

Pulmonary Complications of Obstetric and Gynecologic Conditions

Amisha Jain and Iman R. Sami-Zakhari

Introduction

A fundamental difference between the female reproductive system compared with virtually every other organ system in the body is that it goes through significant changes on a regular basis during the woman's healthy menstrual cycle and not only in a state of disease as is the case for virtually any other organ system. Even more significant are the changes that occur during pregnancy when the entire body changes to accommodate the developing fetus. Although none of these changes are directly related to the respiratory system, they do exert a significant effect in the mechanics of breathing. Thus, the physician who cares for a woman with respiratory symptoms has to consider if and to what extent they are caused, complicated, or exacerbated by an underlying gynecologic or obstetric condition. This chapter focuses on the normal alterations in pulmonary physiology during pregnancy and how it may affect the natural history of specific respiratory diseases and of course how the respiratory disease may affect the pregnancy outcome. Lung disorders related to gynecologic conditions are also described.

A. Jain, M.D. • I.R. Sami-Zakhari, M.D., M.R.C.P. (✉)
Division of Pulmonary and Sleep Medicine, Children's National Health System, George Washington University, School of Medicine and Health Sciences, Washington, DC, USA
e-mail: ajain@childrensnational.org; ISami@childrensnational.org

© Springer International Publishing AG 2018
A.C. Koumbourlis, M.A. Nevin (eds.), *Pulmonary Complications of Non-Pulmonary Pediatric Disorders*, Respiratory Medicine,
https://doi.org/10.1007/978-3-319-69620-1_8

Physiological Changes During Pregnancy

Profound physiological changes occur in both the pulmonary and cardiovascular systems during pregnancy. Understanding these changes and how they may affect other underlying disorders helps in the management of respiratory disease during pregnancy.

Effects on the Upper Airways

In the upper respiratory tract, edema of the nasal mucosa resulting in symptoms of rhinitis (“rhinitis of pregnancy”) has been reported in as many as 20–40% of pregnant women. It characteristically appears during the last 6 weeks of pregnancy in the absence of any infectious or allergic trigger, and it completely resolves within 1–2 weeks after delivery. Its exact cause is not known. Various factors have been implicated in its pathogenesis including the effect of placental growth hormone on the mucosa and increases in the circulating blood volume.

Other alterations in the upper airways include increases in the Mallampati score (that assesses the space between the base of the tongue and the roof of the mouth) and in the neck circumference. The decrease in the size of the upper airways is assumed to be caused by the overall alterations in the lung volumes that affect the caudal traction, and by fat infiltration of the tissues, and it is exacerbated in supine position.

Effects on the Chest Wall

During pregnancy the configuration of the chest wall is altered in order to accommodate the enlarging uterus. The changes include increases in the transverse diameter of the thorax that results into an increase of approximately 50% in the subcostal angle. As a result, the diaphragm is elevated by 4–5 cm. This would significantly impair the ability of the diaphragm to move during inspiration, but it is compensated by an increase in the anteroposterior diameter as well that allows the diaphragm to maintain a fairly normal excursion. However, the overall chest wall compliance decreases. There appears to be no effect on the respiratory muscle strength although the changes in the chest wall configuration probably puts the muscle at a mechanical disadvantage, thus contributing to the increased work of breathing that pregnant women experience. Interestingly, most of the alterations in the chest wall occur primarily during the first trimester of the pregnancy when the uterus is still too small to have any substantial mechanical effect. It is believed that

the chest wall configuration changes as a result of hormonal action, especially of relaxin that relaxes the ligaments of the lower rib cage, thus allowing the increase in the diameters.

Effects on the Lung Volumes and Lung Function

The alterations in the configuration of the chest wall confer surprisingly relatively little change in lung volumes and even less in lung function (Table 1). The most substantial change occurs in the functional residual capacity (FRC) that is usually decreased by about 18% primarily due to a decrease in the expiratory reserve volume (ERV) and residual volume (RV). This is due to elevation of the diaphragm and increased pulmonary blood volume in pregnancy. The inspiratory capacity (IC) remains essentially the same or even increases, and as a result, the total lung capacity (TLC) is only marginally decreased.

There are changes in the respiratory drive and minute ventilation, both of which increase under hormonal influence. The increase in minute ventilation offsets the increased carbon dioxide production, so primary respiratory alkalosis with pH ranging from 7.40 to 7.47 and pCO₂ ranging from 28 to 32 is a normal finding in pregnancy.

Table 1 Changes in lung function during pregnancy

<i>Lung volumes</i>	
TLC	Unchanged or slightly decreased
FRC	Decreased
ERV	Decreased
RV	Decreased
IC	Unchanged or increased
Tidal volume (VT)	Increased
<i>Lower airway function</i>	
FVC	Unchanged or slightly increased
FEV ₁	Unchanged
FEV ₁ /FVC	Unchanged
FEF ₂₅₋₇₅	Unchanged
Airway resistance (raw)	Unchanged
<i>Gas exchange</i>	
Diffusing capacity	Unchanged
pH	Increased (first trimester > third trimester)
PaO ₂	Increased (first trimester > third trimester)
PaCO ₂	Decreased (first trimester < third trimester)
HCO ₃	Decreased

Pulmonary Disorders in Obstetrics

Obstructive Airway Disease

Asthma

Asthma is one of the most common chronic respiratory diseases complicating pregnancy with an estimated prevalence of 3.7–8.4% of all pregnancies. Asthma is clinically characterized by recurrent episodes of reversible bronchoconstriction. There is a bidirectional interaction of asthma and pregnancy where asthma influences pregnancy outcomes and pregnancy affects asthma severity. Poorly controlled asthma is associated with adverse perinatal outcomes; however, when asthma is well controlled, pregnancy is not adversely affected.

Effect of Pregnancy on Asthma

The course of asthma during pregnancy improves in about one-third of women, worsens in one-third, and remains the same in the other one-third. The course is determined by the baseline asthma severity with more severe asthma prior to pregnancy conferring a higher risk of worsening during pregnancy. There is evidence that the course of asthma is similar in subsequent pregnancies. There is evidence that female fetuses are associated with worsening of the maternal asthma, suggesting the influence of hormonal causes.

