CLINICAL OBSTETRICS AND GYNECOLOGY
Volume 66, Number 1, 208–222
Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

Acute Respiratory Distress Syndrome in Pregnancy: Updates in Principles and Practice

ABIGAIL WATTS, MD, and ALEXANDER G. DUARTE, MD
Division of Pulmonary, Critical Care, and Sleep Medicine, University of Texas Medical Branch, Galveston, Texas

Abstract: Acute respiratory failure occurs in 0.05% to 0.3% of pregnancies and is precipitated by pulmonary and nonpulmonary insults. Acute respiratory distress syndrome (ARDS) is the rapid onset of hypoxemic respiratory failure associated with bilateral pulmonary opacities on chest imaging attributed to noncardiogenic pulmonary edema. The pathophysiological features of ARDS include hypoxemia, diminished lung volumes, and decreased lung compliance. While there is a paucity of data concerning ARDS in the pregnant individual, management principles do not vary significantly between pregnant and nonpregnant patients. The following review will discuss the diagnosis and management of the pregnant patient with ARDS.
Key words: acute respiratory distress syndrome, acute respiratory failure, pregnancy

The initial report of acute respiratory distress syndrome (ARDS) described the acute onset of severe hypoxemia despite supplemental oxygen and bilateral radiographic opacities requiring tracheal intubation and initiation of invasive mechanical ventilation.[1–4] This description of ARDS reported diminished lung compliance that improved with the use of mechanical ventilation and positive end-expiratory pressure (PEEP). Subsequently, autopsy examination of the lungs of these patients revealed pulmonary edema, alveolar collapse, and hyaline membrane involvement of the alveoli that pathologically resemble diffuse alveolar damage.[5]

To differentiate ARDS from alternative causes of acute respiratory failure, a definition of ARDS was developed by an American-European Consensus Conference (AECC) in 1994 that included the following criteria: partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) <200, presence of bilateral infiltrates on chest radiography consistent

Correspondence: Alexander G. Duarte, MD, Division of Pulmonary, Critical Care, and Sleep Medicine, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX. E-mail: aduarte@utmb.edu

The authors declare that they have nothing to disclose.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

with pulmonary edema and pulmonary artery wedge pressure ≤ 18 mm Hg or no clinical evidence of elevated left atrial pressure.[6] Furthermore, acute lung injury was introduced to describe patients with milder hypoxemia (PaO_2/FiO_2 between 201 and 300) in addition to the above radiographic and hemodynamic features. However, a limit of the AECC definition concerned lack of information about case definition regarding timing or cause and this resulted in variation in physician interpretation of chest radiographs, leading to delayed recognition or misdiagnosis of ARDS.[7–9] In addition, the AECC definition of ARDS did not outline the causes, often resulting in a misdiagnosis of ARDS. This was in part related to the initial description as an acute process lacking an outlined time course such that subacute or chronic conditions such as hypersensitivity pneumonitis or interstitial lung disease could mimic ARDS.[10] Another limitation of the AECC definition was that degree of hypoxemia was not accounted for by the effects of PEEP on the PaO_2/FiO_2 ratio.[11] As a result, in 2011, an international group of critical care investigators created a modified definition of ARDS. This revised classification was designated as the Berlin Definition[11] (Table 1). The Berlin definition classified patients into 3 distinct categories of severity based on degree of hypoxemia (according to the PaO_2/FiO_2 ratio) and addressed issues regarding onset, chest radiographic features, and suspected cause of the radiographic infiltrates.

The Berlin definition indicates that an early diagnosis of ARDS can be made in the setting of acute bilateral radiographic infiltrates and hypoxemia in patients not requiring invasive mechanical ventilation, thus resulting in timelier recognition and management. This definition also permits the use of chest radiographs or computed tomography (CT) for the identification of alveolar opacities. Furthermore, since pulmonary artery catheters are infrequently used in the care of critically ill patients, wedge pressure determination was no longer a requirement, and physician clinical judgment was replaced regarding the etiology of pulmonary edema.

TABLE 1. Modified Berlin Definition of Acute Respiratory Distress Syndrome

Onset occurs within 1 wk of a known trigger or worsening of respiratory symptoms
Chest imaging (including chest radiograph or chest tomography) reveals bilateral opacities not fully attributed to effusions, lobar collapse, or nodules
Origin of the observed radiographic infiltrates causes respiratory failure not entirely attributed to cardiac failure or volume overload
Oxygenation deficits
Mild: PaO_2/FiO_2 range: 201-300 with PEEP or CPAP 5 cm H_2O
Moderate: PaO_2/FiO_2 range: 101-200 with PEEP or CPAP 5 cm H_2O
Severe: $PaO_2/FiO_2 < 100$ with PEEP or CPAP 5 cm H_2O

CPAP indicates continuous positive airway pressure; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure.

Epidemiology

Standardized definitions of the syndrome have allowed investigators to examine the epidemiology of ARDS in the general population. In 1999, a group of investigators described the incidence of ARDS as 13.5 per 100,000 per year in 150 Nordic intensive care units (ICUs).[12] Similarly, the incidence of ARDS was reported to be 12.6 patients per 100,000 per year at a US urban hospital.[13] In 2002, an international, multisite study of 5183 mechanically ventilated individuals described 9% met diagnostic criteria for ARDS.[14] Subsequently, an international prospective study (LUNG SAFE) employed a standard, screening procedure and found that 10.4% of critically ill patients fulfilled the Berlin criteria for ARDS.[15]

The incidence ARDS during pregnancy has been reported to occur 15.9 to 130 per

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

100,000 deliveries.[16–18] A retrospective, single-center study over a 14-year period identified 41 patients of ARDS with an incidence of 70 patients per 100,000 deliveries.[17] Another single center from Argentina reported critically ill obstetric patients from 1998 to 2005 found an incidence of ARDS of 130 per 100,000 deliveries.[18] In 2018, using administrative claims database, from 2006 to 2012, Rush et al[3] identified 2808 pregnant patients with ARDS requiring mechanical ventilation and reported an incidence of 36.5 per 100,000 deliveries in 2006 and this increased to 59.6 per 100,000 deliveries in 2012. In this study, during the hospital stay, 41% of patients underwent cesarean delivery, 14.6% underwent vaginal delivery and pregnancy outcomes were unclear in the remaining 45%. Notably, pneumonia accounted for the principal cause of ARDS in pregnancy for 25.9%, followed by preeclampsia/eclampsia in 22.1% and puerperal infections in 9.6%. The inpatient mortality for patients with ARDS requiring >96 hours of mechanical ventilation was 14%. Of note, other investigators have reported mortality attributable to ARDS from 24% to 39%.[16–18] The range of reported rates of ARDS in pregnant patients highlights regional and time-based variation that underscores issues related to the diagnostic precision of ARDS. The prevalence and outcomes in pregnant patients with ARDS represent an important future research directive.

