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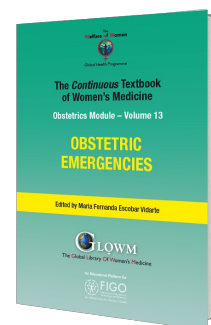
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Chapter

Acute Lung Injury and Acute Respiratory Distress Syndrome (ARDS) during Pregnancy

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INTRODUCTION

The pregnant patient is at risk of developing acute respiratory distress syndrome (ARDS) from a number of obstetric and non-obstetric conditions. Hydrostatic pulmonary edema may also occur, not directly related to known cardiac disease. This chapter briefly reviews some relevant physiological aspects, the causes of ARDS and pulmonary edema in the pregnant patient, and the principles of management. More information relating to ventilator management and general ICU care is available in the Obstetrics Module, Volume 9, *Principles and practice of obstetric high dependency and critical care* of this publication.

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome definition

Acute respiratory distress syndrome (ARDS) was initially described in adults as a condition sudden in onset associated with bilateral radiographic opacities and severe hypoxemia.¹ Pathology in these patients demonstrated pulmonary edema, alveolar collapse and hyaline membrane involvement of the alveoli that resembled neonate hyaline membrane disease. An earlier American-European Consensus Conference (AECC) definition established criteria of bilateral radiological infiltrates, impaired oxygenation and exclusion of hydrostatic pulmonary edema. This was replaced in 2012 by the Berlin definition that addressed timing of the condition, included criteria for positive end-expiratory pressure (PEEP) and that classified patients into three distinct severity categories according to oxygenation criteria (Table 1).² This definition highlights the acute onset of ARDS (within 7 days of the inciting condition) to exclude various chronic

conditions, does not require objective measurements to exclude heart failure, and does not include the term "acute lung injury".

Table 1 Berlin definition for acute respiratory distress syndrome (ARDS).²

Timing	Symptoms of worsening respiratory or new respiratory symptoms that occur within 1 week of known clinical process
Chest imaging	Bilateral infiltrates that cannot be fully explained by atelectasis, lung nodules, or effusions
Origin of edema	Not completely explained by cardiac failure or fluid overload
Oxygenation ($\text{PaO}_2/\text{FiO}_2$) with PEEP or CPAP ≥ 5 cm	Mild = $200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ Moderate = $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$ Severe = $\text{PaO}_2/\text{FiO}_2 < 100 \text{ mmHg}$

EPIDEMIOLOGY

The reported incidence of ARDS in the nonpregnant population varies with the diagnostic definition utilized, but has been reported to be in the range of 5–80 per 100,000 population per year.³ ARDS occurs fairly frequently in pregnancy and is a leading cause of maternal death.⁴ Data to assess the frequency of ARDS in pregnancy are based on small studies with varying definitions, but suggest an incidence of 70–130 cases per 100,000 deliveries.^{4,5} In these studies, mortality is reported at 25–33%.

PATHOPHYSIOLOGY

ARDS is produced by a variety of direct and indirect insults to the lung, such as bacterial pneumonia, viral pneumonitis and inhalation injury (direct), as well as sepsis, transfusion-related and pancreatitis (indirect). Direct causes of ARDS involve local damage to the lung epithelium, whereas indirect causes produce lung damage via systemic inflammation and diffuse endothelial damage.

The pregnant patient is predisposed to the development of pulmonary edema by several mechanisms, namely the increased circulating blood volume in pregnancy, the reduced serum albumin level,⁶ and possibly by upregulation of components of the acute inflammatory response.⁷ Various pregnancy-associated conditions and pregnancy-specific conditions described below may result in ARDS.

The lung injury of ARDS may be exacerbated by inappropriate ventilator management – low tidal volumes are protective,⁸ while high tidal volumes or pressure may cause ventilator-induced lung injury.⁹ As pregnant patients were excluded from all studies of mechanical ventilation in ARDS, little is known about how the pregnant state may impact these findings.

CAUSES

The pregnant patient is at risk of developing ARDS and pulmonary edema from pregnancy-associated complications or other conditions (Table 2).⁶

Table 2 Causes of ARDS during pregnancy.

