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Pregnancy and Severe ARDS with COVID-19: Epidemiology, Diagnosis, Outcomes and Treatment

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ABSTRACT

Pregnancy-related acute respiratory distress syndrome (ARDS) is fast becoming a growing and clinically relevant subgroup of ARDS amidst global outbreaks of various viral respiratory pathogens that include H1N1-influenza, severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), and the most recent COVID-19 pandemic. Pregnancy is a risk factor for severe viral-induced ARDS and commonly associated with poor maternal and fetal outcomes including fetal growth-restriction, preterm birth, and spontaneous abortion. Physiologic changes of pregnancy further compounded by mechanical and immunologic alterations are theorized to impact the development of ARDS from viral pneumonia. The COVID-19 sub-phenotype of ARDS share overlapping molecular features of maternal pathogenicity of pregnancy with respect to immune-dysregulation and endothelial/microvascular injury (i.e., preeclampsia) that may in part explain a trend toward poor maternal and fetal outcomes seen with severe COVID-19 maternal infections. To date, current ARDS diagnostic criteria and treatment management fail to include and consider physiologic adaptations that are unique to maternal physiology of pregnancy and consideration of maternal-fetal interactions. Treatment focused on lung-protective ventilation strategies have been shown to improve clinical outcomes in adults with ARDS but may have adverse maternal-fetal interactions when applied in pregnancy-related ARDS. No specific pharmacotherapy has been identified to improve outcomes in pregnancy with ARDS. Adjunctive therapies aimed at immune-modulation and anti-viral treatment with COVID-19 infection during pregnancy have been reported but data in regard to its efficacy and safety is currently lacking.

1. Introduction

The acute respiratory distress syndrome (ARDS) is a heterogenous disorder characterized by alveolar epithelial barrier disruption and dysregulated inflammation and remains a disease associated with high morbidity and mortality [1]. The recent COVID-19 pandemic has led to a worldwide increase in ARDS [2]. Once regarded as a relatively rare occurrence, pregnancy-related ARDS has now become a more common clinical dilemma that results in poor maternal and fetal outcomes [3–6]. This recent epidemiological trend is likely secondary to recent outbreaks of highly virulent respiratory pathogens (COVID-19, severe acute respiratory syndrome (SARS), middle easy respiratory syndrome (MERS), H1N1 influenza) and the physiologic maternal adaptations of pregnancy that include changes to the respiratory, cardiovascular, immune, and coagulation system that can predispose pregnant women to severe respiratory disease and sepsis [6–8]. This review discusses the historical definitions and epidemiology of pregnancy-related ARDS, pathogenesis of ARDS disease, and a brief discussion of ARDS management with clinical application in pregnancy. Key differences between classical ARDS and the sub-phenotype of COVID-19 ARDS (CARDS) will also be reviewed.

2. Epidemiology

2.1. Pregnancy and ARDS

A large population-based cohort study from 1999 to 2000 reported a historical incidence rate of acute lung injury to be 78.9 cases per 100,000 person-years with an in-hospital mortality rate of 38.5% [9]. In this modern era of Berlin Criteria for ARDS definition and lung

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protective ventilation, the prevalence of ARDS was more recently found to be 10%, with ARDS accounting for 23% of all ventilated patients [10]. It remains a very deadly disease with mortality as high as 34.9% for patients with mild ARDS and 46.1% in those with severe ARDS [10]. There have been at least 8 million cases of COVID-19 in the United States and over 1 million deaths reported by the CDC to date, with initial estimates on the annual incidence of CARDS probably exceeding that of classical ARDS by at least two-fold [11].

The incidence of ARDS during pregnancy is estimated to be similar to the historical incidence of ARDS in the general population. The literature on ARDS in the obstetric population is limited to case reports and series with a wide reported incidence from 17 to 130 cases per 100,000 deliveries [12–14]. These estimates show discrepant regional variation, and significant differences in ARDS definitions and study design that limit the precision of these studies. Maternal deaths related to ARDS have been historically high, ranging from 24 to 39% in older studies [12,13,15]. A recent large epidemiologic review through the US Agency for Health Quality and Research national database reported an annual maternal death rate associated with ARDS ranging from 9 to 14% [16]. Perinatal mortality attributed to maternal ARDS is between 20 and 30% [12,14].

The wide range of maternal mortality rates in ARDS may in part be attributed to variable susceptibility of pregnant women to viral respiratory pathogens and the recent epidemics and pandemics of deadly influenza and novel coronavirus variants. For example, during the H1N1 pandemic in 2009, pregnant women with severe H1N1 infections accounted for 12% of all pregnancy-related deaths [4]. Further, 5% of overall deaths that year were of pregnant women, despite pregnant women comprising only 1% of the total population [5], and pregnant women accounted for 6.3% of influenza-related hospitalizations and 5.9% of ICU admissions [17]. Similarly, high case fatalities for pregnant women were found during the SARS-CoV and MERS-CoV epidemic at 19% and 27% respectively [18].

2.2. Pregnancy and COVID-19

2.2.1. Maternal outcomes

Initial studies reported most pregnant women infected with COVID-19 remained asymptomatic or with self-limited disease without increased susceptibility [19,20]. The reassurance of these initial small regional findings was confounded by retrospective data without appropriate control groups that account for age and comorbidities. Consistent among larger systematic reviews and case control cohort studies accounting for these confounders, pregnancy is a risk factor for the development of severe COVID-19-related illness [21–23], with symptomatic pregnant women having higher rates of ICU admission (10.5 vs 3.9 per 1000 cases), mechanical ventilation support (2.9 vs 1.1 per 1000 cases), need for ECMO (0.7 vs 0.3 per 1000 cases), and maternal death (1.5 vs 1.2 per 1000 cases), compared with symptomatic non-pregnant women of reproductive age [24].

Additionally, COVID-19 is a significant risk factor for both poor maternal and perinatal outcomes. The multi-institutional, multinational INTERCOVID cohort study demonstrated that the diagnosis of COVID-19 alone among consecutively enrolled hospitalized pregnant women was associated with a higher risk of pregnancy complications. The study reported increased preeclampsia/eclampsia (RR 1.76 95% CI 1.27–2.43), severe co-bacterial infections (RR 3.38 95% CI 1.64–7.01), ICU admissions (RR 5.04 95% CI 3.13–8.10), and maternal mortality (RR 22.3 95% CI 2.88–172), in addition to poor neonatal outcomes [25]. Additionally, among hospitalized pregnant women for COVID-19, the majority (50–80%) will deliver during the same hospitalization with a c-section rate of 50% or above, and over 25% of these cases being preterm births [26,27].

