has the highest yield and should be sampled. Specimens can then be sent for viral culture, polymerase chain reaction (PCR), and immunofluorescence (DFA). Direct fluorescent antibody test is rapidly available in most institutions. Though bronchoscopy in most cases is not necessary, varicella may be recovered from bronchial washings by viral PCR and viral culture techniques.

Management/Treatment

Pregnant women suspected of having varicella should be admitted for initiation of antivirals and other supportive treatment. Chest imaging should be performed on admission to evaluate for pulmonary involvement. Antiviral therapy is associated with a reduction in the duration of symptoms when initiated within the first 24 h of onset of the varicella rash. Due to the high risk of varicella pneumonia in pregnancy, empiric antiviral therapy should be initiated while awaiting confirmatory results.

Acyclovir or valacyclovir are the antivirals of choice. Oral acyclovir has low bioavailability that requires it to be administered in frequent doses to achieve therapeutic levels. Valacyclovir has high oral bioavailability and less frequent dosing intervals and is an alternative oral formulation. There is however less experience with valacyclovir compared to acyclovir. Presence of pulmonary symptoms should prompt admission to the ICU and initiation of intravenous acyclovir which has a guaranteed and higher bioavailability. Antiviral therapy is associated with significantly less morbidity and mortality when initiated prior to 72 h. Late presentation with varicella pneumonia should not obviate the initiation of antiviral therapy. A dose of 10–15 mg/kg intravenously every 8 h for 5–10 days is recommended for VZV pneumonia.

Pulmonary bacterial superinfection may occur. Studies characterizing bacterial pathogens likely to cause superinfection are lacking. Thus, empiric broad-spectrum antibiotic coverage should be initiated in pregnant women with pneumonia. Despite acyclovir crossing the placenta in significant amounts, there appears to be no reduction in congenital varicella syndrome with treatment. The neonate should be isolated from the mother in the peripartum period until the mother is deemed noncontagious. Consultation with high-risk obstetrics and neonatology would be useful given the risk of preterm labor and growth restriction.

Passive Immunization

Immunity to varicella consists of both VZV-specific neutralizing antibodies and cell-mediated immunity. Immunity against VZV can be assessed by the use of antibody serologic assays.

Though there are no adequate controlled trials examining the effectiveness of VZIG prophylaxis, VZIG is associated with more than 40–50 % reduction in risk of contracting varicella and a significant reduction in risk of severe disease [40]. VZV can be prevented by vaccination. VZV vaccine is a live attenuated vaccine and is generally not recommended in pregnancy and in immune-suppressed individuals. Varicella can be contracted from herpes zoster lesions as well. Family members with such lesions should minimize contact and cover their lesions to decrease the risk of transmission. Healthcare workers who deal with pregnant women should be screened and vaccinated, and similarly pregnant healthcare workers should avoid contact or exposure to patients with varicella.

Influenza Pneumonia

Infection with influenza virus can result in an acute respiratory illness of varying severity. The majority of healthy individuals infected with influenza is asymptomatic or has minimal symptoms. However, adults with comorbidities, elderly subjects, and healthy pregnant women are at increased risk of severe disease and death. In addition, influenza infection during pregnancy increases the risk of adverse fetal outcomes.

Epidemiology

In a regular endemic season, influenza is estimated to result in 200,000 hospitalizations and 36,000 deaths in the United States. Pregnant women are at increased risk for morbidity (including cardiorespiratory complications) and mortality from influenza compared with nonpregnant controls [43–46] that is more pronounced in the second and third trimester of pregnancy [47]. In 2010, the Pandemic H1N1 Influenza in Pregnancy Working Group reported on 788 pregnant women in the United States with 2009 influenza A(H1N1). Among those, 30 died (5 % of all reported 2009 influenza A (H1N1) influenza deaths in this period). Most hospitalizations and deaths occurred in the third trimester [47]. Pregnant women with comorbidities or those who smoke have an increased risk for severe disease requiring hospital admission compared to those without comorbidities [48, 49].

Effect of Pregnancy on the Disease

As discussed above, these physiological changes make pregnant women more susceptible to acquiring viral infections and subsequent development of severe disease.

Effect of Disease on the Pregnancy

Apart from direct effects to the mother, influenza has been associated with undesirable effects to the fetus. Risks of adverse fetal outcomes vary with the severity of maternal disease. Preterm delivery appears to be the most common and consistent complication associated with influenza pandemics. In the pandemic of 1918 and 1957, higher rates of pregnancy loss, premature delivery, preterm deliveries, as well as other adverse effects were reported. In several reports during the pandemic influenza of 2009 among pregnant women requiring admission, preterm delivery was close to 30 % and was even higher among mothers who were admitted to the ICU

[48, 50, 51]. Several other adverse fetal outcomes of maternal influenza have been reported especially during pandemics, including abortion, fetal distress, and placenta abruption [50, 52].