Etiology

The causes of ARDS may be considered as pulmonary-specific conditions such as pneumonia and toxic inhalation and extrapulmonary conditions such as sepsis, pancreatitis, trauma, and blood product transfusion that can result in severe hypoxemia and alveolar infiltrates on imaging.[4,7] Notably, the most common causes for ARDS include sepsis, trauma, pneumonia, aspiration, and blood product transfusions.[3,15] In ARDS, the formation of noncardiogenic pulmonary edema can be a result of direct or indirect leading to lung injury. Examples of direct lung injury include aspiration pneumonitis, viral, bacterial, or fungal pneumonia, toxic gas inhalation, fat emboli, drowning, pulmonary contusion, and reperfusion injury. In contrast, indirect lung injury can result from sepsis, acute pancreatitis, disseminated intravascular coagulation, trauma, drug overdose, burns, near drowning, adverse medication effect, and blood product transfusions.[7] An international, multicenter study of nonobstetric patients with ARDS found the most common causes of ARDS were pneumonia (59%), extrapulmonary sepsis (16%), aspiration (14%), trauma (4.2%), blood transfusion (3.9%), and pulmonary contusion (3.2%). Interestingly, an identifiable risk factor could not be identified in 8.3% of subjects.[15]

With respect to pregnancy, nonobstetric conditions leading to ARDS include pneumonia, sepsis, viral lung infections [influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)], blood product transfusion, intracerebral hemorrhage, and trauma.[18] A "two-hit" model of ARDS in pregnancy has been proposed, suggesting that a proinflammatory state observed in pregnancy (and during the postpartum period) primes subjects for a robust inflammatory response to a lesser "second hit" or insult resulting in ARDS.[19,20] Various physiological changes occur during pregnancy, including decreased lower esophageal sphincter tone, delayed gastric emptying, and increased intraabdominal pressure during labor and delivery; this can predispose pregnant patients to chemical pneumonitis through aspiration of gastric contents.[21] Sepsis because of pyelonephritis is a risk factor for ARDS in up to 7% of pregnant patients.[22] Yet, a retrospective study from Southern California reported the frequency of pyelonephritis

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

leading to ARDS to be 0.5%, thereby suggesting that prevention and treatment of complicated urinary tract infections may partly explain the decrease.[23]

In the pregnant patient, viral lower respiratory tract infections are a nonobstetric risk factor for ARDS that include influenza A (H1N1), SARS-CoV-1 (middle east respiratory syndrome), and SARS-CoV-2 [coronavirus disease 2019 (COVID-19)].[24–26] Investigators have reported that a higher risk for influenza-associated complications in pregnant patients that includes hospitalization, ICU admission, ARDS, and death.[18,24,26,27] The contemporary COVID-19 pandemic highlights the deleterious effects of viral pneumonias among pregnant patients. Pregnant patients with SARS-COV2 infection are at greater risk of acute hypoxic respiratory failure and ARDS compared with age-matched nonpregnant patients.[28] Maternal and fetal outcomes of 32 pregnant critically ill patients with COVID-19 were recently analyzed in a multicenter cohort analysis; both maternal treatments and outcomes, including survival, receipt of mechanical ventilation, and ICU length of stay were similar among pregnant patients and nonpregnant women of childbearing age. High rates of cesarean delivery and preterm birth were observed among this critically ill cohort with COVID-10.[29]

Obstetric causes of ARDS include eclampsia, puerperal infections, septic abortion, amniotic fluid embolism, venous air embolism, tocolytic therapy, ovarian hyperstimulation syndrome, and retained products of conception.[16–18] Investigators have reported eclampsia as a risk factor for ARDS and eclampsia was noted in 22% of pregnant patients with ARDS.[18] Amniotic fluid embolism is a rare event occurring most frequently late in labor or postpartum.[30] This complication occurs when amniotic fluid enters the maternal circulation via the endocervical veins or placental attachment and infiltrates the pulmonary vasculature, leading to cardiogenic shock, disseminated intravascular coagulation, hemorrhage, and hypoxemia. Noncardiogenic pulmonary edema has been described in patients that survive amniotic fluid embolism.[30] Tocolytic medications, such as terbutaline and ritodrine, used to inhibit uterine contractions associated with preterm labor have also been associated with noncardiogenic pulmonary edema.[31] Notably, the administration of multiple doses of tocolytics and hypervolemia are linked with the development of ARDS. Frequent presenting symptoms of tocolytic-associated ARDS are dyspnea and cough, hypoxemia and bilateral radiographic infiltrates during administration or up to 12 hours after tocolytic discontinuation.

