POSTPARTUM RESPIRATORY DEPRESSION

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INTRODUCTION

No accepted definition of respiratory depression in studies of obstetric patients exists. Studies have variously defined thresholds for clinically significant respiratory depression including the following: need for airway intervention; hypoxia (SpO2 <90%) or bradypnea (respiratory rate (RR) <8 breaths/min) that requires supplemental oxygen; excessive sedation that requires more than verbal stimulation to maintain adequate

KEYWORDS
- Pregnancy
- Postpartum
- Respiratory depression
- Respiratory failure
- Obesity
- Opioid-induced respiratory depression (OIRD)
- Acute respiratory distress syndrome (ARDS)

KEY POINTS
- Modern, ultra-low, and low-doses of neuraxial morphine for postcesarean delivery analgesia are safe and effective, and carry a low risk of respiratory depression for the most obstetric patients.
- For selected comorbidities and conditions acquired in pregnancy, careful consideration of the patient’s unique risks and benefits should be undertaken when using neuraxial morphine for postcesarean analgesia, particularly in combination with other drugs that depress respiration.
- The etiologies of postpartum respiratory depression/failure are numerous. Preexisting diseases such as obstructive sleep apnea (OSA), obesity hypoventilation syndrome (OHS), and cardiopulmonary diseases may interact with conditions acquired during pregnancy or peripartum, as well as drugs administered peripartum, to compound the risk of respiratory compromise in vulnerable patients.
- The detection of respiratory compromise in obstetric patients is complicated by the significant overlap between or confounding by normal maternal physiologic changes. It is important to modify or develop specific alert criteria and algorithms for this population.
- The incidence of severe pulmonary complications such as acute respiratory distress syndrome (ARDS) is on the rise. Novel respiratory viral infections pose a unique risk to pregnant and postpartum patients. The recent H1N1 and COVID-19 pandemics have helped demonstrate the value and safety of mechanical ventilatory support, including ECMO, in this population.

INTRODUCTION

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respiration; or the use of pharmacologic therapy to reverse opioid or benzodiazepine narcosis.\textsuperscript{1–3} When available, some studies have also included measures of hypercapnia or low tidal volumes.\textsuperscript{4,5}

In the obstetric population, the incidence of respiratory depression has been best studied following the administration of neuraxial morphine, but has varied due to differences in study designs, definitions of respiratory depression, and neuraxial morphine doses. A recent systematic review of published reports of clinically significant respiratory depression in women that received neuraxial morphine or diamorphine for postcesarean delivery analgesia reviewed more than 18,000 cases and found a low prevalence of respiratory depression in this population (5.96–8.67 per 10,000).\textsuperscript{1} Furthermore, at contemporary, low-doses of neuraxial morphine or diamorphine, clinically significant respiratory depression was even more rare (1.08–1.63 per 10,000).\textsuperscript{1} They reported no permanent harm or death in this population, even after studying closed claims data.\textsuperscript{6} Although reassuring for healthy obstetric patients, the recent consensus statement endorsed by the Society for Obstetric Anesthesia and Perinatology recommends increased monitoring following neuraxial morphine administration for certain patients at higher risk of respiratory depression, but studies elucidating these risk factors in obstetric patients have been scant, and clinical standards have been largely extrapolated from the general surgical population.\textsuperscript{7}

Certainly, neuraxial morphine administration is not the only potential cause of postpartum respiratory depression or failure. Clinicians should be familiar with the differential diagnosis of respiratory depression/failure in the obstetric population to guide management and to prevent adverse outcomes in vulnerable patients. Although rare, the morbidity associated with postpartum respiratory depression can be significant. From prolonged hospital stays to the need for extracorporeal membrane oxygenation (ECMO) to death, the cost/harm/risk to affected individuals and institutions can be devastating. A retrospective database study by Callaghan and colleagues in 2012 studied severe maternal morbidity during delivery and postpartum hospitalizations between 1998 and 2009 in the United States and the study showed that the rate of adult respiratory distress syndrome (ARDS) in pregnant and recently postpartum women markedly increased during this 12-year period.\textsuperscript{8}

**RISK FACTORS FOR POSTPARTUM RESPIRATORY DEPRESSION**

There are numerous etiologies of postpartum respiratory depression/failure that result in clinically significant outcomes. Preexisting diseases such as obstructive sleep apnea (OSA), obesity hypoventilation syndrome (OHS), and cardiopulmonary diseases may interact with conditions acquired during pregnancy or peripartum, or drugs administered peripartum, to compound the risk of respiratory compromise in vulnerable patients (Fig. 1).\textsuperscript{9}