Effect of Asthma on Pregnancy

Uncontrolled asthma increases the risk of severe maternal and fetal complications including preeclampsia, preterm birth, low birth weight, intrauterine growth restriction, and increased perinatal mortality. Immunological mechanisms in asthma influence pregnancy. It has been shown that poorly controlled asthma in pregnant women is associated with immune reactions that influence fetal growth.

Management

The focus of management is to maintain adequate control of asthma during pregnancy that will improve both maternal and fetal outcomes.

Diagnosis and Monitoring

The diagnosis of asthma is usually known prenatally, but the symptoms may occur for the first time during pregnancy. Spirometry showing lower airway obstruction that is reversible with bronchodilators is very useful in confirming the diagnosis.

However, the absence of an obstructive pattern is not a contraindication to treating the patient if there is sufficient clinical suspicion. Bronchial challenge tests are contraindicated during pregnancy due to the lack of safety data. Performing a skin prick test during pregnancy for the possibility of allergic asthma is also not recommended due to the risk of systemic reactions.

Fractional nitric oxide (FeNO) concentration in exhaled breath is a relatively new tool to monitor asthma control. According to a recent study, FeNO levels are not altered in pregnancy, and they correlate with the level of asthma control. However, as in the nonpregnant population, the limitation of the FeNO is that it reflects primarily the eosinophilic asthma and not all types of asthma. Monthly assessment of asthma control during prenatal visits is strongly recommended as well as patient education.

Treatment

Despite the concern about administering medications during pregnancy and their effect on the fetus, it is safer for pregnant women with asthma to be treated with asthma medications than to experience exacerbations that may increase the risk of perinatal mortality. Most studies have shown no increased perinatal risk with the use of beta-agonist and inhaled corticosteroids. Some epidemiologic studies have shown an increased risk of congenital abnormalities (cleft palate with oral corticosteroids, gastroschisis with bronchodilators) in the offsprings of asthmatic women, but the evidence is far from conclusive. It should be noted that congenital abnormalities develop very early in pregnancy (sometimes before the woman realizes that she is pregnant), and therefore withholding the medications later in pregnancy would confer no benefit.

Albuterol is the preferred reliever medication because of its overall excellent safety profile. Inhaled corticosteroids (ICS) are the preferred controller medication with budesonide being the preferred choice due to the availability of reassuring data in pregnant women. It is important to note that no data indicates that other ICS are unsafe during pregnancy, and if a patient was well controlled before, she should continue taking the same asthma medications during pregnancy.

Long-acting beta-agonists (LABAs) may be used as an alternative controller medication if clinically warranted by symptoms not controlled with ICS. A recent retrospective study showed no difference in the risk profile of step-up therapy with low-dose ICS/LABA inhalers or high-dose ICS in terms of major congenital malformations.

Leukotriene receptor antagonists (LTRAs) seem to be safe based on the animal safety data submitted to FDA; however, availability of human data is scarce.

The use of asthma medications should be continued during labor and delivery. Lumbar epidural anesthesia is preferred over general anesthesia, if cesarean section is required, and ketamine is the preferred anesthetic.

The key in asthma management is remembering that adequate control of asthma can improve the health of both mothers and their babies.

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder affecting the body's exocrine glands, including the pancreas, sweat glands, and lungs. It is the most common life-shortening genetic disorder in Caucasians with a carrier frequency rate of 1 in 25 and an incidence of 1 in 3000 live births in Caucasians. It is present in other races albeit less commonly with an incidence of 1 in 9000 and 1 in 15,000 live births in Hispanic and African-American populations in the United States. The most common gene deletion in 70% of genes is the delta F508, which leads to a misfolded CF transmembrane conductance regulator protein resulting in impaired movement of water and electrolytes across epithelial surfaces. In the last few decades, there have been improvements in treatment and survival, and the median life expectancy is now 41 years. About 4–5% of female patients become pregnant.

Malnutrition and thick cervical mucus may impair female fertility. Despite the concern that pregnancy would have an adverse impact on the mother, a large US review of 680 pregnant women with CF enrolled in the US Cystic Fibrosis Foundation National Patient Registry (1985 to 1997) demonstrated that survival was actually better in the pregnant female group than in the matched 3327 control patients with CF. They had higher predicted percentages of FEV₁ and higher weights. After adjustment of age, colonization with *Pseudomonas aeruginosa*, pancreatic function, and prepregnancy FEV₁, the pregnancy did not appear harmful. In another case-control study, pregnancy had little effect on patients with stable CF, although poor outcomes were seen in those with severe disease. The presence of pulmonary hypertension, cor pulmonale, or FEV₁ < 30% predicted is a relative contraindication to pregnancy.

Management

Prior to pregnancy, genetic counseling should be offered and should include a risk estimate of having a child with CF as it can be as high as 50% if the father is heterozygous for the gene. During pregnancy, fetal surveillance to detect early signs of growth restriction is essential.

Pregnant women with CF need regular monitoring by a dedicated team, to achieve favorable pregnancy outcomes. Commonly reported adverse events are fetal growth restriction and prematurity which includes iatrogenic early delivery because of maternal health deterioration. Women with CF are also at an increased risk of developing gestational diabetes. So screening for diabetes, baseline lung function tests as well as dietary supplementation, enzyme supplements, and chest physical therapy are important. Pulmonary exacerbations should be treated aggressively with antibiotic therapy paying attention to the class of medications and using those approved for use during pregnancy.

There is no contraindication to vaginal delivery; however, there is a small risk of pneumothorax if the second stage is very prolonged. General anesthesia should be minimized. There is no contraindication to breastfeeding, but mothers will need to use nutritional supplements in the postnatal period to ensure adequate caloric intake.

Infectious Diseases

The frequency of pneumonia in pregnancy is similar to that in the general population.

Effect of Pneumonia on Pregnancy

Infants born to women who develop pneumonia during pregnancy have a higher risk of being low birth weight and small for gestational age. Pneumonia may also precipitate preterm labor. Intrauterine and neonatal deaths have also been reported. Poor maternal and fetal outcomes occur primarily in mothers with underlying chronic respiratory illnesses.

Effect of Pregnancy on Pneumonia

Pregnancy increases the risk of complications of pneumonia including respiratory failure, and the mortality is higher.

Bacterial Pneumonia

The most common pathogens causing bacterial pneumonia in pregnancy are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*. The clinical features are similar to those in nonpregnant patients with fever, cough, dyspnea, and rigors as the presenting symptoms. A chest radiograph may be obtained to confirm the diagnosis. Penicillin, cephalosporins, and macrolides are safe antibiotics for use during pregnancy. Tetracyclines should be avoided as they may cause teeth discoloration in the fetus.