Obstetric conditions	Conditions aggravated by pregnancy	Conditions unrelated to pregnancy
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<i>Direct pulmonary injury</i> Obstetric conditions	Conditions aggravated by pregnancy	Conditions unrelated to pregnancy
Amniotic fluid embolism	Gastric acid aspiration	Bacterial pneumonia
Tocolytic pulmonary edema	Viral pneumonitis	Drowning
Trophoblastic disease	Fungal pneumonia (e.g. coccidioidomycosis)	
<i>Indirect/extrapulmonary causes</i>		
Pre-eclampsia	Transfusion-related acute lung injury	Non-obstetric sepsis
Obstetric sepsis		Pancreatitis
Placental abruption		Trauma

Obstetric conditions

Amniotic fluid embolism

Amniotic fluid embolism is a condition precipitated by amniotic fluid entering the maternal circulation, producing a sudden and often catastrophic hemodynamic event, characterized by acute pulmonary hypertension and myocardial dysfunction.¹⁰ The precise pathophysiology is unclear, but may involve humoral factors in the amniotic fluid (leukotrienes, arachidonic acid metabolites, e.g. prostaglandin F2a) or an anaphylactoid reaction. Survivors of the initial event may go on to develop ARDS as well as a disseminated intravascular coagulopathy.

Pulmonary edema secondary to pre-eclampsia

Acute pulmonary edema occurs in a small proportion of patients with pre-eclampsia (approximately 3%), and is more common in obese, chronically hypertensive women.¹¹ This problem most commonly occurs in the early postpartum period, related to fluid administration and return of blood to the central circulation as the uterus contracts. Differentiating between cardiogenic and non-cardiogenic edema is not always immediately possible in the individual patients, and the mechanism is likely multifactorial in origin. A component of hydrostatic edema occurs related to the increased afterload and diastolic dysfunction, and is aggravated by the decreased serum oncotic pressure. However, ARDS also occurs as a result of pre-eclampsia, given that the pathophysiology of pre-eclampsia involves activation of an inflammatory process.¹²

Tocolytic pulmonary edema

A variety of drugs may be used to inhibit uterine contractions in preterm labor, although much less frequently used than previously occurred. Most of these drugs have been associated with the development of pulmonary edema. The most well described drugs are beta-adrenergic agonists,¹³ but this may also occur with calcium antagonists and magnesium. The frequency of this tocolytic-induced pulmonary edema varies from 0.3% to 9%. The mechanism of this effect is unclear, but may involve the prolonged exposure to catecholamines causing myocardial dysfunction, increased capillary permeability, the large volumes of intravenous fluid that may be administered (in response to drug-induced maternal tachycardia), and reduced osmotic pressure. Glucocorticoids administered simultaneously to enhance fetal lung maturity in preterm labor may also compound fluid retention.

The clinical presentation is nonspecific with clinical features of pulmonary edema during or immediately following administration of the tocolytic drug. Treatment requires discontinuing the drug and supportive measures such as oxygen and diuresis.^{6,13} Early management reduces the need for mechanical ventilation. If the pulmonary edema fails to resolve in 12–24 hour, an alternative diagnosis should be considered.⁶

Gestational trophoblastic disease

Pulmonary edema may rarely occur in the patient with benign hydatidiform mole, as a result of trophoblastic pulmonary embolism. As this is an uncommon event, and a differential diagnosis should always be considered: fluid overload, ventricular dysfunction, systemic inflammatory response and thyrotoxicosis which may accompany hydatidiform mole.

Pulmonary complications from trophoblastic embolism usually occur during evacuation of the uterus, and the incidence of pulmonary complications is higher in women later in pregnancy. Treatment is supportive, and resolution usually occurs within 48–72 hours.¹⁴ Pulmonary infiltrate in the woman with molar pregnancy may also be caused by choriocarcinoma with pulmonary metastases.

Nonobstetric conditions

Bacterial pneumonia

Pneumonia is an important cause of maternal morbidity and mortality with a reported incidence similar to that in the general population, varying from 1 in 367 to 1 in 2388 deliveries.^{15,16} Pregnancy does increase the risk for major complications of pneumonia, including ARDS and respiratory failure. The microbiologic spectrum of pneumonia in pregnancy is not different to the usual organisms found in community-acquired pneumonia. Unfortunately, the diagnosis of pneumonia may be delayed because of an inappropriate reluctance to obtain a chest radiograph.