Diagnosis

ARDS is characterized as acute hypoxic respiratory failure due to a systemic inflammatory process leading to increased pulmonary vascular permeability with loss of aerated lung parenchyma, resulting in hypoxemia and pulmonary opacities. Interestingly, the physiological changes of pregnancy are thought to potentially predispose to pulmonary edema, as parturient patients develop an increase in plasma and blood volume and reduction in plasma protein oncotic pressure.[32] Frequent symptoms associated with ARDS include dyspnea, cough, fever, and fatigue. The nonspecific nature of these symptoms can make the diagnosis of ARDS exceptionally challenging, and the need for increasing supplemental oxygen should alert the clinician to consideration of ARDS in a patient with a predisposing condition such as sepsis, bacteremia, pneumonia, pancreatitis, or blood transfusion. The clinical features of ARDS include tachypnea, accessory muscle use, and bilateral crackles on chest auscultation, and these will frequently develop within 6 to 72 hours after the predisposing injury

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

followed by rapid progression. Radiographic chest findings can reveal typical features of diffuse, bilateral lung infiltrates that may initially appear as asymmetric, dependent lobar opacities that progress to involve both lungs[33] (Fig. 1). Incorporation of thoracic CT imaging to the diagnosis of ARDS has led to substitution over chest radiography. Compared with chest radiography, the image resolution obtained with thoracic CT is more sensitive in the early detection of interstitial lung markings and opacities associated with ARDS (Fig. 2). Lung ultrasonography has not been established as an imaging criterion for ARDS, yet several reports

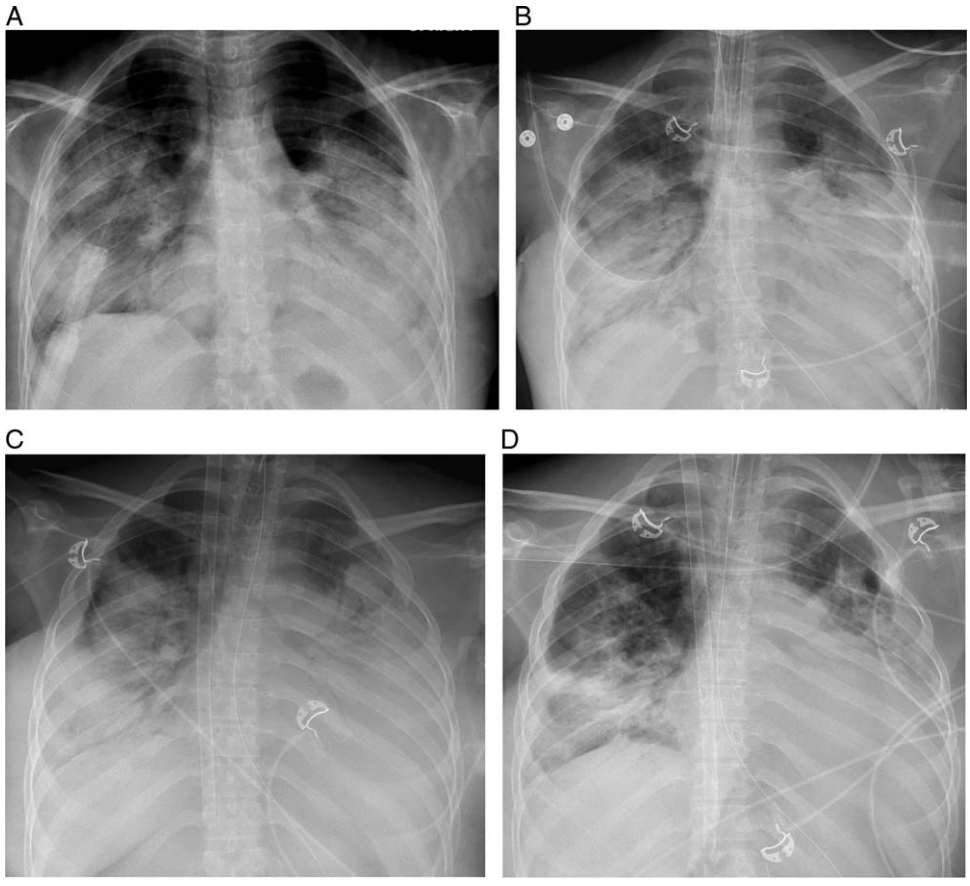

FIGURE 1. Serial chest radiography of a 27-year-old pregnant patients with acute respiratory distress syndrome from COVID-19 pneumonia; over the course of 35 days, patient's oxygen requirements progressed from high flow nasal oxygen (A) to tracheal intubation and invasive mechanical ventilation (B), to extracorporeal membrane oxygenation (C, D). Plain chest radiography demonstrates widespread coalescent opacities and scattered air bronchograms. Normal heart size, lack of Kerley B lines, rapid radiographic improvement with diuretic therapy, and absence of pleural effusions aid in differentiating acute respiratory distress syndrome from cardiogenic pulmonary edema. In addition, alveolar infiltrates in acute respiratory distress syndrome tend to involve all areas of the lung diffusely (as seen above), rather than the characteristic perihilar pattern of alveolar infiltrates observed in cardiogenic pulmonary edema.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

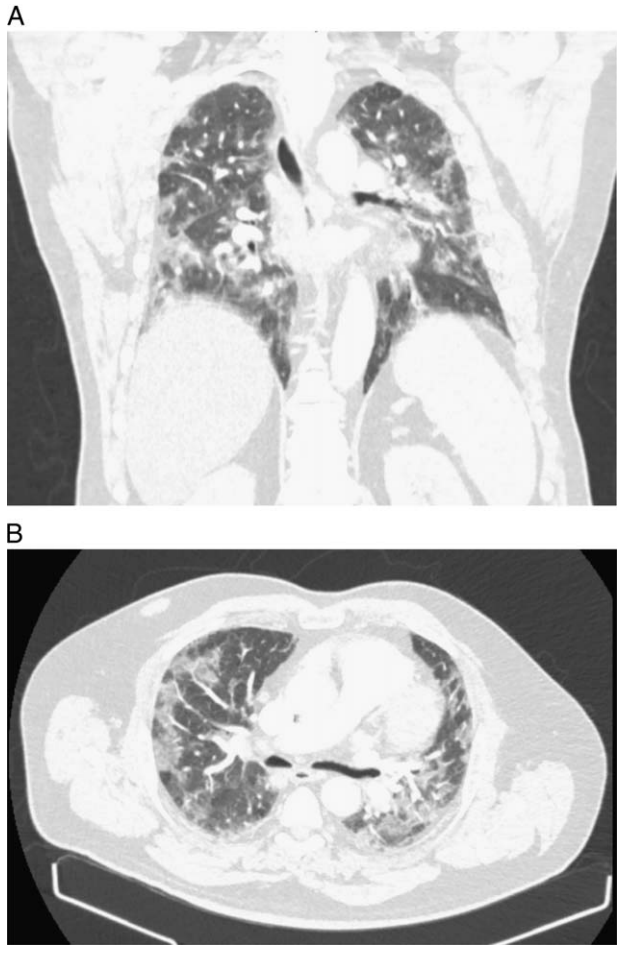

FIGURE 2. Coronal (A) and axial (B) computed tomography of the chest of a 68-year-old patient with acute respiratory distress syndrome secondary to COVID-19 pneumonia early in the disease state. Computed tomography demonstrates bilateral, widespread ground glass attenuation interspersed with areas of normal lung. Ground glass opacification is a nonspecific finding suggestive of diminished air content within the affected lung.