Viral Pneumonia

Influenza epidemics have shown that the morbidity and mortality rate in pregnant women is higher compared with nonpregnant women. Influenza vaccination has been shown to reduce hospitalization rates among pregnant women; therefore, the Centers for Disease Control and Prevention (CDC) recommends inactivated influenza vaccine during the second and third trimesters of pregnancy.

In 2009, a previously unrecognized strain of influenza A (H1N1) virus emerged and caused increased morbidity and mortality in pregnant women. Treatment with oseltamivir in pregnant women provided better protection against maternal-fetal transmission.

Maternal varicella pneumonia is associated with high mortality rates. Antiviral therapy with acyclovir reduces the mortality rates in pregnant patients and should be considered in the treatment of active disease. Passive immunization with varicella

zoster immune globulin (VariZIG) has been shown to reduce the risk of congenital varicella syndrome and is also effective in preventing maternal complications of varicella. The live attenuated vaccine against varicella is contraindicated in pregnancy.

Fungal Pneumonia

Fungal pneumonias are not common during pregnancy. Coccidioidomycosis is the most extensively studied fungal infection in pregnancy and can affect the outcome if it is disseminated. Compared with the general population, the risk of disseminated infection is higher in pregnant women, especially in the third trimester of pregnancy. Possible reasons are impairment of cell-mediated immunity and a stimulatory effect of progesterone on fungal proliferation. Amphotericin is the preferred antifungal for disseminated coccidioidomycosis. Azoles should be avoided during pregnancy due to an association with branchial cleft abnormalities. There is no evidence that other fungal infections, including blastomycosis, histoplasmosis, sporotrichosis, and cryptococcosis, are more severe during pregnancy.

Pneumonia complicating HIV infection in pregnancy is most commonly caused by a yeastlike fungus *Pneumocystis jirovecii*; it should be suspected in the presence of hypoxia that is out of proportion to the chest X-ray findings. Treatment is with high-dose co-trimoxazole/pentamidine with folate supplementation.

Tuberculosis

Pregnancy and tuberculosis have little effect on one another. Patients are often asymptomatic but can present with typical symptoms of cough, night sweats, hemoptysis, and weight loss. Tuberculin skin testing can be used for screening patients, and treatment should not be delayed during pregnancy. Rifampicin, isoniazid, and ethambutol are standard antitubercular drugs approved by the CDC due to their acceptable safety profile. Streptomycin is associated with congenital deafness and is contraindicated. Guidelines for the evaluation and management of newborns born to mothers with tuberculosis should be followed.

Aspiration Pneumonia

Aspiration pneumonia is a major cause of maternal morbidity and mortality. The pregnant woman is predisposed to aspiration during labor and delivery due to increased intra-abdominal pressure from the gravid uterus, relaxed gastroesophageal sphincter due to the effect of progesterone, delayed gastric emptying, vigorous abdominal palpation during examinations, and sedation and analgesia given in the delivery room.

Aspiration of the acidic gastric contents with a pH less than 2.5 induces chemical pneumonitis and pulmonary edema. Most cases of aspiration occur at the time of delivery. If general anesthesia or endotracheal intubation is needed, prophylaxis in the form of H₂ blockers, metoclopramide, or sodium citrate is often given before intubation.

The clinical presentation includes tachypnea, bronchospasm, hypoxemia, and hypotension with chest radiograph findings of either isolated or diffuse infiltrates. The timing of presentation depends on the volume of the aspirate with large volumes causing immediate asphyxiation and smaller volumes becoming apparent 6–8 h after the event. Respiratory failure can sometimes manifest in the postpartum period.

Management is supportive and includes oxygen, bronchodilators, and ventilatory support. Antibiotics should be considered early if there is suspicion of bacterial infection. The common bacterial pathogens are *Staphylococcus aureus*, gram-negatives, or anaerobes originating from the oropharynx.

Restrictive Lung Diseases

Restrictive lung diseases are characterized by a decrease in total lung capacity. This can be caused by abnormalities in the pleura, chest wall, and neuromuscular apparatus or alterations in the lung parenchyma. In most cases, due to the large pulmonary reserve, pregnancy is unaffected; however, in severe restriction, problems may arise during pregnancy and labor due to impaired reserve and higher oxygen demands. The gravid uterus pushes the diaphragm upward, thereby further worsening the restriction. As a general rule, patients with a FVC of <1 L or <50% of predicted FVC and those who have pulmonary hypertension are at greater risk of cardiopulmonary complications and hence should consider avoiding pregnancy or consider a therapeutic termination.

Kyphoscoliosis

Kyphoscoliosis is an abnormality of the spine characterized by posterior or lateral curvature or both. Almost half of the cases are idiopathic.

Effect of Kyphoscoliosis on Pregnancy

Depending on the site of primary curvature in pregnant females, there can be cardiopulmonary complications or obstetrical complications such as cephalopelvic disproportion. Other obstetrical complications experienced by pregnant women with kyphoscoliosis include prematurity and low birth weight.

Effect of Pregnancy on Kyphoscoliosis

It is controversial if spinal curvature will worsen during pregnancy. Studies have shown that the risk of progression of the curvature is low unless the scoliosis is unstable at the time of pregnancy. The presence of kyphoscoliosis during pregnancy may cause back pain.

Sarcoidosis

Sarcoidosis is a multisystem disorder of unknown etiology that is characterized by noncaseating epithelioid granulomas. The most common site of granuloma formation is the lungs. Other organs include the lymph nodes, eyes, skin, liver, heart, and nervous system.

Since the disease can involve any organ system, clinical manifestations are variable ranging from dyspnea, nonproductive cough, and chest pain to fever, joint/muscle aches, visual changes, and erythema nodosum. The disease has a variable course with spontaneous remissions occurring in nearly two-thirds of patients.

Effect of Sarcoidosis on Pregnancy

Sarcoidosis has not been found to adversely affect pregnancy outcomes. It is not transmitted to the fetus and does not increase the incidence of maternal or fetal complications.