There may be a subset of pregnant women at risk of severe respiratory illness with COVID-19 [28,29]. In a large review of over 192 studies that totaled 64,000 pregnant women with suspected or confirmed

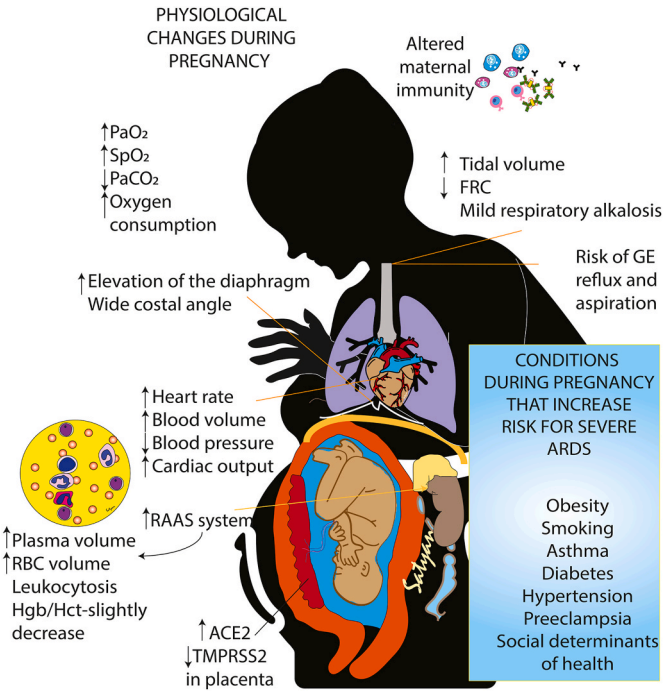

Fig. 1. Physiological changes during pregnancy that contribute to respiratory compromise and susceptibility to COVID-19 induced lung disease. The yellow inset box shows risk factors and associations for severe COVID-19 disease among pregnant women. ACE2 – angiotensin converting enzyme 2, TMPRSS2 – transmembrane serine protease receptor, GE – gastroesophageal, FRC – functional residual capacity, Hgb – hemoglobin, Hct – hematocrit. Copyright Satyan Lakshminrusimha.

COVID-19, 17.4% had developed pneumonia and 13.4% had developed ARDS [21,30]. Known risk factors for severe COVID-19 and maternal death include advanced maternal age, overweight/obesity, smoking, Black and Hispanic ethnic minority, pre-existing medical conditions such as hypertension, asthma, and diabetes, and the presence of more than one comorbidity (Fig. 1) [20,28–31]. Preeclampsia is both a risk factor for severe-COVID-19 among pregnant women [30,32], and an adverse obstetric-event outcome related to acute COVID-19 infection [3]. Among hospitalized pregnant women with COVID-19, 69% of women have severe disease, based on pre-specified criteria that includes an arterial partial pressure of oxygen divided by the fraction (percent) of inspired oxygen (P/F) ratio of <300, and 31% had critical disease, marked with respiratory failure needing mechanical ventilation support or the presence of shock with multiple organ dysfunction [33]. All women in this study with critical disease were in advanced gestation of pregnancy (>24 weeks gestation) and the mean body mass index of the overall cohort was 34kg/m2. These findings are consistent with the COVIDPREG study that found the risk factors for maternal intubation include obesity (cause-specific hazard ratio (CSH) 2.0, 95% CI 1.05–3.8, $p = 0.03$) and term of pregnancy (CSH 1.07, 95%CI (1.02–1.1), per + 1 week gestation, $p = 0.01$) in their multivariate analysis [34]. Among these women admitted to the ICU, 39% were intubated, 8% required V–V ECMO support, and 37% went on to require urgent facilitated maternal delivery in the ICU with maternal respiratory worsening as the main indication for majority of these cases. The CANCOVID-Pres observational study also confirmed an increased risk of adverse maternal outcomes [35]. Further, with the onset of the Delta variant (B 1.6.17.2), regional US data found an increase in vaccine-breakthrough infections and pregnant women admitted with severe disease, with more than 25% of these women requiring hospital admission for severe or critical illness with the Delta Variant [36].

Table 1
AECC and Berlin definition of acute respiratory distress syndrome.

Characteristics	1994 AECC Definition	2012 Berlin Definition
Onset	Acute Onset	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest Imaging	Bilateral infiltrates	Bilateral opacities on Xray or CT scan-not fully explained by effusions, lobar/lung collapse, or nodules
Origin of Edema	Exclusion of left atrial hypertension or pulmonary wedge pressure $\leq$18 mmHg	Respiratory failure not fully explained by cardiac function or volume overload. Need objective assessment (i.e.. echocardiography) to exclude hydrostatic edema if no risk factor is present
Oxygenation	- $PaO_2/FiO_2 \leq 300$ mmHg is ALI - $PaO_2/FiO_2 \leq 200$ is ARDS	Acute onset of hypoxemia defined as $PaO_2/FiO_2 < 300$ mmHg on at least PEEP 5cmH_2O[a] - PaO_2/FiO_2 of 201–300 mmHg is mild ARDS - $PaO_2/FiO_2$of 101–200 mmHg is moderate ARDS - $PaO_2/FiO_2 \leq 100$ mmHg is severe ARDS

[a] PEEP may be delivered non-invasively if the criteria are in the mild category. ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; SpO_2, peripheral capillary oxygen saturation.

2.2.2. *Fetal outcomes*

With the initial onset of the COVID-19 pandemic, the primary concerns regarding fetal outcomes were with respect to COVID-19 and vertical transmission. The placenta usually acts as an effective barrier preventing maternal transmission to the fetus. However, known viral pathogens (i.e., CMV, HSV, VZV, and Zika) have demonstrated vertical transmission and the consequence of devastating congenital infections and intrauterine death [37]. COVID-19 has shown minimal risk of vertical transmission in pregnancy [33,38,39].