Viral pneumonia

Viral pneumonitis, particularly influenza pneumonitis, is associated with increased mortality rates compared with the general population, likely due to the alterations in cell-mediated immunity.¹⁷ The maternal mortality rate in influenza pandemics is higher than in the general population. The 2009 influenza A (H1N1) pandemic was associated with a high incidence of severe disease and respiratory failure in pregnant women.¹⁸ Outcome is improved with the early institution of anti-viral therapy (within 48 hours of symptoms). Oseltamivir was used quite extensively in pregnancy during the 2009 pandemic with good results.¹⁹ Vaccination is an effective preventative measure, and a low uptake of vaccination was common in pregnant patients developing severe respiratory failure in this pandemic.²⁰

Varicella pneumonitis may also be associated with adverse outcomes in pregnancy. Although one review reported a 35% mortality rate in pregnancy compared with 11% in other adults,²¹ not all studies have confirmed this increased incidence or mortality in pregnancy. Acyclovir therapy is effective to reduce mortality in gravid patients.²²

Other non-obstetric infections

Severe sepsis may be complicated by ARDS and as discussed above, the pregnant patient is likely to be more susceptible to ARDS than others. Case series have documented an association between pyelonephritis in pregnancy and the development of ARDS.²³ This is likely a result of the fact that pyelonephritis is a common cause of severe sepsis in pregnancy, rather than any specific relationship between this condition and ARDS.

Gastric acid aspiration

Pregnant patients are at risk of developing gastric acid aspiration during labor, producing maternal acute lung injury (Mendelson syndrome).²⁴ Contributing factors include increased intra-abdominal pressure, lowering the tone of the esophageal sphincter (due to progesterone), and use of the supine position for delivery. The majority of cases of aspiration occur in the delivery suite. The low pH of the gastric contents causes chemical pneumonitis and ARDS. Pregnant women should always be considered to have a full stomach. It should also be noted that endotracheal intubation of the pregnant patient is more difficult than in the non-pregnant population, and appropriate precautions should be taken.²⁵

Transfusion related acute lung injury

Transfusion related acute lung injury (TRALI) manifests with the sudden onset of dyspnea and tachypnea occurring during, or within 6 hours of, transfusion of plasma-containing blood products. It is an important cause of acute respiratory failure in pregnancy.²⁶ The mechanism involves sequestration of activated neutrophils in pulmonary capillaries, likely related to anti-leukocyte antibodies in some donor units. The differential diagnosis includes circulatory fluid overload. Management is supportive and most patients improve within a few days, although fatal outcomes may occur.

MANAGEMENT

Respiratory physiologic changes in pregnancy

Management of the pregnant woman with ARDS needs to take into account the respiratory physiological changes accompanying pregnancy. Loss of lung volume due to the enlarging uterus is largely offset by widening of the anteroposterior and transverse diameters. However, a progressive decrease in functional residual capacity (FRC) occurs, reduced by 10–25% by term.²⁷ Lung compliance is not altered, but chest wall and total respiratory compliance are reduced in the third trimester.²⁸ Minute ventilation is increased during pregnancy; this begins in the first trimester and reaches 20–40% above baseline by term. The major mechanism is an increase in tidal volume of approximately 30–35%,²⁹ mediated by the increase in respiratory drive produced by elevated serum progesterone levels. Blood gas measurement in pregnancy reveals a respiratory alkalosis with compensatory renal excretion of bicarbonate. PaCO₂ is reduced at about 28–32 mmHg (3.7–4.3 kPa) and plasma bicarbonate falls to 18–21 mEq/L.³⁰ Although the alveolar-to-arterial oxygen tension difference (PAO₂-PaO₂) is unchanged by pregnancy, as FRC diminishes towards term, an increased PAO₂-PaO₂ may develop in the supine position. Maternal oxygen consumption and CO₂ production increase due to both fetal and maternal metabolic processes, reaching 20–33% above baseline by the third trimester. This increased oxygen consumption in the presence of a reduced FRC (oxygen reservoir) makes the pregnant patient very susceptible to the rapid development of hypoxia in response to hypoventilation or apnea.³¹ Alkalosis (respiratory or metabolic) reduces uterine blood flow and adversely affects fetal oxygenation.³²