have described this as a useful in the diagnosis, and an attractive feature involves the lack of ionizing radiation. In patients with ARDS, thoracic ultrasonography can demonstrate multiple "B-lines" that are the result of thickened interlobular septa and/or ground glass opacities.[34] To determine if cardiogenic pulmonary edema is the cause for acute respiratory failure, clinicians can for the presence of jugular venous distention and conduct cardiac auscultation for S3, S4 gallop, or murmurs. Furthermore, serum brain natriuretic peptide may be useful, as a serum level <100 pg/mL can be used to identify patients with ARDS with a sensitivity of 27%, specificity of 95%, positive predictive value of 90%, and negative predictive value 44%.[35] Importantly, serum brain natriuretic peptide levels >100 pg/mL do not exclude ARDS. Use of transthoracic echocardiography is a useful diagnostic modality to evaluate for mitral or aortic valvular disorders as well as severe left

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

ventricular systolic dysfunction. As a more definitive and invasive approach, right heart catheterization can be performed if the cause of the pulmonary edema cannot be excluded.

Supportive Care

The process involving management of the pregnant patient with ARDS requires identification and source control of the provoking cause, antibiotic administration, conservative fluid resuscitation, hemodynamic support, oxygen supplementation, and initiation of invasive or noninvasive mechanical ventilation. A central goal in management requires early identification and treatment of the underlying etiology with diagnostic assessment directed at infectious conditions, such as pneumonia, chorioamnionitis, pyelonephritis or postpartum endometritis, necrotizing fasciitis, and toxic shock syndrome.[36–38] In particular, appropriate antibiotic selection and prompt administration are important, as antibiotic delivery within the first hour of documented septic shock is associated with improved outcomes.[39–41] Inspection of surgical sites to identify soft tissue infections, abdominal imaging to evaluate for potential occult abscesses, and removal of intravenous catheters can mitigate the systemic consequences of sepsis. The clinician should also consider other causes of ARDS, such as pancreatitis, amniotic fluid embolism, and transfusion-related acute lung injury. Conservative fluid management with serum lactate monitoring is essential to ensure adequate organ perfusion.[42] Intravenous fluid resuscitation is important to maintain adequate tissue perfusion, but excessive resuscitation may lead to worsening pulmonary opacities, decreases in lung compliance, and further. Another cornerstone of therapy is supplemental oxygen administration provided by face mask or high flow nasal cannula to maintain an oxygen saturation $> 92\%$ with frequent assessment for the need for escalation to invasive mechanical ventilation.

In the treatment of acute hypoxemic respiratory failure, high flow nasal cannula oxygen delivery ensures dependable FiO_2 and improved patient comfort compared with delivery via conventional face mask.[43] Investigators have reported successful outcomes with high flow supplemental oxygen administration by high flow nasal cannula in the treatment of ARDS and viral pneumonia(influenza, SARS-CoV-2).[44,45] However, a prospective, multicenter, randomized clinical trial conducted in Europe compared high flow nasal cannula, conventional face mask and noninvasive ventilation (NIV) in nonobstetric patients with acute hypoxemic respiratory failure reported a similar intubation rate in all groups.[46] The observation of similar rates of intubation among patients treated with high flow nasal cannula and NIV may be due to delayed intubation and institution of mechanical ventilation.[47,48] Although NIV is often used in the care of patients with acute exacerbations of chronic obstructive pulmonary disease and cardiogenic pulmonary edema, it is controversial in the treatment of ARDS. A systematic review comparing examined the use of NIV in patients with acute hypoxic respiratory failure and concluded a scarcity of data to support its use in ARDS, and that it should be avoided as first-line therapy.[49]

In the management of pregnant patients with ARDS, several case reports have described NIV as a method of ventilatory support.[50–53] An attractive feature of NIV is that it does not require the use of sedating medications and can reduce complications associated with intubation and mechanical ventilation. Yet, there is not sufficient evidence to recommend use of NIV instead of high flow nasal cannula as initial therapy in pregnant patients with ARDS, as there are no formal clinical studies. If the clinician uses

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

NIV for ventilatory support of the patient with ARDS, it should be used early in the management of hemodynamically stable patients with PaO_2/FiO_2 of 200 to 300. Frequent clinical assessments including arterial blood gas measurements 30 to 45 minutes after initiation of NIV are needed and when signs of increasing tachypnea, poor mental status, or worsening oxygenation develop, the clinician should proceed with tracheal intubation and initiation of invasive mechanical ventilation.

Mechanical Ventilation

Mechanical ventilation is a vital component of critical care management. The goal of mechanical ventilation is to ensure acceptable gas exchange, relieve excessive loads placed on respiratory muscles by the altered pulmonary mechanics while minimizing harm to the lungs. In ARDS, epithelial and endothelial injury leads to formation of noncardiogenic edema with protein-rich fluid and cellular debris that occupies gas exchange lung units resulting in hypoxemia and diminished lung distensibility.[7] Airspace filling with fluid, cellular material, and depletion of lung surfactant results in loss of lung compliance, as measured by volume per unit of pressure, such that mechanical work of breathing increases. Chest CT imaging is used to quantify the amount of aerated, partially aerated and airless lung and this proportion varies with disease severity and stage of ARDS; early (day 1) versus late (day 7). Moreover, a large proportion of the lung parenchyma is airless, and this often exceeds 50% of lung at end expiration. These observations led to introduction of the concept of the baby lung that describes the small amount of lung capable of being ventilated to fulfill the physiological requirements of an adult with ARDS.[50] The baby lung is a functional construct to describe the reduction in aerated lung available for gas exchange and reinforces the need to deliver smaller tidal volumes to achieve adequate oxygenation and prevent lung overdistension and volutrauma.