Animal models of maternal hypoxia demonstrate an upregulation of the angiotensin converting enzyme 2 (ACE2) receptor, the SARS CoV2 receptor for viral entry, in placental tissue [40] but with low co-expression of the serine protease receptor (TMPRSS2), a receptor that is critical for S protein priming needed with COVID-19 viral entry [41,42]. Placental pathology of severe CARDS mothers has shown no significant morphologic changes related to in-utero infection, but instead has signs of hypoxic changes and placental insufficiency, marked with decidual arteriopathy and features of maternal vascular mal-perfusion [3,43,44]. Although there have been some case reports of placental swabs positive for COVID-19 in both asymptomatic and symptomatic COVID-19 mothers at delivery, neonates born to COVID-19 mothers at delivery have largely been negative for COVID-19 [3,26,39,45]. Further, significant neonatal respiratory distress appears rare in COVID-19 positive neonates [46].

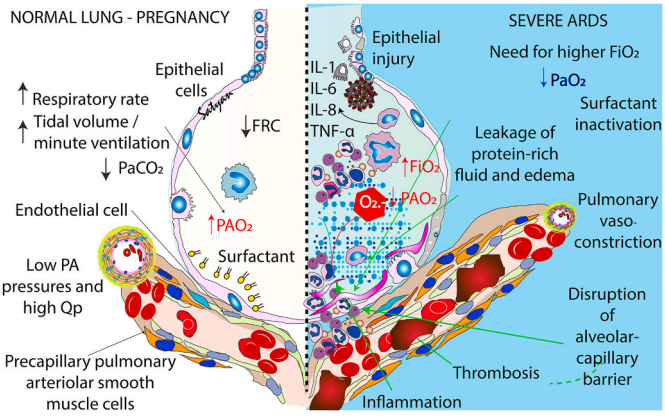

Fig. 2. Pathophysiology of COVID-19 associated ARDS in pregnancy. Physiological changes in a normal lung during pregnancy are shown on the left side. The alveolar-capillary barrier is conducive for gas exchange in a normal lung. Pathological changes with severe ARDS include epithelial injury, leakage of proteinaceous fluid into the alveoli, oxidative injury, inflammation, microthrombi and endothelial damage in the pulmonary vessels. FRC – functional residual capacity, IL – interleukin, TNF-α (tumor necrosis factor – alpha), O_2^- - superoxide anions, PA – pulmonary artery, Qp – pulmonary blood flow. Copyright Satyan Lakshminrusimha.

Neonatal morbidity has been related to higher rates of low birth weight (16%), preterm birth (15–23%), and neonatal intensive care admissions (24%) [3,25–27,32,33,38]. Two recent studies have confirmed small but statistically significant adverse neonatal outcomes with maternal COVID-19 infections [35,47]. Although rates of overall still-births and perinatal mortality remain relatively low [26,27], there is an increased risk of still-births and neonatal death in COVID-19 positive mothers compared to COVID-19 negative mothers [32].

3. Diagnostic criteria

3.1. *Adaptation of adult ARDS criteria to ARDS in pregnancy*

ARDS is characterized clinically by acute hypoxemia, non-cardiogenic pulmonary edema, and reduced pulmonary compliance. It was first described in an initial case series by Ashbaugh et al. in 1967 [48], but without a unifying diagnosis until the American-European Consensus Criteria (AECC) in 1994 [49]. However, several issues arose from the AECC criteria, and in 2012, members of the ARDS definition task force had revised and introduced the Berlin definition in response (Table 1) [50]. Since its application, the Berlin criteria provides better predictive enrichment, but the diagnosis remains clinically challenging and underrecognized.

Thus far, there is no clear consensus on pregnancy-specific ARDS criteria [51–53]. It has been proposed that "obstetric-related ARDS" be limited to the onset within the duration of pregnancy and 1-week post-partum, while others have included ante-partum and post-partum patients of up to 1-month [12,51,54]. To date, the PALICC (Pediatric Acute Lung Injury Consensus Criteria) developed in 2015, is the only widely accepted specific ARDS criteria developed following the Berlin modification, to address key differences in a specific sub-population (pediatric ARDS (PARDS)) [55]. As in PARDS, there are physiologic differences that need to be considered with ARDS in pregnancy. The primary etiologies of obstetric ARDS are often distinct from nonpregnant ARDS with specific obstetric causes: tocolytic-induced pulmonary edema, amniotic fluid embolism, preeclampsia, acute fatty liver of pregnancy, gastric aspiration, placental abruption, obstetric hemorrhage, chorioamnionitis, endometritis, septic abortion and retained products of conception [12,14,56,57]. The potential etiologies of obstetric-related ARDS can impact the primary pathophysiology of disease, in addition to the progression and outcome of disease. Second, application of adult stratifications of hypoxemia severity (mild, moderate, severe) do not take in account the higher physiologic PaO2 levels seen in pregnancy and other important maternal-fetal interactions at varying PaO2 thresholds.

In pregnancy, mean PaO2 levels are greater than 100 mmHg and significantly higher at all phases of pregnancy compared to non-pregnant women due to increase in minute ventilation, with tidal volume increasing by 30–35% and alveolar ventilation by 50–70% [58,59]. Maternal oxygen consumption increases incrementally throughout pregnancy, by 20–33% per term gestation, due to increased fetal demands and maternal metabolic processes [59,60]. Mild respiratory alkalosis shifts the oxygen dissociation curve to the left and slightly higher PaO2 levels optimize oxygen delivery to maternal tissues and fetus. The maternal thresholds of acute hypoxia that result in fetal

hypoxia and shock are unknown. Acute compromise in maternal oxygen delivery shifts uteroplacental blood flow to maternal vital organs, with precipitous declines in fetal oxygen delivery [61]. Animal models showing even mild to moderate reductions in maternal arterial saturations (to levels of 85%) can have a significant impact of fetal venous oxygenation content, nearing thresholds that result in fetal anaerobic metabolism increasing the risk of central nervous system damage [62,63]. The diagnostic precision of adult ARDS criteria in pregnancy and its validity at predicting adverse maternal and fetal outcomes needs to be further studied.