Effect of Pregnancy on Sarcoidosis

Improvement in sarcoidosis occurs during pregnancy with a tendency to relapse in the postnatal period. Factors that indicate a poor prognosis in pregnancy include parenchymal infiltrates on chest radiograph, advanced radiographic staging, low inflammatory activity, advanced maternal age, requirement for drugs other than steroids for disease control, and the presence of extrapulmonary disease. Except for severely affected patients, sarcoidosis is not a contraindication to pregnancy.

Management

The diagnosis usually warrants a tissue biopsy of the involved organ that shows noncaseating granulomas. The patient may also have other laboratory abnormalities including an increased angiotensin-converting enzyme (ACE) level, elevated liver enzymes, and hypercalcemia.

Pulmonary function tests are abnormal in many patients and generally show a restrictive pattern but may be normal or obstructed if there is endobronchial involvement, stenosis, or airway distortion from parenchymal disease. There may also be a reduction in diffusion capacity.

Systemic steroids are the main stay of therapy and should be continued in pregnancy.

Acute Respiratory Distress Syndrome in Pregnancy

Acute respiratory distress syndrome (ARDS) is a severe form of acute lung injury characterized by severe hypoxemia and bilateral pulmonary infiltrates resulting from increased alveolar-capillary permeability.

ARDS in pregnancy can develop from obstetric and non-obstetric complication. The common obstetric causes are chorioamnionitis, amniotic fluid embolism, trophoblastic embolism, and placental abruption. The most common non-obstetric causes are pneumonia, sepsis, and aspiration.

Due to the changes in the definition of ARDS, it has been difficult to determine the true prevalence of the condition with estimates ranging from 1.5 to 75 cases per 100,000 population. The prevalence of ARDS during pregnancy is comparable to the number in the general population; however, the mortality rates of ARDS for both the mother and the fetus are high.

There is not enough evidence available regarding the management of ARDS in pregnancy, and treatment strategies are extrapolated from the studies on the general population. A multidisciplinary approach is necessary to optimize maternal and fetal outcomes and manage ARDS in pregnancy.

Pulmonary Edema and Pulmonary Vascular Disease

Pulmonary Edema

Acute pulmonary edema in pregnancy is an uncommon yet significant cause of morbidity and mortality with an estimated incidence of 0.08–0.5%. It was reported as the fourth most common form of maternal morbidity in the Scottish Confidential Audit of Severe Maternal Morbidity, which is one of the largest maternal morbidity audits. Acute pulmonary edema may occur during the antenatal, intrapartum, or postpartum periods.

Pregnant women are at an increased risk for pulmonary edema due to the hypervolemia and high cardiac output of pregnancy, the occasional need for tocolytic drugs that affect the vascular bed, and some clinical conditions unique to pregnancy. It is now recognized that in addition to fluid accumulation and retention,

fluid redistribution from the systemic circulation to the pulmonary circulation also plays an important role in causation of pulmonary edema.

Clinically, the patient presents with acute onset of breathlessness, orthopnea, cough, tachycardia, tachypnea, and hypoxemia. Chest X-ray, ECG, and echocardiography may help establish the diagnosis. In contrast to nonpregnant women, serum concentration of B-type natriuretic peptide is not widely utilized in pregnancy.

Transthoracic echocardiography is very helpful in diagnosis and management of the pulmonary edema as it enables assessment of cardiac systolic function.

Treatment is supportive and includes fluid restriction, circulation control with vasodilators, oxygenation, mechanical ventilation if needed, and close monitoring.

Pulmonary Embolism

Pulmonary embolism (PE) is a leading cause of maternal mortality accounting for 20% of maternal deaths in the United States. The estimated incidence of pulmonary embolism is 10.6 per 100,000 with the highest risk during the postpartum period.

Pregnant patients are predisposed to thromboembolic disease for several reasons including (1) an increase in several coagulation factors and a decrease in fibrinolytic activity, leading to a hypercoagulable state, (2) venous stasis caused by uterine compression of the inferior vena cava and the left iliac vein, and (3) trauma to pelvic veins at the time of delivery. This might account for the peak incidence of thromboembolism in the postpartum period, especially after cesarean section.

Other risk factors for developing thromboembolism include a past history of thromboembolism during pregnancy or while taking oral contraceptives, patients more than 35 years of age, prolonged bed rest, complicated or cesarean delivery, and inherited coagulation defects.

Clinical symptoms of pulmonary embolism (PE) include acute onset of dyspnea, tachypnea, tachycardia, and pleuritic chest pain that can rapidly progress to arrhythmias, syncope, and cardiovascular collapse if the PE is massive.

Despite the current availability of an array of diagnostic tests, diagnosis of a pregnant woman with suspected PE is very challenging. Recent ATS guidelines from the American Thoracic Society for evaluation of suspected PE in pregnancy recommend performing a chest radiograph (CXR) as the first test; if the chest X-ray is normal, then lung scintigraphy/ventilation-perfusion (V/Q) scan is recommended and finally computed tomographic pulmonary angiography (CTPA) rather than digital subtraction angiography (DSA) if the ventilation-perfusion (V/Q) scan is negative.

The patient can also be evaluated for the presence of a deep venous thrombosis (DVT), the presence of which increases the likelihood that the patient has a PE. Again, it is very difficult to diagnose DVT during pregnancy since contrast venography, which is the diagnostic test for DVT in nonpregnant patient, is usually performed in a limited manner to minimize the radiation exposure, thus decreasing the sensitivity of the test.

Treatment of DVT and PE necessitates the use of anticoagulants. Heparin is the drug of choice since warfarin crosses the placenta and can cause fetal dysmorphism, congenital heart defects, and growth retardation. Low-molecular-weight heparin (LMWH) is an alternative to standard heparin treatment and appears to be safe in pregnancy with fewer adverse effects such as thrombocytopenia and osteoporosis.

Treatment should be given throughout pregnancy and continued for about 4–6 weeks after delivery. If thrombosis occurs late in the pregnancy, treatment may be required for up to 3 months after delivery.

Thrombolytic therapy has also been used successfully in life-threatening thromboembolism during pregnancy. Other management options for a massive pulmonary embolism in pregnancy include surgical embolectomy and catheter-directed therapy.

Amniotic Fluid Embolism

During uncomplicated pregnancies, small amounts of amniotic fluid may enter the maternal circulation. Amniotic fluid contains fetal debris, including desquamated squamous cells, meconium, lanugo hair, and mucin. In a very small percentage of deliveries (estimated at 7.7 per 100,000 deliveries), amniotic fluid embolism develops with high maternal mortality rates of 80–90%. Clinical signs include sudden onset of severe dyspnea, hypoxemia, cyanosis, cardiovascular collapse, seizures, and coma that may occur during labor and delivery. This may progress to ARDS and disseminated intravascular coagulation (DIC).