Before initiation of mechanical ventilation, clinicians are reminded of the upper airway anatomic changes often occur with pregnancy that may result in difficulty with orotracheal intubation.[51,54] During labor, upper airway hyperemia and edema can complicate orotracheal intubation.[55,56] Also, decreased lung volumes (secondary to uterine enlargement and diaphragmatic elevation) and increased oxygen consumption associated with pregnancy can predispose to rapid hypoxemia during intubation. Thus, preoxygenation with use of a facemask, high flow nasal cannula or NIV is essential to prevent oxygen desaturation during intubation.[55–58] To minimize gastric aspiration, rapid-sequence intubation with a sedative and neuromuscular paralytic has been recommended. For the difficult airway or failed intubation in the obstetric patient, a set of algorithms and guidelines have previously been published.[51–53]

Currently, there is a lack of randomized clinical trials comparing different ventilator strategies in pregnant patients with ARDS. Consequently, the approach to mechanical ventilation in the pregnant patient with ARDS is directed by clinical trials involving nonpregnant patients that supports us of a low tidal volume, lung protective strategy.

Mechanical ventilation of the pregnant patient with ARDS is guided by a similar treatment strategy as in nonpregnant patients specifically lung protective ventilation strategy with low tidal volume and PEEP.[59] Retrospective case series concerning mechanical ventilation during pregnancy for acute hypoxemic respiratory failure have described epidemiology, causes, and maternal-fetal survival.[16–19,22] Unfortunately, there is limited data regarding physiological or clinical outcomes with use of different ventilation strategies

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

in pregnant patients with acute respiratory failure.

Initiation and selection of mechanical ventilation settings are by physiological and clinical endpoints. When mechanical ventilation is initiated, the clinician may start at FiO_2 of 1.0 with the intention of lowering the FiO_2 to the lowest amount that will provide the desired improvement in gas exchange as noted on arterial blood gas measurements and pulse oximetry.[59] Due to concerns that high concentrations of inhaled oxygen for prolonged periods are associated with potential pulmonary toxicity, adjustment of the FiO_2 is necessary with a maternal oxygenation target of $PaO_2 > 70$ mm Hg or oxygen saturation 94% to 96% to avoid fetal distress though the data for this is scarce.[16,22]

Historically, clinicians selected ventilator tidal volumes of 10 to 15 mL/kg based on ideal body weight, and this practice was informed largely by experiences with paralyzed patients with normal lung function undergoing surgery or with neuromuscular weakness during the poliomyelitis epidemic.[60] Though, the use of lung volumes (10 to 15 mL/kg) in patients with lung injury due to pneumonia or sepsis leads to volutrauma due to airway overdistention. A pivotal multicenter trial compared the outcomes of 861 patients with ARDS randomized to receive mechanical ventilation with a tidal volume 6 or 12 mL/kg based on predicted body weight.[61] Notably, pregnant patients were excluded from study participation. As part of the mechanical ventilation strategy, the low tidal volume group had their tidal volumes adjusted to a range of 4 to 6 mL/kg in order maintain plateau pressure ≤ 30 cm H_2O. Importantly, the predicted body weight was determined using the following formula: 45.5+0.91(centimeters of height −152.4). The investigators reported a significantly lower mortality for patients ventilated at 6 mL/kg compared with those ventilated at 12 mL/kg group (31% vs. 40%, respectively). Recent consensus guidelines recommend that adult patients with ARDS undergoing invasive mechanical ventilation should receive a ventilator strategy with tidal volume of 4 to 8 mL/kg predicted body weight and a plateau pressure 30 cm H_2O).[62]

In pregnant patients with acute hypoxic respiratory failure requiring mechanical ventilation, there is no prospective clinical trials, and the majority of reports are retrospective in nature. A case series from 4 referral centers between 2003 and 2014 reported on ventilator strategy and clinical outcomes in 29 critically ill parturients receiving invasive mechanical ventilation.[63] The authors reported 3 maternal deaths and 3 neonatal deaths. Mean tidal volume was 6.4 mL/kg based on actual body weight but was actually 7.7 mL/kg based on predicted body weight. Notably, the authors did not report any episodes of barotrauma. In addition, 10 patients gave birth while receiving mechanical ventilation with modest improvements in oxygenation and lung compliance.[63]

PEEP

The use of PEEP in the ARDS though initially controversial is now accepted as a standard component of mechanical ventilation.[4] In patients with ARDS, application of PEEP improves oxygenation through recruitment of collapsed, airless regions of the lung that reduce intrapulmonary shunting.[7] There is scarce prospective data regarding the effects of PEEP on maternal outcomes of parturients with ARDS, however, this has been examined in nonpregnant subjects with ARDS. A large, multicenter trial assessed clinical outcomes of 549 patients with ARDS treated with a low volume ventilation strategy of 6 mL/kg that were randomized to receive high PEEP (mean: 13.2 ± 3.5 cm H_2O) or low PEEP (mean: 8.3 ± 3.2 cm H_2O).[64] The authors found similar 60-day mortality, ventilator-free days, and incidence of barotrauma for

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

both groups. A subsequent analysis of 6 randomized control trials that included 2580 patients with ARDS examined the outcomes in patients treated with 6 mL/kg tidal volume ventilation receiving high (15.1 ± 3.6 cm H_2O) and low (9.1 ± 2.7 cm H_2O) PEEP. Patients treated with higher PEEP demonstrated better oxygenation with no difference in barotrauma, organ failure, or ventilator-free days compared with the low PEEP group.[64] Furthermore, patients with moderate to severe ARDS ($PaO_2/FiO_2 \leq 200$) treated with lower PEEP had a significantly lower mortality.[65] While a prospective clinical trial to evaluate PEEP in pregnant patients has not been performed, use of a low tidal volume strategy has been successfully implemented in pregnant patients with influenza A pneumonia.[66] Thus, application of low tidal volume strategy of 6 mL/kg while maintaining plateau pressure ≤ 30 cm H_2O and application of PEEP to provide PaO_2 65 to 90 mm Hg appears to be a beneficial strategy in the pregnant patient with ARDS.