4. ARDS pathophysiology

ARDS can be caused by a variety of insults to the alveolar capillary barrier that include both direct pulmonary (bacterial and viral pneumonia, inhalational injury, aspiration) and indirect non-pulmonary sources (non-pulmonary sepsis, trauma, transfusion-related injury) [64]. The normal alveolar-capillary unit consists of a single layer of endothelial cells and an alveolar epithelial layer lined mainly with type I and type II alveolar cells (Fig. 2), that restrict the passage of small solutes and allow for mainly the diffusion of carbon dioxide and oxygen [1,65]. Further, type I and type II alveolar cells have additional capacity to absorb excess alveolar fluid via ion transport channels, with further fluid resorption into the lung interstitium.

The pathophysiology of ARDS is complex but can be primarily characterized by injury to the alveolar capillary barrier leading to alveolar edema with high protein fluid, decreased alveolar fluid clearance via direct alveolar cellular injury, and subsequent surfactant loss [66–68]. Injury to the capillary endothelium increases endothelial permeability and further activates and propagates a systemic inflammatory response and coagulation cascade [1,67]. Intra-alveolar macrophages release chemotactic factors and chemokines that enhance neutrophil and circulating macrophage recruitment from the impaired lung microvasculature into the interstitium and alveolar space. It is these key pathogenic features of ARDS: alveolar epithelial injury, capillary endothelial injury, hyperinflammation, and coagulation and fibrinolysis dysfunction, that characterize the acute exudative phase of ARDS marked with hallmark features of hypoxemia from intra-pulmonary shunt and dead space, impaired ventilation, and poor respiratory compliance [69]. The use of positive pressure ventilation especially with high tidal volume and its increased shearing effects and high airway pressure, further disrupts the integrity of the lung epithelium and endothelium and exacerbates a cascade of biomechanical inflammatory injury and alveolar edema [70,71]. The key pathogenic features of ARDS have led to primary research in selected plasma biomarkers of ARDS, to aid in classifying patients by predominant molecular pathogenesis (i.e., hyperinflammation, pro-coagulation) and sub-phenotypes, for risk prediction and targeted therapy development [64,72,73].

4.1. Clinical manifestations and pathologic features of COVID-19 ARDS sub-phenotype

Viral-induced ARDS are typically characterized by direct alveolar epithelial injury, disrupted intercellular junctions, and resultant cellular death [74]. Epithelial cell death via apoptotic or necrotic mechanisms are caused from direct lytic viral infections, neutrophil-derived mediators, and inflammatory macrophages, with loss of the alveolar epithelial barrier integrity. In contrast, with respect to CARDS, there is increasing evidence to suggest CARDS is primarily characterized by endothelial disruption from impaired microvascular permeability, significant thrombotic burden, and microcirculatory dysfunction with systemic inflammation. Autopsy studies of patients who have died from COVID-19 reveal findings of both classic ARDS marked with diffuse alveolar damage, hyaline membrane formation, and alveolar cell wall injury, but also significant pulmonary intracapillary thrombotic burden and of small pulmonary arteries [75,76].

The L-type CARDS phenotype has been described as a unique subtype of CARDS with normal respiratory system compliance but with severe hypoxemia attributed to ventilation perfusion mismatch from pulmonary vasoconstriction [77,78]. Some clinicians argue that the L-type CARDS is the earlier stage of CARDS and may further progress to an H-type (classical features of ARDS), characterized by poor respiratory system compliance, increased lung weight, and non-aerated gravity-dependent regions [79]. Among these sub-groups of patients with CARDS, those with both poor respiratory compliance and high thrombotic burden with elevated d-dimers, have the highest risk of death demonstrating mortality rates of 56% [80]. Most deaths related to CARDS have evidence of thrombotic disseminated intravascular coagulation and multi-organ failure usually in patients with known comorbid risk factors that include hypertension, cardiovascular disease, diabetes mellitus, lymphopenia, and kidney disease [81]. Radiographic features unique to CARDS include peripheral distribution of opacified disease, frost-glass opacities, bilateral and multifocal lung disease, vascular thickening, with a lower lung disease predominance [82,83].

Table 2
Maternal physiologic considerations in pregnancy with manifestation of ARDS.

System	Physiologic Changes
Respiratory	• Upward displacement of diaphragm decreasing expiratory reserve volume and functional residual capacity • Chest wall expansion • Hyperemia, mucosal hypersecretion, and edema of the upper respiratory tract secondary to hormonal changes • Increased respiratory drive secondary to sensitivity of central chemoreceptors of the hypothalamus from hormonal changes mimic respiratory illness and delay early diagnosis of respiratory disease
Cardiovascular	• Increase in maternal plasma volume and cardiac output • Decrease in systemic vascular resistance
Renal	• Increase in ACE2 activity and hormonal components of the renin-angiotensin aldosterone system (RAAS)
Hematological	• Increase in pro-coagulant clotting factors • Decrease in fibrinolytic activity
Immunity	• Immune chronology with advancing gestation that may increase risk of immune dysregulation: 1) first trimester and third characterized by pro-inflammatory state to promote implantation and labor 2) Second trimester characterized by anti-inflammatory stage to promote fetal growth • Shift in T cell population towards T-helper 2 polarization promoting humoral response over cellular response • Impaired adaptive immune response and impaired viral clearance • Susceptibility to cytokine storm from innate immune system overactivation • Further immunomodulatory roles of pregnancy hormones and increase susceptibility of viral pathogens of the respiratory mucosa
Gastrointestinal	• Lower esophageal tone increasing risk of aspiration and gastrointestinal reflux

5. Physiologic considerations in pregnancy and development of ARDS

There are interacting multi-system physiologic changes during pregnancy that increase the risk of severe lower respiratory tract infections and the manifestation of ARDS (Table 2 and Fig. 1). These physiologic adaptive changes seen with maternal immunity, respiratory and cardiovascular physiology will be discussed in detail within the context of severe COVID-19 infection.