Radiological imaging in pregnancy

The diagnosis of ARDS relies on the finding of bilateral pulmonary infiltrates on chest X-ray or CT scan, and a brief discussion regarding the risks of ionizing radiation in pregnancy is therefore relevant. As a general rule, the risk is low and maternal investigations should not be withheld if they are necessary for management. Ionizing radiation can produce a number of effects on the fetus depending on the gestation of exposure. These adverse effects include teratogenicity, abnormal neurological development and an increased risk of childhood leukemia. Fetal teratogenicity risks are greatest during first trimester and related to the total dose administered (usually requiring >50 mGy).^{33,34} Carcinogenesis (development of childhood cancer) arises due to DNA mutations which can occur at any radiation dose with no absolute lower safe threshold. The risk with low fetal radiation exposure is minimal, increasing to an approximate 1/300 to 1/900 risk of childhood cancer at a fetal dose of 50mGy.³⁴ A well-shielded chest X-ray to the mother will expose the fetus to about 0.01 mGy and a chest CT to about 0.66 mGy.³³ In contrast, a CT abdomen and pelvis (for example required following maternal trauma) will expose the fetus to up to 50 mGy increasing the risk of childhood leukemia.³⁴ A recent study evaluated 319 pregnant women exposed to radiological studies below the diaphragm at 2–15 weeks' gestation.³⁵ No increased risk of malformations, intrauterine death or growth restriction were demonstrated.

ICU management

While there are few differences in the management of the pregnant patient who has ARDS compared with one who is not pregnant, most studies of ARDS management have excluded pregnant patients. ICU management and mechanical ventilation in pregnant patient are covered in more detail in the Volume 9, *Principles and practice of obstetric high dependency and critical care*, of the Obstetrics modules of this publication, but some aspects are briefly summarized here.

1. Non-invasive ventilation has the potential benefits of reducing the complications of intubation and avoiding sedative drugs. This modality should be reserved for patients who are alert and protecting their airway, and with an expectation for a short-term need for ventilator support.³²
2. Few data exist to direct oxygenation and carbon dioxide targets in the pregnant patient. It seems reasonable to aim for a maternal oxygen saturation greater than 92% (but avoiding hyperoxia, which may be harmful). Hypocapnia causes uterine arterial vasoconstriction impairing oxygen delivery to the fetus.³⁶ Moderate hypercapnia may be tolerated.³⁷

3. Endotracheal intubation in the critically ill pregnant woman carries significant risks, due to the difficulty in pre-oxygenation (reduced FRC), the more rapid oxygen consumption, and anatomic changes to the upper airway (edema and mucosal friability).³⁸ Intubation should be performed by the most experienced operator available.
4. Prolonged ICU mechanical ventilation has not been extensively studied in the pregnant patient, and it seems reasonable to follow the usual principles applicable to the nonpregnant patient.
5. Less conventional interventions (inhaled NO, prone positioning, extracorporeal membrane oxygenation (ECMO)) have all been reported with success in pregnancy in limited reports.
6. Delivery in the pregnant woman with severe ARDS may be considered, in an attempt to improve maternal respiratory status. While some women may demonstrate some improvement in oxygenation or lung compliance, this does not always occur.³⁹ Delivery should be reserved for the fetus at risk due to severe maternal hypoxemia at a gestation with a reasonable expectation of survival.

PRACTICE RECOMMENDATIONS

- **ARDS may occur in pregnancy from a variety of obstetric and non-obstetric conditions, rapidly causing hypoxemia and respiratory failure.**
- **Treatment of most conditions is supportive, and in the absence of pregnancy-specific data usual management protocols should be used.**
- **Delivery does not necessarily improve the maternal condition, and should usually be reserved for situations where the fetus is at risk and will also benefit from the intervention.**

CONFLICTS OF INTEREST

Author statement awaited.

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