The normal physiologic changes in the respiratory system during pregnancy can complicate characterizing and detecting respiratory depression (Table 1).\textsuperscript{10} Confounding variables can interact to mask certain key diagnostic parameters. For example, pregnant women experience a normal increase in RR that is mediated by relatively higher progesterone levels; a pregnant patient may seem to have a “normal” RR (for a nonpregnant woman) while actually having depressed respirations (for a pregnant woman). Similarly, when the hypercarbia expected with respiratory depression is combined with the chronic respiratory alkalosis of pregnancy, the \( P_{CO_2} \) laboratory value may appear “normal.” Given all this, it is important for providers to be aware of pregnancy physiology and use normal vital signs and laboratory values of pregnancy to evaluate pregnant patients.
Each pregnant patient is unique and the risk of respiratory depression in an individual postpartum woman will vary with their specific risk factors. As in the general population, obstetric patients with underlying cardiovascular, neurologic, renal, and pulmonary comorbidities are more likely to suffer opioid-induced respiratory depression (OIRD) and respiratory compromise from other etiologies.2,7 Next, we will review some common preexisting as well as pregnancy-related conditions to consider when evaluating a pregnant patient’s risk for respiratory depression.

**Preexisting conditions**

**Obesity**

Obesity has been cited as a common risk factor for all-cause maternal morbidity and mortality,11 as well as anesthesia-related maternal mortality.12,13 When compared with...
individuals with normal body mass, obese patients present with a restrictive respiratory pattern characterized by reduced forced vital capacity (FVC), reduced forced expiratory volume after 1 s (FEV₁), potentially reduced total lung capacity (TLC), and decreased functional residual capacity (FRC). These spirometry changes result from, at least in part, structural alterations of the thorax and abdomen that reduce the compliance of the rib cage and the mobility of the diaphragm. A similar phenomenon is observed in pregnancy as the gravid uterus displaces the diaphragm cephalad resulting in a decreased FRC. However, compensatory changes such as the expansion of the ribcage allow for the preservation of TLC and spirometry to remain within normal limits overall. When pregnancy physiology is superimposed on the pathophysiology of obesity, significant respiratory compromise can result (Table 2). Obesity is associated with a decreased FRC and pregnancy further exacerbates this. As a consequence, these patients have diminished respiratory reserve in situations of hypoventilation or apnea, and this can complicate airway management and intubation (Fig. 2).

This interaction has become increasingly relevant in the care of obstetric patients as obesity rates have increased in many countries. The Centers for Disease Control and Prevention (CDC) reports that, of the women who gave birth in the United States in 2014, more than 50% were categorically overweight (body mass index (BMI): 25.0–29.9 kg/m²) or obese (BMI: >29.9 kg/m²) before pregnancy. The prevalence of super obesity (defined as BMI >50 kg/m²) is increasing at a faster rate than other classes of obesity in the US population. Women with obesity, especially super obesity, have a higher rate of peripartum complications and postpartum intensive care unit (ICU) admissions than nonobese women. In one recent study, the most common indication for postpartum ICU admission among obese women was cardiopulmonary complications.

The recent consensus statement endorsed by the Society for Obstetric Anesthesia and Perinatology recommends increased monitoring following neuraxial morphine administration for patients with BMI ≥40 kg/m², but studies to guide monitoring strategies for these higher risk patients have been scant. Single-center retrospective studies that have examined the incidence of respiratory depression events in postpartum women that have received low-dose neuraxial morphine have demonstrated a very low prevalence of adverse events even among obese postpartum women. Neuraxial morphine is an effective form of postcesarean delivery analgesia and should not be withheld from obese women out of concern for

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<th>Lung volumes and spirometry</th>
<th>Pregnancy</th>
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<tr>
<td>FEV₁</td>
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<td>FVC</td>
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Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume after 1 s; TLC, total lung capacity; FRC, functional residual capacity.

* Decreased with morbid obesity BMI greater than 40 kg/m².

Sleep-disordered breathing

A strong association exists between obesity and sleep-disordered breathing conditions such as snoring, OSA, and OHS. The prevalence of OSA among obese pregnant persons has been reported as 12% to 28% in various small prospective studies. Maternal OSA has been linked to increased peripartum morbidity and mortality and adverse fetal outcomes. When compared with those without OSA, pregnant persons with OSA have a significantly higher risk of hypertensive disorders of pregnancy, gestational diabetes, cardiomyopathy, congestive heart failure, pulmonary edema, hysterectomy, prolonged hospital stays, and admissions to the ICU.