The molecular mechanisms of maternal immunopathology of pregnancy that increase susceptibility to severe viral disease and adverse fetal outcomes especially with certain RNA viruses that include influenza (H1N1) and novel coronaviruses (SARS, MERS, and COVID-19) are complex and needs further investigation. In COVID-19, severe lymphopenia and an imbalance between T regulatory to TH17 cells are seen in

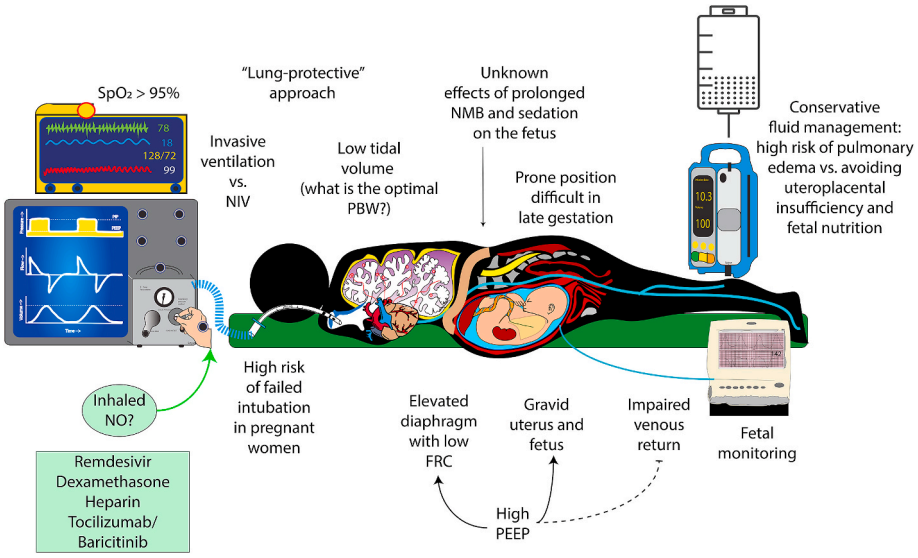

Fig. 3. General principles of management of COVID-19 associated ARDS in pregnancy. Benefits and potential concerns of some of the therapeutic strategies are shown. NO – nitric oxide, NIV – non-invasive ventilation, PBW – predicted body weight, NMB – neuromuscular blockade, PEEP – positive end-expiratory pressure. See Table 3 for additional information. Copyright Satyan Lakshminrusimha.

those with severe COVID-19 and multi-organ failure [84]. An increase in TH17 cells relative to T regulatory cells can incite an uncontrolled cytokine storm and tissue pathology [85,86]. In pregnancy, CD4 T cell subset imbalance is a known molecular mechanism of immunopathology in fetal loss and severe pregnancy complications such as preeclampsia [87–89]. In physiologic pregnancy, the tight regulation of Treg/TH17 and increase in Treg cells allows for implantation and growth of the semi-allogenic fetus [90]. The deregulation of Treg/Th17 cells has been proposed as an important mechanism in the pathogenesis of adverse pregnancy outcomes observed with severely infected COVID-19 pregnant women [84].

Hemodynamic adaptations in pregnancy ensure adequate uterine blood and fetal-maternal exchange are primarily regulated by the renin-angiotensin aldosterone system (RAAS). All hormonal components of the RAAS system are upregulated leading to an increase in maternal plasma volume and cardiac output and decrease in systemic vascular resistance via upregulation in some Ang-(1–7) levels via ACE2 enzymatic activity [91–93]. Viral entry into the host cell in COVID-19 infection is via the ACE2 receptor [94]. The competitive inhibition and suppression of ACE2 activity with an acute COVID infection is thought to molecularly explain, in part, the significant endothelial dysfunction and disordered coagulation seen with severe infection [95]. Severe COVID-19 infection and pathologic hypertensive disorders of pregnancy (i.e., preeclampsia) share similar pathophysiologic features of microvascular thrombosis and multi-organ dysfunction via a dysregulated RAAS system and ACE2 suppression [96–99]. In both states, additional complement activation is seen that may further exacerbate a pro-coagulopathic condition and generate thrombotic endovascular injury [100,101]. These similar overlapping cellular mechanisms of injury raise the possibility that pregnant women, especially in those at high risk, are at significant risk for both severe COVID-19 infection with multi-system organ involvement and precipitating severe preeclampsia.

6. Treatment/management

The mainstay of ARDS management remains limited to supportive care [69,102]. The landmark ARMA trial supported by the US National and Heart Lung and Blood Institute ARDS Network published in 2000 [103], compared the effects of high tidal volume (TV) ventilation (12 ml/kg of predicted body weight {PBW}) to lower tidal volume ventilation (6 ml/kg of PBW), and found a lower TV approach improved survival, shortened duration of mechanical ventilation, and attenuated the systemic inflammatory response with recovery of extra-pulmonary organ failure. Since this historic clinical study, the central focus of ARDS management has been to minimize the disruptive mechanical forces of invasive ventilation as well as minimize excessive oxygen therapy that have been known to further propagate lung inflammation and impair lung healing. Despite a vast number of clinical treatment trials published to date, there have been only a handful of studies showing a positive outcome [102,104,105]. The standard supportive strategy to current adult ARDS management includes mechanical ventilation, neuromuscular blockade, prone positioning, fluid management and rescue therapies (i.e., inhaled nitric oxide). Important clinical considerations in pregnancy and the COVID ARDS sub-phenotype, with each respective strategy will be discussed (Fig. 3).

6.1. Mechanical ventilation

6.1.1. Low tidal volume

Since the ARMA trial and further support from many clinical and preclinical studies [106–108], the focus of mechanical ventilatory support is to minimize the role of mechanical shearing forces on generating secondary lung injury. In the ARDS lung, there is non-uniformly aerated lung, with consolidated areas of diseased inflamed lung and non-aerated gravity dependent regions [109,110]. Low tidal volume (TV) ventilation prevents regional overdistention with positive pressure ventilation and avoid the stress and strain of mechanical ventilatory forces on the diseased lung. The current standard of approach is to scale TV to PBW and to minimize driving pressure with target plateau pressures to <30 cmH_20 [103].