Pharmacologic Therapy

In the management of ARDS, different pharmacologic agents have been explored but have not demonstrated clinically significant impact on patient outcomes.[67] For example, corticosteroid use has been examined in the treatment of ARDS, and improvements in oxygenation with low to moderate methylprednisolone doses have been reported (< 2.5 mg/kg/d).[68,69] However, the role of corticosteroids in the treatment of ARDS remains controversial. Meta-analyses have described improvements in oxygenation, reductions in ventilator-free days, and decreased ICU length of stay in patients with ARDS treated with corticosteroids; however, the effect of corticosteroids on mortality in patients with ARDS remains unclear.[70,71] Moreover, in patients with ARDS due to influenza A (H1N1) pneumonia, which included 14 pregnant patients, worsened mortality.[72] Conversely, the RECOVERY trial was an open-label trial that examined the impact of dexamethasone (6 mg/d for 10 d) on mortality in patients hospitalized with COVID-19. At the time of enrollment, 1007 patients were mechanically ventilated and dexamethasone administration resulted in reduced 28-day mortality compared with usual care.[73] Moreover, a meta-analysis of 7 clinical trials examined outcomes in critically ill patients with COVIS-19, including the RECOVERY, and reported a decreased 28-day mortality in mechanically ventilated patients treated with corticosteroids.[74] Yet, many important questions remain to be answered including the benefit and optimal dosing in ARDS subphenotypes, the guidance of therapy by biomarkers, duration of treatment, and occurrence of adverse effects such as nosocomial infections.

Extracorporeal Life Support

For patients with severe ARDS, extracorporeal membrane oxygenation (ECMO) has been employed as salvage therapy. During the 2009 influenza A pandemic, investigators described the initiation of ECMO for the treatment of refractory hypoxemia related to severe influenza pneumonia.[66,75–77] In the United States, during the 2009 influenza pandemic, 509 pregnant women were hospitalized with acute influenza infection and 115 (22.6%) required ICU admission while 30 did not survive.[24] As a result of this influenza pandemic, ECMO was initiated in parturients with ARDS and several case series reported successful use of venovenous ECMO in patients with ARDS secondary to influenza A pneumonia.[66,77] A meta-analysis of the maternal outcomes of 39 parturients with ARDS complicated by influenza A pneumonia reported frequent use of venovenous ECMO and found a 74.6% maternal

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

survival and 70% live birth rate.[78] During the COVID-19 pandemic, ECMO use has been described in several case series of pregnant patients with ARDS.[79–81] One case series of 9 pregnant patients with ARDS due to COVID-19 treated used venovenous ECMO and reported 100% maternal survival with no major ECMO-related complications. Patients had a median PaO_2/FiO_2 62 mm Hg and median ECMO duration of 10 days.[79] A single-center case series described 5 pregnant and 5 postpartum patients with COVID-19 infection treated with venovenous ECMO. Of the 5 pregnant women, 2 had intrauterine fetal demise and 3 underwent delivery for maternal hemodynamic instability. The median length of ECMO use was 22 days. In-hospital mortality was 20% with 6 patients discharged home.[80] A retrospective report of the Extracorporeal Life Support Organization (ELSO) registry compared outcomes of 100 pregnant or peripartum and 1080 nonpregnant patients requiring ECMO due to COVID-19 pneumonia. Before ECMO, both groups demonstrated severe ARDS with PaO_2/FiO_2 <100, though the pregnant group had fewer comorbidities and were younger; 32 years versus 49 years. The authors conclude that use of VV ECMO in pregnant/postpartum compared with nonpregnant female patients was associated with lower mortality, 84% and 51.5%; respectively.[81] As for complications, fewer ECMO-related renal complications were observed in pregnant/peripartum patients and similar bleeding complications compared with nonpregnant patients.

Additional Therapies

Additional therapies for refractory hypoxemia (particularly in pregnant patients with ARDS) remain controversial. Neuromuscular blockade is sometimes employed in cases of refractory hypoxemia to enhance ventilator-patient synchrony and reduce oxygen consumption. In the ELSO-based registry, 71% of pregnant and peripartum patients were treated with neuromuscular paralysis.[81] Current recommendations are to use neuromuscular paralysis for limited duration (~48 h) to prevent complications such as neuromyopathy or awareness with paralysis.

In nonpregnant patients with ARDS, prone positioning is an effective salvage therapy[82] and before the 2019 COVID pandemic, prone positioning was infrequently used in pregnant patients. However, in pregnant patients with moderate to severe ARDS prone positioning has been reported to be safe and effective.[83–87] In addition, the ELSO-based registry reported 58% of pregnant and peripartum patients were prone positioned before ECMO initiation.[81] Modification of prone positioning, especially in patients in the third trimester (24 to 28 wk), involves use of padding or blankets and pillows above and below the gravid uterus to avoid aortocaval compression.[84] The Society for Maternal-Fetal Medicine suggests that prone positioning is feasible in both pregnant and postpartum patients.[85]

Finally, the role of delivery in the management of ARDS in pregnant patients is unclear. Timing of delivery in critically ill patients depends on a number of factors, including maternal disease severity, gestational age, and patient preferences. Guidelines from the Society of Maternal-Fetal Medicine suggest consideration of controlled delivery in the management of refractory hypoxemia in pregnant patients with COVID-19 at or after 32 weeks gestation. At this time, the exact role and timing of delivery in the management of ARDS in pregnant patients remains unclear.[85]

References

1. Lapinsky SE. Management of acute respiratory failure in pregnancy. *Semin Respir Crit Care Med.* 2017;38:201–207.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