Sleep-disordered breathing

Postpartum Respiratory Depression

Fig. 2. Differences in time to desaturation after preoxygenation reflect the compound effect of pregnancy and obesity on functional residual capacity. A healthy, nonpregnant patient can tolerate approximately 9 minutes of apnea before desaturation. That time is reduced by 60% in a healthy, pregnant patient at term (3–4 minutes), and 80% in a morbidly obese, pregnant patient at term (98 seconds). (Data from Baraka AS, Hanna MT, Jabbour SI, et al. Preoxygenation of pregnant and nonpregnant women in the head-up versus supine position. Anesth Analg. 1992;75(5):757-759; Hines RL, Marschall KE. Stoelting’s anesthesia and co-existing disease. In: Seventh edition. ed. Philadelphia, PA: Elsevier; 2018: Chapter 31.)

In nonobstetrical postsurgical patients, OSA is associated with an increased risk of postoperative respiratory failure. Longitudinal studies on OSA during pregnancy suggest that airway obstruction worsens as pregnancy progresses, particularly if patients develop preeclampsia.

The Society for Obstetric Anesthesia and Perinatology guidelines recommend increased monitoring following neuraxial morphine administration for high-risk patients such as those with OSA, but no studies have been conducted in this population to guide postoperative monitoring strategies and guidance is extrapolated from the nonobstetrical literature. However, obstetric patients with OSA should be carefully monitored, and noninvasive ventilation should be continued in the hospital and adjusted as needed; sedating medications should be avoided when possible and used judiciously with appropriate monitoring when unavoidable as in the case of magnesium.

### Restrictive and obstructive lung diseases

Obstetric patients with underlying lung disease are at increased risk for pulmonary complications and respiratory depression in the postpartum period. Restrictive lung disease is a risk factor for hypoxic or hypercapnic respiratory failure in pregnancy and the postpartum period and may manifest varied pathologic conditions during the peripartum period. A retrospective case series of 15 pregnancies in 12 women with significant interstitial lung disease or chest wall abnormalities found that patients with restrictive lung disease had high rates of premature delivery (60%) and of cesarean delivery (67%). Many required supplemental oxygen or ventilatory support during labor or postpartum (40%). Although pregnancy may be well tolerated by these patients, increased metabolic demands and work of breathing during labor and delivery may lead to acute decompensation and so appropriate resources should be readily available. Adequate labor analgesia is important to help control pain and work of breathing.

Patients with obstructive lung disease may also experience worsening chronic pulmonary dysfunction during pregnancy with an increased risk of postpartum respiratory depression. Asthma is common among pregnant women and its rates are increasing; approximately 1 in 10 pregnant women has asthma. An association exists between asthma and obstetric complications such as preeclampsia, placental abruption, placenta previa, hemorrhage, and cesarean delivery. Asthma seems to confer additional vulnerability to respiratory viral infections as well as more serious complications from them. A prospective study of 285 pregnant patients found that 71% of

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<th>Common medications associated with sedation and respiratory depression</th>
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<td><strong>Anesthetics &amp; Analgesics</strong></td>
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<td>Clonidine</td>
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women with asthma reported at least one “common cold” during pregnancy versus 46% of women without asthma.\textsuperscript{43} Apart from the risk of respiratory compromise from an asthma exacerbation or status asthmaticus, the comorbidities associated with asthma may increase a patient’s overall risk of postpartum respiratory complications.

Careful consideration of the risks and benefits of uterotonics for managing postpartum hemorrhage (PPH) is crucial for all patients, but especially those with asthma. Carboprost is a synthetic analog of prostaglandin F2-alpha commonly used to induce abortion or treat PPH secondary to uterine atony. The medication has several common side effects including nausea, vomiting, diarrhea, fever, and bronchoconstriction. Although all patients are at risk for bronchospasm with the administration of carboprost, patients with a history of asthma are more likely to suffer severe or life-threatening reactions.\textsuperscript{44,45} For this reason, the carboprost material safety data sheet caution against its use in patients with a history of reactive airway disease.

**Neuromuscular disorders**

Pregnant patients with neuromuscular disorders are also at increased risk for respiratory compromise.\textsuperscript{46–48} Although the physiologic changes to respiratory mechanics in pregnancy may offset some of the pulmonary compromise seen in these patients at baseline, the compensation is often overwhelmed and may manifest as worsening, chronically poor pulmonary function. With some conditions such as spinal muscular atrophy (SMA), pulmonary function will improve shortly after delivery,\textsuperscript{49,50} whereas with other conditions, such as myasthenia gravis (MG), the presentation may be more variable.\textsuperscript{46–48}

SMA is an autosomal recessive disease caused by the degeneration of the anterior horn cells in the spinal cord and brain stem that results in generalized muscle weakness and atrophy including the thoracoabdominal wall which leads to severe restrictive lung disease and reduced lung volumes.\textsuperscript{46–49} SMA presents at birth, during childhood, or young adulthood. Pregnancy in patients with SMA can cause chronic alveolar hypoventilation to further deteriorate and result in acute-on-chronic respiratory failure.\textsuperscript{49,50} This tends to improve after delivery, but these patients are best managed with close specialist monitoring throughout pregnancy.