It is important to note that there are no formal studies evaluating the efficacy of low TV ventilation in pregnant and postpartum women [111]. For now, both American College of Obstetricians and Gynecologists (ACOG) and Society of Maternal Fetal Medicine (SMFM) recommends a "lung protective strategy approach" but with saturation goals of >95% for all critically ill pregnant women, inclusive of CARDS [112–114]. A ventilator strategy that provides optimal lung protection during pregnancy needs further area of study. Compared to non-pregnant women with ARDS, there are potentially significant differences in the distribution of aerated lung and gravity dependent areas of atelectasis and diseased lung, due to the upward displacement of the diaphragm, compensatory rib expansion with a subcostal angle

widening (from 68 to 103°), and a baseline decrease in functional residual capacity (FRC) [111,115–117]. Radiographic phenotypic assessment of ARDS have not been assessed in the pregnancy population, and thus responsiveness to ventilator manipulations is further limited. Application of target TV ventilation to PBW calculation also needs further study in pregnancy. The use of PBW in the calculations of TV in the ARDSnet protocol are fixed and are also based on nonpregnant data for ideal body weight for height [111].

In addition, the clinical application of a low TV ventilation approach is facilitated by the allowances of permissive hypoxia and hypercapnia (ARDSnet goals: PaO2 of 55–80 mmHg, SpO2 88–95% and pH of 7.3–7.45). The goals of a safe permissible threshold of lower PaO2 and PCO2 goals in pregnancy is unknown but limited when considering the risk of adverse maternal-fetal interactions and fetal hypoxia. As stated earlier, the normative PaO2 and SPo2 ranges are even higher among healthy pregnant [118–120] with expert opinion suggesting the PaO2 goals in pregnancy should be at least >70 mmHg and SpO2 > 95% [121,122].

Permissive hypercapnia and pCO2 thresholds are also important considerations of an applied ventilation strategy in ARDS within pregnancy. Pregnant women have a known higher minute ventilation, when compared to non-pregnant women, and chronic respiratory alkalosis (with pH of 7.4–7.45, pCO2 27–32 mmHg) with renal compensation (HCO3 18–21 mEq/L) [123]. The upper maternal thresholds of pCO2 goals to allow for low TV ventilation approach is unknown, with concerns that maternal and fetal hypercapnia are known to be tightly associated with each other. The allowance of fetal hypercapnia and acidosis results in a rightward shift in the oxyhemoglobin curve, limiting binding of oxygen molecules to fetal hemoglobin, and impairing fetal oxygenation [111,124].

6.1.2. PEEP

Positive-end expiratory pressure (PEEP) is an important lung protective strategy in ARDS to not only help maintain adequate oxygenation, but for maintenance of alveolar recruitment and prevent cyclic collapse of distal airspaces with a low tidal volume. There have been several clinical trials to assess a given PEEP strategy, and to date, no single clinical trial has shown clinical superiority with a PEEP strategy [125–127]. However, a meta-analysis has shown higher PEEP improves survival among a sub-group of patients with moderate to severe ARDS [128]. Compared to classical ARDS, it has been proposed that the CARDS is a disease of severe hypoxemia but of largely compliant lungs, with severe hypoxemia related more to dead-space and V/Q mismatch from microvascular thrombi than of non-aerated lung regions. Thus, some have argued that of limited benefit with a high PEEP strategy in CARDS [77], with small studies showing no additional clinical benefit of high PEEP support [129,130].

In pregnancy, a high PEEP strategy for ventilatory support is generally considered controversial. With a high PEEP strategy, there may be some benefit with alveolar recruitment, especially considering a low baseline FRC. However, pregnant patients are at risk of significant hemodynamic changes, especially in late gestation with positive pressure support [131–133]. Hypotension with resultant maternal and fetal shock can result from impaired venous return from high intrathoracic pressure paired with a compressed inferior vena cava (IVC) from an expanding uterus. Thus, the risks and benefits of the upper thresholds of PEEP support applied in pregnancy must be thoroughly considered and close maternal and fetal monitoring is needed for any manipulation of end-expiratory pressure.

6.1.3. Non-invasive positive pressure ventilation

The advent of non-invasive ventilation (NIV) has been shown to reduce the need for endotracheal intubations and mortality among adult patients with varied etiologies of acute respiratory failure. However, whether NIV is beneficial in ARDS is unclear [1,134]. There have been some studies that have shown it may be beneficial in mild ARDS and may avoid secondary iatrogenic complications (i.e., delirium, neuromuscular weakness, and nosocomial infections) [135–137]. Conversely, there are clinical concerns that the use of prolonged NIV without significant improvement may delay intubation and invasive mechanical ventilation support. Additionally, with the inability to control for minute ventilation with NIV, patients with evolving and worsening ARDS may experience further deleterious effects from high TV ventilation. A recent sub-study of the LUNG SAFE trial showed the use of NIV was associated with higher ICU mortality than in those who were matched-controlled with invasive ventilation [10]. Further the use of NIV was independently associated with under-recognition of ARDS by clinicians at study entry and throughout the clinical trial. In contrast, the FLORALI study showed in patients with acute hypoxemic failure (marked with P/F < 300), the use of high flow improved 90-day survival compared to those with standard oxygen support or non-invasive ventilation, and reduced rates of intubation in those with moderate to severe hypoxemia (P/F < 200 mm Hg) [138]. The use of NIV in COVID-19 patients outside the ICU was associated with success rates between 60 and 75% [139].

There is limited data regarding clinical use of NIV and its effectiveness in pregnancy. Routine use as an oxygen modality is not recommended given concerns for higher risk of aspiration secondary to physiological changes of decreased lower esophageal tone, delayed gastric emptying, risk of aspiration, and increased intrabdominal pressure [51,131]. However, the routine use of NIV/HFNC support has been more widely reported in the literature for management of respiratory failure in COVID-19 and pregnancy. In a large systematic review of pregnant women with COVID-19, ICU admission rate was 7.2% and 15.1% required the use of NIV [27]. The COVIDPREG study reported high flow nasal cannula and non-invasive ventilation successfully managed as its sole oxygenation technique in 51% of critically ill pregnant women with severe COVID-19, with 29% of women requiring several different oxygenation modalities and 39% of the overall cohort needing intubation and invasive ventilation support [34]. Endotracheal intubation in pregnancy is difficult. The incidence of failed intubations is eight times greater than that of the non-pregnant population [56,140]. Increased mucosal edema of the upper airway, the anatomic changes related to pregnancy, and poor FRC make pregnancies high risk for a difficult airway and intolerant of withstanding prolonged periods of apnea [56]. Further, supine positioning late in gestation and the increased intrathoracic pressure with positive pressure ventilation may result in significant hypotension during the peri-intubation period and high risk for adverse maternal-fetal interactions [111].