Risk factors for developing amniotic fluid embolism include premature rupture of membranes, advanced maternal age, meconium staining of amniotic fluid, multiparity, and cesarean section. Disruption of the uterine veins has a role in pathogenesis. Two possible sites of entry are at the site of placental separation and small tears in the lower uterus and endocervix. It is unclear how much amniotic fluid is required to initiate the syndrome. The diagnosis can be made by the presence of a large amount of fetal squamous cells, mucin, and lanugo in the blood removed from the distal lumen of a wedged pulmonary artery catheter.

Treatment is primarily supportive for disseminated intravascular coagulation and cardiopulmonary failure.

Air Embolism

Venous air embolism results from entrapment of air in the venous system. It is an infrequent complication of pregnancy but can occasionally occur during labor and delivery especially during cesarean sections, induced abortions, manual extraction of placenta, and vacuum and forceps delivery. It has been also reported as a possible complication of oro-genital sex during pregnancy.

Air passes beneath the fetal membranes and into the circulation of the subplacental sinuses. Nonfatal air embolism during cesarean section may be more common than appreciated (studies suggest an incidence as high as 50%). A lethal air embolism

may follow a bolus of 3–5 cc/kg of air. The clinical presentation is acute onset tachypnea, chest pain, and gasping due to obstruction of pulmonary arterial blood flow. Diagnosis is very difficult and requires a high index of suspicion. Transesophageal echocardiogram offers the most sensitive measurement of air trapped within the right atrium or ventricle; however, it has the limitation of being invasive. Precordial Doppler is less sensitive but noninvasive.

Management includes optimum patient positioning, aspiration of air, discontinuation of nitrous oxide, administration of 100% oxygen, and flooding the surgical site with saline to prevent further air entry. There are case reports of maternal and fetal death with venous air embolism, so familiarity with this syndrome is important if prompt and appropriate therapy is to be provided.

Pulmonary Arteriovenous Malformation

Pulmonary arteriovenous malformations (PAVMs) are abnormal communications between the pulmonary and systemic circulation, which cause a right-to-left shunt. More than half of the cases reported during pregnancy are associated with hereditary telangiectasia, an autosomal dominant disorder characterized by the development of multiple arteriovenous malformations in the skin, mucous membranes, and/or visceral organs.

These PAVMs may expand during pregnancy because of the increase in blood volume, cardiac output, and venous distensibility, which increases the likelihood of rupture leading to life-threatening hemoptysis and hemothorax.

Diagnosis is based upon transthoracic contrast echocardiography and CT scan that also help to plan percutaneous embolization, which is the treatment of choice during pregnancy.

Spontaneous Pneumothorax in Pregnancy

Spontaneous pneumothorax is primary when it occurs in a person with no apparent lung disease or secondary as a complication of preexisting lung disease. It is rare in pregnancy. It can occur in the pre- or postpartum period but is most common during labor when the increase in alveolar intrathoracic pressure causes rupture of previously unrecognized blebs in the subpleural space.

Common predisposing factors for pneumothorax in pregnancy are previous respiratory infections, asthma, or a previous pneumothorax unrelated to pregnancy.

The diagnosis may be obscured due to other causes of dyspnea in pregnancy or the discomfort of parturition. This is a potentially serious situation since any impairment in ventilation during pregnancy can have detrimental effects on both the mother

and fetus. Spontaneous pneumothorax should be considered in a pregnant woman with acute onset dyspnea, chest pain, or history of prior pneumothorax. Prompt recognition and timely treatment of pneumothorax can prevent complications. The diagnosis can be confirmed with a chest radiograph with an abdominal shield.

Initial management is generally based on the size of the pneumothorax and may involve observation, drainage with a chest tube, or video-assisted thoracotomy (VATS). If the pneumothorax occurs close to term and is large enough to require placement of a chest tube, induction of labor should be considered with the chest tube in place to avoid recurrence during labor.

There is no evidence that cesarean section is necessary, and it should be performed for obstetric indications only. Patients with recurrent pneumothorax, who require VATS, should undergo surgery after the period of organogenesis and before the pregnancy is too far advanced.

Lung Transplant Patients

Improvement in survival and quality of life in patients with lung transplants has prompted them to consider pregnancy. Successful pregnancy is possible after lung transplantation, but it requires planning and a multidisciplinary team approach involving materno-fetal medicine, respiratory and transplant medicine, anesthesia, neonatology, genetics, and social services.

Since the first successful pregnancy reported in 1996 in a patient with single lung transplant, there have been several successful pregnancies. The 2010 report of the National Transplantation Pregnancy Registry reported 30 pregnancies in 21 lung transplant recipients, of which 18 were live births. Cystic fibrosis was the most common cause of lung transplant in 10 out of 21 recipients.

According to the most recently (in 2013) published management update on pregnancy after solid organ transplantation, it is recommended that pregnancy should be avoided for at least 1 year after transplant to minimize the episodes of acute rejection. It is also recommended that adequate and stable graft function should be achieved before pregnancy.

Patients should be counseled regarding the increased risk for both maternal and neonatal complications including prematurity and low birth weight. Of note is that the frequency of congenital malformations is similar to that of the general population (3–4%). The risk of rejection in patients who have stable graft function is not increased, except for patients with lung transplants who have a higher incidence of acute rejection compared with other organs (lung, 36%; heart, 20%; liver, 10%; kidney, 9%).

Lung transplant recipients are at a higher risk of developing hypertension and renal dysfunction. These comorbidities increase the risk of preeclampsia and preterm delivery, (6–13% vs. 2–7% in the general population).

Vaginal delivery is acceptable unless cesarean section is indicated for obstetric reasons. Breastfeeding should be avoided to prevent exposure of the newborn to immunosuppressive drugs.

Obstructive Sleep Apnea

Physiological and hormonal changes of pregnancy may predispose pregnant women to developing OSA. However, the prevalence of OSA among women of reproductive age is estimated to be 5–6%, but the exact prevalence of OSA among pregnant women is not known.