2. Pollock W, Rose L, Dennis C-L. Pregnant and postpartum admissions to the intensive care unit: as systematic review. *Intensive Care Med*. 2010;36: 1465–1474.
3. Rush B, Martinka P, Kilb B, et al. Acute respiratory distress syndrome in pregnant women. *Obstet Gynecol*. 2017;129:530–535.
4. Ashbaugh DG, Bigelow DB, Petty TL, et al. Acute respiratory distress in adults. *Lancet*. 1967;2:319–323.
5. Thille AW, Esteban A, Fernandez-Segoviano P, et al. Comparison of the Berlin Definition for acute respiratory distress syndrome at autopsy. *Am J Respir Crit Care Med*. 2013;187:761–767.
6. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149:818–824.
7. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nat Rev Dis Primers*. 2019;5:18.
8. Rubenfeld GD, Caldwell E, Granton JT, et al. Interobserver variability in applying a radiographic definition for ARDS. *Chest*. 1999;116:1347–1353.
9. Meade MO, Cook RJ, Guyatt GH, et al. Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2000;161:85–90.
10. Schwarz MI, Albert RK. Imitators of the ARDS" Implications for diagnosis and treatment. *Chest*. 2004;125:1530–1535.
11. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307:2526–2533.
12. Luhr OR, Antonsen K, Karlsson M, et al. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. The ARF Study Group. *Am J Respir Crit Care Med*. 1999;159: 1849–1861.
13. Hudson LD, Steinberg KP. Epidemiology of acute lung injury and ARDS. *Chest*. 1999;116(suppl 1): 74S–82S.
14. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA*. 2002;287:345–355.
15. Bellani G, Laffey JG, Phan T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016; 315:788–800.
16. Catanzarite V, Willms D, Wong D, et al. Acute respiratory distress syndrome in pregnancy and the puerperium: causes, courses, and outcomes. *Obstet Gynecol*. 2001;97:760–764.
17. Perry KG, Martin RW, Blake PG, et al. Maternal mortality associated with adult respiratory distress syndrome. *South Med J*. 1998;91: 441–444.
18. Vasquez DN, Estenssoro E, Canales S, et al. Clinical characteristics and outcomes of obstetric patients requiring ICU admission. *Chest*. 2007;131: 718–724.
19. Sheng C, Yu YH, Zhao KS, et al. Acute lung inflammatory response and injury after hemorrhagic shock are more severe in postpartum rabbits. *Crit Care Med*. 2012;40:1570–1577.
20. Lapinsky S. Pregnancy joins the hit list. *Crit Care Med*. 2012;40:1679–1680.
21. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. *Am J Obstet Gynecol*. 1946;52:191–205.
22. Cole DE, Taylor TL, McCullough DM, et al. Acute respiratory distress syndrome in pregnancy. *Crit Care Med*. 2005;33(suppl):S269–S278.
23. Wing DA, Fassett MJ, Getahun D. Acute pyelonephritis in pregnancy: an 18-year retrospective analysis. *Am J Obstet Gynecol*. 2014;210:219. e1–219.e6.
24. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A (H1N1) virus illness among pregnant women in the United States. *JAMA*. 2010;303:1517–1525.
25. Di Mascio D, Khalil A, Saccone G, et al. Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy. *Am J Obstet Gynecol MFM*. 2020;2:100110.
26. Holstein R, Dawood FS, O'Halloran A, et al. Characteristics and outcomes of hospitalized pregnant women with influenza, 2010 to 2019. A repeated cross-sectional study. *Ann Int Med*. 2022;175:149–158.
27. Rasmussen SA, Jamieson DJ. Influenza and pregnancy in the United States: before, during and after 2009 H1N1. *Clin Obstet Gynecol*. 2012;55: 487–497.
28. Overton EE, Goffman D, Friedman AM. The epidemiology of COVID-19 in pregnancy. *Clin Obstet Gynecol*. 2022;65:110–122.
29. Easter SR, Gupta S, Brenner SK, et al. Outcomes of critically ill pregnant women with COVID-19 in the United States. *Am J Respir Crit Care Med*. 2021;203:122–125.
30. Pacheco L, Clark S, Klassen M, et al. Amniotic fluid embolism: principles of early clinical managment. *Am J Obstet Gynecol*. 2020;222:48–52.
31. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med*. 1989; 110:714–718.
32. Bandi VD, Munnur U, Matthay MA. Acute lung injury and acute respiratory distress syndrome in pregnancy. *Crit Care Clinics*. 2004;20: 577–607.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