6.1.4. Timing of delivery

These concerns related to mechanical ventilation (MV) support in pregnancy also highlight the important question of when mechanical relief with a facilitated delivery is warranted. Thus far, it is unclear whether delivery results in significant maternal clinical improvement and increased survival [14,141]. The COVIDPREG reports a facilitated delivery at a rate of 37% among critically ill mothers with severe COVID pneumonia, with mainly maternal indications to improve oxygenation and ventilation in 80% of these patients [34]. Delivery resulted in an increase in P/F ratio by 9% ($p = 0.02$) and a decrease in driving pressure by 27% ($p = 0.02$), and plateau pressure by 8% ($p = 0.05$). Obese mothers experienced the greatest improvement in driving pressure following delivery (80 vs 56%, $p = 0.19$).

The SMFM at this time recommends the timing of delivery in critically ill pregnant patients be individualized and based on a shared decision-making model discussed with the family, maternal-fetal medicine and critical care teams [113]. If delivery is considered based on the severity of hypoxemia alone, it is recommended that other rescue options be considered such as alternative ventilatory methods, prone positioning and ECLS support, especially with a gestational age of less than 32 weeks.

6.1.5. Neuromuscular blockade (NMB)

In ARDS, spontaneously breathing patients even with high level of sedation may experience ventilator dyssynchrony and resultant elevated transpulmonary pressures, further exacerbating ventilator induced lung injury [142,143]. The use of early NMB improves 90-day survival and ventilator-free days with early use of cisatracurium in those with moderate to severe ARDS (P/F < 150) [104], in an initial randomized controlled trial, but these results could not be replicated in a more recent clinical trial [144]. The use of NMB is not recommended for early routine use in severe ARDS with MV but may be considered an option for those requiring deep sedation to facilitate a lung protective strategy, minimize ventilator dyssynchrony, and/or for prone positioning.

The long term maternal-fetal effects from continuous sedation/analgesic and NMB medications are unknown. With MV in a critically ill peripartum patient being a historically rare clinical conundrum, many maternal-fetal medicine specialists are unfamiliar with sedation management, and there are no formal guidelines with a personalized approach to pregnancy [133]. Non-depolarizing NMB cross the placenta in variable amounts with little known about the fetal effects of neuromuscular infusion [145]. There have been reports of short term partial neuromuscular weakness of neonates with most clinical studies limited to its use in short-term peri-partum use during C-section [145–148]. Older case reports of fetal paralysis and development of neonatal arthrogryposis with prolonged maternal administration of NMB have been reported, but there are no cases of this effect with modern day use of non-depolarizing agents [149]. Currently, there is no major contraindication for paralysis to facilitate maternal ventilation and oxygenation in ARDS and pregnancy [112,150,151], with major obstetric societies recommending minimized duration as clinically tolerated [122,151,152].

6.1.6. Proning

The use of prone positioning in ARDS has been proposed to improve oxygenation and reduce secondary ventilator-induced lung injury by homogenizing areas of regional overdistention and atelectasis. The PROSEVA trial showed its early application improved 28-day and 90-day survival with an extended 16-h per day proning protocol, among those with moderate to severe ARDS [105]. Since publication, prone positioning has been incorporated by many critical care physicians as part of standard therapy in patients with severe refractory hypoxemia. Proning awake patients with COVID-19 resulted in reduced need for intubation and invasive mechanical ventilation [153]. Further, a recent systematic review and meta-analysis of published studies have shown improvement in oxygenation parameters in intubated patients with severe COVID pneumonia [154].

Clinical experience and expertise surrounding application of prone positioning in late gestation is limited and institutionally specific. Although with the recent COVID-pandemic, clinical algorithms and educational videos have been increasingly published in the medical literature [155], with special attention made to offload the gravid uterus and avoid aortocaval compression [155,156]. In addition, prone positioning has been shown in clinical studies to be technically feasible and well-tolerated among a study of healthy pregnant volunteers in the third trimester, without any significant hemodynamic effect or signs of fetal distress [157]. A study of 100 pregnant patients with COVID-19 found 8 needed mechanical ventilation and 4 underwent proning with improvement in P/F ratios [158], A larger retrospective study had demonstrated both safety and maternal and fetal tolerability of prolonged serial proning sessions (median duration 16 h) in 17 consecutive pregnant patients (mean gestation of 32 weeks) with severe-COVID pneumonia needing mechanical ventilation [159]. Larger studies are needed to evaluate the clinical efficacy of prolonged daily proning on maternal and neonatal outcomes in pregnant patients with severe ARDS.

6.1.7. Fluid management

The optimal strategy for fluid management in ARDS is clinically challenging, balancing the risk of increased pulmonary edema with the risk of decreased perfusion pressure to vital organs with restrictive fluid management approach. In animal models of acute lung injury, increases in vascular hydrostatic pressure has been shown to worsen pulmonary edema and by decreasing pulmonary vascular pressure, alveolar edema is improved. In 2008, the NHLBI ARDSnet published the Fluid and Catheter Treatment trial (FACTT) evaluating the effectiveness of a conversative vs liberal fluid strategy, utilizing data from serial measurements of either a central venous pressure or a pulmonary arterial wedge pressure, to guide a strict fluid management protocol [160]. Irrespective of mode of vascular filling pressure measurement, a conservative fluid management arm showed a significant increase in ventilator free days, improved oxygenation, and decreased ICU days. However, there was no significant reduction in mortality. Following the FACCT trial, a simplified approach conservative fluid management approach (FACCT LITE) utilizing CVP and urine output to guide fluid management was published and has further shown similar outcomes as the original conservative fluid strategy protocol with respect to ventilator-free days and survival. Conservative fluid implementation strategies such as routine use of diuretics and a net negative fluid balance of 500–1000 ml/day in patients with hemodynamic stability, have been recommended in the management of ARDS [1].

There are many physiologic considerations to consider with conservative fluid directed goals in pregnancy, which include maternal-fetal interactions and maintaining adequate uteroplacental blood flow in the setting of maternal hypoxia. The physiologic changes that occur in late pregnancy and labor include dynamic changes related to cardiac output, systemic vascular resistance, and pulmonary capillary wedge pressure [111]. Many of these physiologic changes increase risk of pulmonary edema particularly in late gestation, a phenomenon thought primarily driven by hydrostatic capillary forces [111,161]. Thus, there is a degree of clinical uncertainty when deciding optimal fluid management.