Diagnosis

Symptoms of influenza in pregnancy are similar to symptoms outside of pregnancy. Influenza virus-mediated leukopenia may make the host more susceptible to bacterial infections. Secondary bacterial pneumonia is characterized by the appearance of a new fever and productive cough during early convalescence.

Radiologic findings are generally similar to other viral pneumonias, and more extensive findings are associated with more severe complications. Tree in bud opacities may also be seen. Laboratory findings may include an elevated or low white count, lymphopenia, and hyponatremia. Myoglobinuria and renal failure can occur rarely. Cardiac muscle damage with associated electrocardiographic changes, disturbances of rhythm, and high levels of cardiac enzymes have been reported after influenza virus infection.

Sputum cultures may be revealing in the event of bacterial superinfection. *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and group A hemolytic streptococci are the bacterial pathogens most commonly isolated in adults with influenza.

A definitive diagnosis of influenza requires laboratory confirmation. Diagnostic tests for influenza fall into four broad categories: virus isolation [culture], detection of viral proteins, detection of viral nucleic acid, and serological diagnosis. Detection of viral nucleic acid allows for typing and subtyping of the specific virus strain.

Management/Treatment

Supportive Management

Treatment of influenza consists of supportive management and specific antiviral therapy. Optimizing supportive treatment is central to the management of influenza and probably of more benefit than specific antiviral therapy. Supportive therapy is similar to other types of pneumonia as discussed above.

Pharmacotherapy

As with most drugs, information about safety and effectiveness of anti-influenza drugs during pregnancy is scarce. In view of potential severe maternal disease from influenza and adverse fetal outcomes, benefits of treatment with antivirals likely

outweigh the potential risks to the fetus. There are two classes of antiviral drugs currently in general clinical use: adamantanes, (examples of which include amantadine and rimantadine) and neuraminidase inhibitors such as oseltamivir, zanamivir, and peramivir. Adamantanes are active against influenza A only, increase influenza A resistance to adamantanes, and are associated with embryotoxicity in animal studies. As such they are not recommended in pregnancy.

Neuraminidase inhibitors are active against influenza A and B viruses. They are preferred in all adults and in pregnancy. Though studies in pregnancy are inadequate, extensive use of oseltamivir in pregnancy during the 2009 HIN1 pandemic was not associated with adverse effects specific to the drug. Neuraminidase inhibitors reduce the duration and severity of symptoms and duration of viral shedding when initiated within 48 h of symptom onset [43, 48, 53, 54]. There is also evidence to support reduction in complication rate, duration of hospitalization, and mortality in adults. Observational studies published during the 2009 pandemic demonstrated that, among pregnant women hospitalized with pandemic H1N1 infection, treatment with oseltamivir was associated with fewer intensive care unit admissions, less use of mechanical ventilation, and decreased mortality [43, 48]. Empiric treatment should always be initiated in the gravid woman when influenza is suspected while awaiting confirmatory results as delay in initiation of treatment is associated with an increased risk of severe outcomes, ICU admission, and death [48, 49, 55]. Pregnant mothers presenting after 48 h of symptom onset should still be initiated on therapy as there is evidence of benefit even when initiated after 2 days of symptom onset. Initiation of antiviral therapy within the first 48 h is associated with the most benefit [43, 48, 49, 53, 56]. There is less experience with zanamivir which is administered by inhalation route. Zanamivir is also contraindicated in patients with asthma as it has a potential of worsening respiratory symptoms [57]. For patients requiring admission to ICU for influenza pneumonia or in cases of suspected secondary bacterial infection, empiric antibiotic therapy should be initiated. Sputum culture may be helpful in the case of isolation of resistant bacteria that may warrant changes or broadening of antibiotic coverage.

Prevention and Vaccination

In pregnant women, influenza vaccination induces an antibody response similar to that in nonpregnant women. CDC and WHO recommend pregnant women or women who will be pregnant during the winter or peak influenza season to be prioritized for vaccination. In addition to protection to the mothers, influenza vaccination may offer protection to the neonate as well as contribute to herd immunity in other family members. Pregnant mothers who have not been vaccinated or those with comorbidities such as asthma who have been exposed to influenza may benefit from antiviral prophylaxis. Oseltamivir is preferred for prophylaxis due to its ease of administration.