There is some evidence suggesting that OSA is associated with adverse maternal and fetal outcomes, due to low oxygen levels during apneic episodes. There are some protective mechanisms against OSA during pregnancy. High levels of progesterone have a stimulatory effect on the respiratory system, a decrease in REM sleep in later stages of pregnancy, and the rightward shift of the oxyhemoglobin dissociation curve. OSA generally occurs in obese patients and is precipitated by the estrogen-induced airway mucosal edema and vascular congestion.

Snoring is the most common symptom of OSA, but it is less specific than witnessed apneas and choking sensations during sleep for a diagnosis of OSA. There are no specific guidelines for screening pregnant women for OSA; however, it is prudent to evaluate pregnant women with loud snoring and witnessed apneas with overnight polysomnography.

Nasal continuous positive airway pressure (CPAP) is generally well tolerated during pregnancy. Patients should also be encouraged to follow conservative measures such as sleeping in the side position, elevation of the head of the bed, and avoiding the use of alcohol and sedatives.

Postpartum withdrawal of therapy with close follow-up should be considered due to rapid improvement of sleep apnea symptoms in the postnatal period.

Contraception and Pregnancy in Rare Lung Diseases

Rare Diseases are defined as conditions affecting less than 1 in 2000 people (in Europe) or less than 200,000 individuals (in the United States). Rare lung diseases (RLD) constitute 3% of these rare diseases. RLD are chronic in character and often have a poor prognosis. Advances in medicine have improved the survival and the quality of life in these patients, so they seek medical advice in planning their reproductive life.

However, in certain conditions, pregnancy is contraindicated due to the adverse effect on the course of the disease. In lymphangioleiomyomatosis (LAM), there is a very high risk of pneumothorax and loss of lung function, and in primary pulmonary hypertension (PPH), there is a high risk of mortality.

The contraceptive method should be individualized based on the personal choices of the patients and on the underlying disease process. All patients can safely use condoms. Oral contraceptives should be used cautiously in patients with cystic fibrosis due to poor absorption; they are absolutely contraindicated in LAM due to disease progression from exogenous estrogen. Since pregnancy is contraindicated in LAM, surgical sterilization should be considered in patients with LAM and PPH. Consideration should also be given to the future possibility of lung transplantation; therefore, combined hormone contraceptives should be avoided due to the risk of pulmonary thromboembolism. Currently, the experience in managing the reproductive health of women with RLD is limited, but based on the current experience, individualized and multidisciplinary approach is recommended to assist patients in making the best decisions about contraception and pregnancy.

Gynecologic Disorders and the Lungs

Thoracic Endometriosis Syndrome

Endometriosis is a condition characterized by the presence of endometrial tissue outside of the uterine cavity or myometrium. It is encountered most commonly in pelvic structures such as the ovary, uterine ligaments, pelvic peritoneum, cervix, labia, and vagina. Thoracic endometriosis syndrome (TES) is defined as the presence of endometrial tissue in or around the lung. Endometrial tissue may be present in the lung parenchyma, visceral and parietal pleura, diaphragm, and endobronchial sites. There are four distinct clinical entities:

- (a) Catamenial pneumothorax
- (b) Catamenial hemothorax
- (c) Hemoptysis
- (d) Pulmonary nodules

The clinical manifestations of TES imply the presence of endometrial tissue in the thoracic cavity that undergoes cyclical sloughing in response to the physiologic hormonal variations, and the clinical presentation depends on the affected structures.

How endometrial tissue migrates to the thoracic cavity has remained elusive; however, three theories have been proposed to explain it:

- (a) Retrograde menstruation with subsequent transperitoneal-transdiaphragmatic migration of endometrial tissue
- (b) Coelomic metaplasia
- (c) Lymphatic or hematogenous embolization from the uterus or pelvis

The disease probably has a multifactorial etiology, since none of these theories can fully explain all the clinical manifestations of TES.

Since TES is a rare condition, a high index of suspicion is the key to timely diagnosis. The clinical presentation is of a woman in her reproductive years (with a peak incidence between the ages of 30 and 35 years), who reports recurrent episodes of chest pain, dyspnea, or cough around the time of her menstrual cycle. Catamenial pneumothorax accounts for only 2.5–5% of cases of spontaneous pneumothorax in women even though it is the presenting symptom in 73% of cases of TES, followed by hemothorax in 14% and hemoptysis in 7%.

Physical examination findings are nonspecific. CT and MRI have been shown to be helpful in the diagnosis. MRI may be superior to CT since it helps in differentiating pleural from parenchymal implants. Bronchoscopy has a limited role in diagnosis due to the peripheral location of the disease and the low diagnostic yield of bronchial washings. In the era of endoscopic surgery, VATS allows direct visualization of the lung and diaphragmatic surfaces for endometrial implants. The size of the implants usually ranges from a few millimeters to a centimeter, and depending on the timing during the menstrual cycle, their color varies from brown to violet. Exploratory thoracotomy now has a limited role in the diagnosis and is used in cases of failure of VATS exploration.

Catamenial Pneumothorax

Catamenial pneumothorax (CP) refers to the occurrence of spontaneous pneumothorax during menstruation. It is also known as menstruation-related spontaneous pneumothorax (MSP) which was first reported in the 1950s by Maurer et al., who defined it as pneumothorax occurring within 24–72 h after onset of menses. In 1972, Lillington et al. introduced the term catamenial pneumothorax for spontaneous pneumothorax associated with menses. Previously considered to be rare, current knowledge suggests that CP is a more common reason for spontaneous pneumothoraces in women of reproductive age. As mentioned in the previous section, CP is frequently associated with thoracic endometriosis syndrome (TES), but there might be other etiological mechanisms. The etiology of the remainder is obscure, but a number of theories have been proposed. During menstruation, the absence of the normal cervical mucus plug provides a connection between the ambient air and the abdominal cavity through the uterus and fallopian tubes, hence allowing the air to move across the diaphragm through right-sided diaphragmatic fenestrations into the pleural space. This may account for the fact that 90–95% of MSPs are right-sided. A second theory is that bronchospasm with air trapping and pneumothorax may occur due to high levels of prostaglandin F₂ during menstruation. The third theory is that pleural blebs or bullae are more prone to rupture during menstruation because of hormonal changes. For cases that are not clearly associated with systemic

endometriosis, thoracoscopy during menstruation helps determine the etiology. Successful treatment necessitates a combined medical and surgical approach.