6.2. Rescue therapies

6.2.1. Nitric oxide

Inhaled nitric oxide (iNO) can achieve selective vasodilation of the pulmonary circulation in areas of ventilation, improving ventilation perfusion matching and oxygenation in ARDS [162]. However, no clinical studies have demonstrated improvement in clinical outcomes in ARDS patients, even in those with severe ARDS [163]. The CARDS sub-phenotype, marked with pulmonary micro-thrombosis endothelial injury and microvascular vasoconstriction, has been proposed as a sub-phenotype that may benefit from iNO. In addition, in-vitro studies have shown that iNO may have antiviral activity against certain strains of coronavirus. A large multi-center randomized control trial is currently investigating the treatment effect of iNO on oxygenation and overall survival in those with severe ARDS secondary to COVID-19 pneumonia [164]. So far, small prospective cohort studies investigating the use of iNO as a rescue therapy following proning in severe-COVID pneumonia have not shown significant immediate improvements in oxygenation [165–167]. The use of iNO should be considered as a short-term rescue therapy and as a therapeutic bridge to ECLS or other adjunct therapies, especially in consideration of potential theoretical benefits with the COVID ARDS sub-phenotype.

The therapeutic use and safety profile of iNO in pregnancy is very limited in study. Case reports have reported improvement in oxygenation and no neonatal complications at delivery, in the treatment of maternal pulmonary hypertension [168,169]. A case series of six pregnant women treated with high dose iNO for the treatment of severe COVID, showed maternal tolerance, with no reports of maternal methemoglobinemia, and further no fetal or neonatal complications attributed to iNO use [164]. The use of ECLS for CARDS is reviewed in this issue.

Table 3
Adjunctive therapies in severe COVID-19.

	Mechanism of Action	Clinical Indications	NIH COVID-19 Treatment Guideline Panel
Remdesevir	• Anti-viral that acts to inhibit COVID-19 RNA dependent RNA polymerase (RdRp)	• Hospitalized patients without oxygen supplementation but high risk of progressing to severe COVID-19 or minimal supplemental oxygen requirement	• Monotherapy (without adjuvant steroids)
		• Hospitalized patients with conventional supplemental oxygen support	• In conjunction with dexamethasone
		• Hospitalized patients with HFNC, NIV, MV, or ECMO	• Clinicians may consider addition of remdesivir with recommended immunomodulator combinations. Does not recommend the use of Remdesevir without immunomodulators
Tocilizumab	• Interleukin-6 receptor blocker	• Hospitalized and requires HFNC oxygen, NIV, MV or ECMO	• In conjunction with dexamethasone
Baricitinib	• Janus Kinase 1 and 2 (JAK1/JAK2) inhibitor	• Hospitalized and requires HFNC oxygen, NIV, MV or ECMO	• In conjunction with dexamethasone
Dexamethasone	• Glucocorticoid	• Hospitalized patients with conventional oxygen requirement	• In conjunction with remdesevir; if remdesivir cannot be obtained then dexamethasone monotherapy
		• Hospitalized patients with rapidly increasing oxygen needs and systemic inflammation	• Dexamethasone plus PO barcitinib or alternatively Dexamethasone plus IV tocilizumab. If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained, dexamethasone monoterhapy recommeded as alternative
		• Hospitalized with HFNC, NIV, MV, or ECMO	• Dexamethasone plus PO baricitinib or alternatively Dexamethasone plus IV tocilizumab. If baricitinib, tofacitinib, tocilizumab, or sarilumab cannot be obtained, dexamethasone monotherapy recommended as alternative
Heparin	• Anticoagulant by inactivating thrombin and activated factor X	• Hospitalized patients not requiring oxygen (unless contraindicated)	• Prophylactic dosing
		• Hospitalized patients with conventional oxygen and elevated D-dimer	• Therapeutic dosing
		• ICU admitted patients requiring HFNC, NIV, or MV	• Prophylactic dosing
		• ECMO or CRRT	• Per institutional therapeutic anticoagulation policy

ECMO, extracorporeal membrane oxygenation; NIV, non-invasive ventilation; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; NIH, National Institute of Health.

6.2.2. *Adjunctive therapies in COVID-19*

Table 3 provides a list of the most common drugs used as adjunct therapy among those hospitalized with COVID-19 infection. Data on the safety and efficacy of these drugs are lacking, specifically in pregnant CARDS patients. Therapeutic management of pregnant patients with severe COVID-19 are recommended as the same as any other adult with severe infection with the following exceptions: 1) the panel recommends against the use of molnupiravir (anti-viral) due to concern of fetal teratogenicity in animal studies and 2) no formal recommendation for the use of therapeutic anticoagulation in those without evidence of venous thromboembolism [170]. Anti-SARS-CoV-2 monoclonal antibody products (mAB) are not currently authorized for use in the US due to concern for lack of susceptibility with current circulant subvariants of COVID-19. A recent large propensity-matched cohort study of pregnant women, with moderate-to-severe COVID-19 infection, reported a reassuring safety profile without increase in obstetric-related complications among those treated with mAB products, although there was no difference in clinical outcomes with mAB use compared to those without treatment[171].

7. Conclusion

ARDS remains a significant underrecognized and deadly illness, with the COVID-19 pandemic leading to a worldwide increase in the incidence of ARDS. Pregnancy is now a widely recognized risk factor for severe viral-induced ARDS due to impart the interacting physiologic adaptations of pregnancy. Like prior epidemics with H1N1, SARS, and MERS, COVID-19 is associated with poor maternal and fetal outcomes. Severe COVID-19 infection shares similar overlapping cellular mechanisms of microvascular injury and immunopathogenesis related to pathogenic disorders of pregnancy and spontaneous intrauterine fetal loss, that may explain this epidemiologic trend. Supportive care related to lung-protective strategy, neuromuscular blockade and conservative fluid approach are not studied within the pregnancy ARDS subpopulation and pose potential limitations in application due to concern for adverse maternal-fetal interactions. Application of current adjunctive pharmacologic therapies in COVID-19 share similar limitations in use.

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