Sleep-Disordered Breathing

Sleep-disordered breathing (SDB) is a spectrum of disorders that encompasses snoring and upper airway resistance, obstructive sleep apnea (OSA), and other disorders. OSA is a disorder characterized by periodic and recurrent collapse of the upper airway during sleep. Obesity, age, and upper airway and facial abnormalities are the most recognized risk factors for the disorder. OSA is prevalent in patients with chronic hypertension, cardiovascular disease, and metabolic disorders such as diabetes mellitus. The pregnant population appears to be at risk for the disorder given anatomic upper airway changes that occur in pregnancy as well as physiological changes and hormones. Snoring occurs in close to 35 % of pregnant women [58]. The prevalence of OSA in pregnancy is not well known, but preliminary data suggest that close to 60 % of loud snorers in pregnancy have at least mild OSA. The natural history of snoring around pregnancy is, however, unclear. There are some data suggesting that OSA actually improves in untreated postpartum women around 3 months after delivery. Data on OSA predating pregnancy is missing and pregestational and gestational OSA may have different clinical consequences.

Screening

There is a significant lack in screening for the disorder by obstetric providers according to a recent study, even in obese patients [59]. Notably, the Berlin questionnaire, a widely used screening tool in the nonpregnant population, appears to have poor positive and negative predictive values in pregnancy [60]. Snoring and excessive daytime sleepiness may be important predictors [61]. Chronic hypertension, age, obesity, and snoring appear to have a good predictive value for OSA in high-risk populations [62]. Further validation of this potential predictive model in different pregnant populations is needed.

Pregnancy, Fetal, and Neonatal Outcomes

Snoring and OSA have been shown to be associated with a variety of adverse pregnancy outcomes including gestational hypertension, gestational diabetes, and cesarean deliveries. Gestational hypertension is the most studied link with numerous studies on snoring as well as OSA showing a two- to threefold increased risk of gestational hypertension in snorers, even after adjusting for confounders such as body mass index [63]. Mechanistic studies are lacking and the directionality of the association not well clarified, but it is possible that intermittent hypoxia, flow limitation, poor sleep, and arousals may play a role in causing endothelial dysfunction, inflammation, and hypercoagulability that are common to the two disorders.

A few studies to date have also shown worse abnormalities in glucose metabolism and a higher prevalence of gestational diabetes in women complaining of loud snoring and poor sleep [58, 64]. Gestational diabetes has been associated with a fivefold increase in the risk of type II diabetes at 5 years and a ninefold risk at 9 years [65]. Snoring, poor sleep, and OSA have all been associated with a higher risk of unplanned cesarean deliveries. This association may be harder to explain and may depend on the actual reason leading to unplanned cesarean delivery such as obstetric, fetal, or medical causes.

The impact of SDB on fetal and neonatal outcomes has also been studied, but the results of such studies have been more conflicting. Growth restriction has been reported to be associated with snoring in some studies but not in others. The effect on Apgar scores also appears to be controversial. There are some case reports and case series suggesting fetal decelerations secondary to sleep apnea, but a recent study evaluating synchronized limited sleep studies and fetal monitors have failed to show a significantly higher prevalence of late decelerations [60].

Management/Treatment

Once diagnosed, treatment of OSA is approved in patients with an apnea hypopnea index AHI >15 or those with AHI >5 who have symptoms that are known to respond to therapy such as daytime sleepiness. There are no specific guidelines on therapy initiation in pregnancy yet for various reasons. As stated above, the natural history of the disorder around the perinatal period is not well known. Thus, it is possible that, with weight loss and reversal of pregnancy physiology, the disorder may resolve or at least improve in the postpartum period. In addition, there have been no trials to date that have shown that treatment of OSA in pregnancy would improve pregnancy or fetal outcomes. This reason likely contributes to the fact that the disorder remains underscreened and underdiagnosed [59]. Based on current data, weight loss is unlikely to be an option in pregnancy because of concern that it may affect the nutritional status of the mother and therefore fetal well-being. Alcohol and cigarette smoking avoidance is another therapeutic strategy in pregnancy that carries additional pregnancy-specific benefits. Outside of pregnancy, CPAP therapy has been shown to improve quality of life and daytime sleepiness with some data suggesting improvement in cardiovascular outcomes such as hypertension. It is likely that these effects of CPAP are also true in pregnancy. Observational studies have shown improvement in daytime fatigue and daytime somnolence in pregnant women with OSA treated with CPAP and re-titrated around midpregnancy [66]. In women with preeclampsia, small, randomized trials have shown that in-laboratory positive airway pressure therapy improves hemodynamics, uric acid, and cardiac output compared to untreated women [67, 68]. Until future studies of CPAP therapy are available in pregnancy, indications for therapy are likely the same as in the non-pregnant population. We are awaiting trials evaluating the effect of PAP therapy on pregnancy-specific outcomes to be able to determine the "urgency" of starting PAP

therapy in pregnancy. The type of PAP therapy that is most beneficial in pregnancy is unknown. However, auto-titrating PAP therapy has the advantage of avoiding repeat re-titration of pressure requirements.

In summary, pregnant women with the above disorders need to be managed with pregnancy physiology and fetal effects of the disease and the therapy in mind.

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