33. Ball L, Vercesi V, Constantino F, et al. Lung imaging; how to get better look inside the lung. *Ann Transl Med*. 2017;5:294.
34. Chiumello D, Papa GFS, Artigas A, et al. ERS statement on chest imaging in acute respiratory failure. *Eur Respir J*. 2019;54:1900435.
35. Levitt JE, Vinayak AG, Gehlbach BK, et al. Diagnostic utility of B-type natriuretic peptide in critically ill patients with pulmonary edema: a prospective cohort study. *Crit Care*. 2008;12: R3.
36. Barton JR, Sibai BM. Severe sepsis and septic shock in pregnancy. *Obstet Gynecol*. 2012;120: 689–706.
37. Plante LA. Management of sepsis and septic shock for the obstetrician-gynecologist. *Obstet Gynecol Clin North Am*. 2016;43:659–678.
38. Longo D, Stevens DL, Bryant AE. Necrotizing soft tissue infections. *New Engl J Med*. 2017;377: 2253–2265.
39. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589–1596.
40. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med*. 2017; 376:2235–2244.
41. Liu VX, Fielding-Singh V, Greene JD, et al. The timing of early antibiotics and hospital mortality in sepsis. *Am J Respir Crit Care Med*. 2017;196: 856–863.
42. Semler MV, Wheeler AP, Thompson BT, et al. Impact of initial central venous pressure on outcomes of conservative versus liberal fluid management in acute respiratory distress syndrome. *Crit Care Med*. 2016;44:782–789.
43. Spoletini G, Alotaibi M, Blasi F, et al. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest*. 2015;148:253–261.
44. Rello J, Pérez M, Roca O, et al. High-flow nasal therapy in adults with severe acute respiratory infection: a cohort study in patients with 2009 influenza A/H1N1. *J Crit Care*. 2012;27: 434.
45. Ranieri VM, Tonetti T, Navalesi P, et al. High-flow oxygen for severe hypoxemia: oxygenation response and outcome in patients with COVID-19. *Am J Respir Crit Care Med*. 2022; 205:431–439.
46. Frat J-P, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372: 2185–2196.
47. Bellani G, Laffey JG, Pham T, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome: insights from the LUNG SAFE Study. *Am J Respir Crit Care Med*. 2017; 195:67–77.
48. Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med*. 2015 ;41:623–632.
49. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J*. 2017;50:1602426.
50. Frassanito L, Draisci G, Pinto R, et al. Successful application of helmet non-invasive ventilation in a parturient with acute respiratory distress syndrome. *Minerva Anestiol*. 2011;77:1121–1123.
51. Djibre M, Berkane N, Salengro A, et al. Non-invasive management of acute respiratory distress syndrome related to influenza A (H1N1) virus pneumonia in a pregnant woman. *Intensive Care Med*. 2010;36:373–374.
52. Gattinoni L, Marini JJ, Pesenti A, et al. The "baby lung" became an adult. *Int Care Med*. 2016;42:663–673.
53. Mushambi MC, Kinsell SM, Popat M, et al. Obstetric Anaesthetists'Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics. *Anaesthesia*. 2015;70:1286–1306.
54. Mosier JM, Sakles JC, Law JA, et al. Tracheal intubation in the critically ill where we came from & where we should go. *Am J Respir Crit Care Med*. 2020;201:775–788.
55. Kodali BS, Chandrasekhar S, Bulich LN, et al. Airway changes during labor and delivery. *Anesthesiology*. 2008;108:357–362.
56. Frat JP, Ricard JD, Quenot JP, et al. Non-invasive ventilation versus high-flow nasal cannula oxygen therapy with apnoeic oxygenation for preoxygenation before intubation of patients with acute hypoxaemic respiratory failure. *Lancet Resp Med*. 2019;7:303–312.
57. Sjöblom A, Broms J, Hedberg M, et al. Preoxygenation using high flow nasal oxygen vs tight face mask during rapid sequence intubation. *Anaesthesia*. 2021;76:1176–1183.
58. Zhou S, Zhou Y, Cao X, et al. The efficacy of high flow nasal oxygenation for maintaining maternal oxygenation during rapid sequence induction in pregnancy: a prospective randomised clinical trial. *Eur J Anesthesiol*. 2021;38:1052–1058.
59. Pham T, Brochard L, Slutsky AS. Mechanical ventilation: state of the art. *Mayo Clin Proc*. 2017; 92:1382–1400.
60. Slutsky AS. History of mechanical ventilation. *Am J Respir Crit Care Med*. 2015;191:1106–1115.
61. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301–1308.
62. Fan E, Del Sorbo L, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195:1253–1263.
63. Lapinsky SE, Rojas-Suarez JA, Crozier TM, et al. Mechanical ventilation in critically-ill pregnant women: a case series. *Int J Obstet Anesth*. 2015; 24:323–328.
64. Brower RG, Lanken PN, MacIntyre N, et al. National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2004;351:327–336.
65. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303:865–873.
66. The ANZIC influenza Investigators and Australian Maternity Outcomes Surveillance System. Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study. *BMJ*. 2010;340:c1279.
67. Fan E, Brodie, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. *JAMA*. 2018;319:698–710.
68. Meduri GU, Headley AS, Golden E, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1998;2802: 159–165.
69. Steinberg KP, Hudson LD, Goodman RB, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical trials network efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354: 1671–1684.
70. Tang BM, Craig JC, Eslick GD, et al. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care Med*. 2009;37: 1594–1603.
71. Peter JV, John P, Graham PL, et al. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ*. 2008;336: 1006–1009.
72. Brun-Buisson C, Richard JC, Mercat A, et al. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2011;183: 1200–1206.
73. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med*. 2021;384:693–704.
74. Sterne JAC, Murthy S, Diaz JV, et al. Association between systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324: 1330–1341.
75. Patroniti N, Zangrillo A, Pappalardo F, et al. The Italian ECMO network experience during the 2009 influenza A (H1N1) pandemic: preparation for severe respiratory emergency outbreaks. *Intensive Care Med*. 2011;37: 1447–1457.
76. Nair P, Davies AR, Beca J, et al. Extracorporeal membrane oxygenation for severe ARDS in pregnant and postpartum women during the 2009 H1N1 pandemic. *Intensive Care Med*. 2011; 37:648–654.
77. Pham T, Combes A, Roze H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)–induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*. 2013;187:276–285.
78. Saad AF, Rahman M, Maybauer DM, et al. Extracorporeal oxygenation in pregnant and post partum women with H1N1-related acute respiratory distress syndrome: a systematic review. *Obstet Gynecol*. 2016;127:241–247.
79. Barrantes JH, Ortoleva J, O'Neil ER, et al. Successful treatment of pregnant and postpartum women with severe COVID-19 associated acute respiratory distress syndrome with extracorporeal membrane oxygenation. *ASAIO J*. 2021;67: 132–136.
80. Shih E, Dimaio JM, Squiers JJ, et al. Treatment of acute respiratory distress syndrome from COVID-19 with extracorporeal membrane oxygenation in obstetrical patients. *Am J Obstet Gynecol MFM*. 2022;4:100537.
81. ONeil ER, Lin H, Shamshirsaz AA, et al. Pregnant and peripartum women with COVID-19 have high survival with extracorporeal membrane oxygenation. *Am J Respir Crit Care Med*. 2022; 205:248–250.
82. Guerin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368:2159–2168.
83. Samanta S, Samanta S, Wij J, et al. How safe is the prone position in acute respiratory distress syndrome. *Am J Emerg Med*. 2014;32:687.e1–687.e3.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

84. Tolcher MC, McKinney JR, Eppes CS, et al. Prone positioning for pregnant women with hypoxemia due to coronavirus disease 2019 (COVID-19). *Obstet Gynecol*. 2020;136:259–261.
85. Cojocaru L, Turan OM, Levine A, et al. Proning modus operandi in pregnancies complicated by acute respiratory distress syndrome secondary to COVID-19. *J Matern Fetal Neonatal Med*. 2021;25:1–10.
86. Cavalcante FML, Fernandes CDS, Rocha LDS, et al. Use of prone position in pregnant women with COVID-19 or other health conditions. *Rev Lat Am Enfermagem*. 2021;29:e3494.
87. Society for Maternal-Fetal Medicine. Management considerations for pregnant patients with COVID-19. *COVID Clinical*; 2021. Available at: https://www.smfm.org/covidclinical.

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.