The medical therapy of TES primarily focuses on blocking the hormonal support from the ovaries that fosters the growth of the endometrial tissue. It consists of oral contraceptives, progestational agents, danazol, and gonadotropin-releasing hormone (GnRH) agonists. Surgical approaches include excision, local laser ablation, or pleurodesis. The recurrence rate with medical treatment exceeds 50% and subsequently requires surgical management. Conversely, there are reports of recurrence after surgical treatment of MSP that responded to subsequent hormonal therapy, so the current opinion is a sequential medical-surgical or surgical-medical approach.

Lymphangioliomyomatosis

Lymphangioliomyomatosis (LAM) was a disease of unknown origin in the mid-1990s, with no effective treatment. During the last decade, substantial progress has been made in understanding the natural history of the disease with support from NHLBI (National Heart, Lung, and Blood Institute). Once defined as a fatal disease of women of childbearing age, it is now known that LAM occurs in postmenopausal women as well.

LAM is a rare, slowly progressive, multisystem disorder of women characterized by proliferation of abnormal smooth muscle-like cells (LAM cells) associated with cystic lesions in the lungs and in the axial lymphatics (lymphangioliomyomas) and angiomyolipomas. In the lungs, the cells are present along the pulmonary blood vessels, lymphatics, and bronchioles.

LAM occurs in association with tuberous sclerosis complex (TSC) which is an autosomal dominant syndrome characterized by multisystem hamartoma-like tumor growths or sporadically with no evidence of a genetic abnormality. Sporadic LAM is rare with a prevalence of 2–5/million. In both cases, LAM is caused by a mutation in one of the two tumor suppressor genes TSC1 or TSC2 that produce hamartin and tuberin, respectively.

LAM most frequently presents with progressive breathlessness, recurrent pneumothorax, hemoptysis, or chylothorax. Extrapulmonary manifestations include an intra-abdominal hemorrhage or an abdominal mass. Patients who present with dyspnea and hemoptysis generally have a more severe disease and higher mortality than those presenting with pneumothorax.

LAM histology score (LHS), quantitative CT scan, and pulmonary function testing including exercise testing assist in assessing severity of the disease. Airflow obstruction and decreased lung diffusion capacity are the most frequent lung function abnormalities in LAM. Exercise tests are frequently abnormal in LAM patients who have low-grade pulmonary hypertension which worsens on exercise. Currently the best methods to assess the severity and progression of lung disease are frequent monitoring of FEV1 and DLCO and the 6-min walk test.

The focus of current research is to identify possible treatment targets. Studies have shown a potential role for sirolimus (rapamycin), an immunosuppressant drug that inhibits the hyperphosphorylation of ribosomal protein S6 and p70S6 kinase activation which is unregulated in LAM cells in the absence of tuberin (protein product of TSC2 gene). Another potential drug doxycycline is an inhibitor of matrix metalloproteinase (MMP) and has shown improvement in FEV1 and DLCO when used in the treatment of patients with severe LAM. Antiestrogen therapy and oophorectomy, which were once considered conventional therapies, are no longer universally recommended.

Trophoblastic Embolization

Gestational trophoblastic disease (GTD) is a term used for a rare group of pregnancy-related disorders ranging from benign, partial, and complete hydatidiform mole, invasive and metastatic mole, and malignant choriocarcinoma.

Trophoblastic pulmonary embolization is a rare complication of GTD and can occur following abdominal hysterectomy for invasive mole as well as after molar evacuation. The clinical course is dramatic with acute onset dyspnea, tachypnea, bilateral pulmonary infiltrates, and low oxygen levels. Possible etiologies for pulmonary findings include pulmonary trophoblastic embolization, hypervolemia, aspiration, DIC, and hyperthyroidism.

Although not very common, pulmonary trophoblastic embolization should be considered part of the differential diagnosis if a patient has acute onset respiratory distress in the postoperative period.

Malignant choriocarcinoma is associated with metastases to the lungs, which is the most common site of metastases.

Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome (OHSS) is an exaggerated response to the use of exogenous gonadotropins to induce ovulation for in vitro fertilization.

The syndrome has a broad spectrum of clinical presentations ranging from abdominal pain from ovarian enlargement, ovarian cysts, ascites, dyspnea, intravascular volume depletion, and acute renal failure.

OHSS is characterized by increased capillary permeability resulting in fluid shift from the intravascular space to third space compartments. Various factors have been previously implicated in the process including estrogen, prolactin, histamine, and prostaglandins, but recently it is thought to be related to vasoactive mediators such as interleukins, tumor necrosis factor- α , endothelin-1, and vascular endothelial growth factor (VEGF).

Risk factors to developing OHSS include young age, low body weight, polycystic ovary syndrome (PCOS), use of higher dose of exogenous gonadotropins, and previous episodes of OHSS.

Pulmonary manifestations include dyspnea that may result from decreased diaphragmatic movement due to abdominal enlargement. Other rare complications include pleural effusion, pulmonary edema, atelectasis, and acute respiratory distress syndrome (ARDS). Pulmonary embolism is a life-threatening complication and may occur due to hypercoagulable state.

Treatment is supportive and directed at maintaining intravascular blood volume. OHSS is a self-limiting disease, so most patients respond to medical therapy, and surgical intervention is required only for complications such as ruptured ovarian cyst or ovarian torsion. Thoracentesis may be needed for bilateral or persistent pleural effusions.

Polycystic Ovarian Syndrome and Obstructive Sleep Apnea

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder affecting almost 5–8% of females and characterized by menstrual irregularity, hyperandrogenism, obesity, and polycystic ovaries.

Patients with PCOS are at increased risk of various metabolic derangements such as insulin resistance, glucose intolerance, dyslipidemia, and hypertension.

Obstructive sleep apnea (OSA) has been recently recognized as a significant contributing factor to the pathophysiology of metabolic derangements in PCOS. Recent studies have shown that there are two distinct clinical entities: PCOS with OSA and PCOS without OSA. PCOS women with OSA may be at much higher risk for the development of diabetes and cardiovascular disease than PCOS women without OSA. The risk for OSA in PCOS is 30-fold higher than in similarly obese women.

It is proposed that OSA possibly triggers one or more of three major hormonal responses that contribute to the metabolic abnormalities associated with it. They are:

- (a) Activation of the hypothalamic-pituitary-adrenal (HPA) axis with increased cortisol production and secretion
- (b) Increased catecholamine output from sympathetic nervous system stimulation
- (c) Increased release of adipokines from the adipose tissue

Treatment of patients with OSA in PCOS with CPAP is important as it improves the metabolic profile.

Bibliography

1. Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung. *Am Rev Respir Dis.* 1980;121(3):559–81.

2. Hegewald MJ, Crapo RO. Respiratory physiology in pregnancy. *Clin Chest Med.* 2011;32(1):1–13.
3. Bhatia P, Bhatia K. Pregnancy and the lungs. *Postgrad Med J.* 2000;76(901):683–9.
4. Dombrowski MP, Schatz M. Asthma in pregnancy. *Clin Obstet Gynecol.* 2010;53(2):301–10.
5. Stone S, Nelson-Piercy C. Respiratory disease in pregnancy. *Obstet Gynaecol Reprod Med.* 2009;20(1):14–21.
6. Mehta N, Chen K, Hardy E, Powrie R. Respiratory disease in pregnancy. *Best Pract Res Clin Obstet Gynaecol.* 2015;29(5):598–611.
7. Mehta N, Chen K, Powrie RO. Prescribing for the pregnant patient. *Cleve Clin J Med.* 2014;81(6):367–72.
8. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program Asthma and Pregnancy Working Group. NAEPP expert panel report. Managing asthma during pregnancy: recommendations for pharmacologic treatment—2004 update. *J Allergy Clin Immunol.* 2005;115(1):34–46.
9. Tamasi L, Horvath I, Bohacs A, Muller V, Losonczy G, Schatz M. Asthma in pregnancy—immunological changes and clinical management. *Respir Med.* 2011;105(2):159–64.
10. Gilljam M, Antoniou M, Shin J, Dupuis A, Corey M, Tullis DE. Pregnancy in cystic fibrosis. Fetal and maternal outcome. *Chest.* 2000;118(1):85–91.
11. Gyi KM, Hodson ME, Yacoub MY. Pregnancy in cystic fibrosis lung transplant recipients: case series and review. *J Cyst Fibros.* 2006;5(3):171–5.
12. Coscia LA, Constantinescu S, Moritz MJ, Frank AM, Ramirez CB, Maley WR, et al. Report from the national transplantation pregnancy registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl.* 2009:103–22.
13. Shaner J, Coscia LA, Constantinescu S, McGrory CH, Doria C, Moritz MJ, et al. Pregnancy after lung transplant. *Prog Transplant.* 2012;22(2):134–40.
14. Divithotawela C, Chambers D, Hopkins P. Pregnancy after lung transplant: case report. *Breathe (Sheff).* 2015;11(4):291–5.
15. Sciscione AC, Ivester T, Largoza M, Manley J, Shlossman P, Colmorgen GH. Acute pulmonary edema in pregnancy. *Obstet Gynecol.* 2003;101(3):511–15. doi: S0029784402027333.
16. Venkata C, Venkateshiah SB. Sleep-disordered breathing during pregnancy. *J Am Board Fam Med.* 2009;22(2):158–68.
17. Shechter A, Varin F, Boivin DB. Circadian variation of sleep during the follicular and luteal phases of the menstrual cycle. *Sleep.* 2010;33(5):647–56.
18. Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endocrinol Metab.* 2001;86(2):517–20.
19. Batman PA, Thomlinson J, Moore VC, Sykes R. Death due to air embolism during sexual intercourse in the puerperium. *Postgrad Med J.* 1998;74(876):612–3.
20. Dennis AT, Solnordal CB. Acute pulmonary oedema in pregnant women. *Anaesthesia.* 2012;67(6):646–59.
21. Esplin MS, Varner MW. Progression of pulmonary arteriovenous malformation during pregnancy: case report and review of the literature. *Obstet Gynecol Surv.* 1997;52(4):248–53.
22. Gossage JR, Kanj G. Pulmonary arteriovenous malformations. A state of the art review. *Am J Respir Crit Care Med.* 1998;158(2):643–61.
23. Alifano M, Trisolini R, Cancellieri A, Regnard JF. Thoracic endometriosis: current knowledge. *Ann Thorac Surg.* 2006;81(2):761–69. doi: S0003-4975(05)01322-6.
24. Azizad-Pinto P, Clarke D. Thoracic endometriosis syndrome: case report and review of the literature. *Perm J.* 2014;18(3):61–5.
25. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. *Lancet.* 2010;376(9742):717–29.

26. Garner EI, Chang-Lee WY, Lu KH, Goldstein DP, Berkowitz RS. Trophoblastic pulmonary embolization after hysterectomy for invasive complete mole. A case report. *J Reprod Med.* 1999;44(10):908–12.
27. Ngan HY, Seckl MJ, Berkowitz RS, Xiang Y, Golfier F, Sekharan PK, et al. Update on the diagnosis and management of gestational trophoblastic disease. *Int J Gynaecol Obstet.* 2015;131(Suppl 2):S123–6.
28. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangiomyomatosis. *N Engl J Med.* 2008;358(2):140–51.
29. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med.* 2007;357(21):2153–65.
30. Korom S, Canyurt H, Missbach A, Schneiter D, Kurrer MO, Haller U, et al. Catamenial pneumothorax revisited: clinical approach and systematic review of the literature. *J Thorac Cardiovasc Surg.* 2004;128(4):502–8.
31. Sahn SA, Heffner JE. Spontaneous pneumothorax. *N Engl J Med.* 2000;342(12):868–74.
32. Lara B, Fornet I, Goya M, López F, De Miguel JR, Molina M, et al. Contraception, pregnancy and rare respiratory diseases. *Arch Bronconeumol.* 2012;48(10):372–8.
33. Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boiselle PM, Hurwitz LM, et al. American Thoracic Society documents: an official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline—evaluation of suspected pulmonary embolism in pregnancy. *Radiology.* 2012;262(2):635–46.
34. Nitsche K, Ehrmann DA. Obstructive sleep apnea and metabolic dysfunction in polycystic ovary syndrome. *Best Pract Res Clin Endocrinol Metab.* 2010;24(5):717–30.
35. Peavy H, Gail D, Kiley J, Shurin S. A national heart, lung, and blood institute history and perspective on lymphangiomyomatosis. *Lymphat Res Biol.* 2010;8(1):5–8.
36. Practice Committee of the American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. *Fertil Steril.* 2003;80(5):1309–14.