Patients with MG experience skeletal muscle weakness and easy fatigability due to the autoimmune attack of neuromuscular junction acetylcholine receptors.\textsuperscript{46–48} MG can first present in pregnancy or the postpartum period and is diagnosed in an estimated 1 in 20,000 pregnancies.\textsuperscript{51} For those patients diagnosed with MG before conception, their pregnancy course can vary and some may even note improved MG symptoms.\textsuperscript{52} When postpartum MG exacerbations do occur they are often sudden and associated with respiratory failure.\textsuperscript{47} MG patients are especially sensitive to certain medications. Some medications, such as nondepolarizing neuromuscular blocking drugs, can be used with caution\textsuperscript{52}; others, such as magnesium sulfate, should be avoided.\textsuperscript{53} Magnesium sulfate is commonly administered in pregnancy for preterm fetal neuroprotection\textsuperscript{54} and seizure prophylaxis in mothers with pre-eclampsia.\textsuperscript{53,55} Unfortunately, studies have shown that therapeutic magnesium administration can trigger a myasthenic crisis so it has been historically contraindicated for eclampsia prophylaxis in MG patients.\textsuperscript{56,57} In a case report, by Ozcan and colleagues, the authors describe a patient diagnosed with both MG and term pre-eclampsia who was safely managed and delivered without magnesium through the cooperation of obstetric, neurology, and anesthesiology teams.\textsuperscript{53}

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), or Guillain–Barre syndrome, is a rare, acute neuropathy characterized by progressive, ascending
weakness that can result in respiratory compromise. Although studies have shown no difference in risk of developing AIDP during pregnancy than the general population, postpartum risk is increased. Within the first month postpartum, the risk of AIDP is tripled over the general population.

**Opioid use and misuse**

Opioid use during pregnancy has increased over the last 2 decades, mirroring the opioid epidemic in the general population. In a 2010 national survey of reproductive age women, 4.4% pregnant women and 11% nonpregnant women reported illicit drug use or opioid misuse in the last month. This spans all racial/ethnic, socioeconomic, and geographic populations. The American College of Obstetricians and Gynecologists (ACOG) advocates for substance use screening as a part of standard, comprehensive obstetric care for all patients. Screening tools should differentiate between medical therapy, opioid misuse, and opioid use disorder to direct appropriate treatment. Treatment is essential as substance use during pregnancy is a major risk factor for pregnancy-associated deaths. Importantly, the postpartum period is a vulnerable time for relapse and continuity of care should be maintained so patients are supported during their times of transition.

Broadly, opioid use is associated with dose-dependent respiratory depression. Patients who chronically use or abuse opioids are at risk for opioid tolerance and may require higher doses of opioids—increasing their risk of respiratory depression—to achieve the same degree of analgesia. Multi-modal analgesia with nonsedating medications is essential for safe and effective analgesia in this population. As discussed in several sections of this article, appropriate monitoring is a key to minimize the risk of OIRD in the postpartum patient (see Fig. 3).

**Pregnancy-related conditions**

In a 2017 retrospective analysis of obstetric patients admitted to the ICU requiring intubation and mechanical ventilation, Hung and colleagues found that PPH (28%, n = 20/71) and severe preeclampsia (18%, n = 13/71) were leading causes of respiratory failure. ICU admission is a rare but significant peripartum complication (0.7–8.8 per 1000 deliveries) that warrants reviewing the most common causes of maternal respiratory failure: preeclampsia, peripartum cardiomyopathy (PPCM), hemorrhage, amniotic fluid embolism (AFE), and infection.

**Preeclampsia**

Preeclampsia is a hypertensive disorder of pregnancy characterized by elevated blood pressure and end-organ damage and/or dysfunction (eg, renal, hepatic, pulmonary, central nervous system; Table 4). Preeclampsia is associated with abnormal placental vascular development which contributes to generalized endothelial dysfunction and a systemic proinflammatory state. A patient with preeclampsia is at an increased risk of respiratory failure secondary associated with pulmonary edema, altered mental status, and therapeutic side effects. Pulmonary edema interferes with gas exchange and can cause a range of symptoms from mild dyspnea to severe hypoxia and cardiopulmonary collapse. Seizures associated with eclampsia can compromise the upper airway with loss of protective reflexes, obstruction, and aspiration all contributing to potential respiratory insufficiency. Postictal states can also cause respiratory depression through central apnea and decreased arousability.

Definitive treatment for preeclampsia is delivery due to placental pathologic condition, but preeclampsia can also present in the postpartum period. Although no curative medical therapy exists, antihypertensives and magnesium sulfate are key for

managing pathophysiologic perturbations associated with preeclampsia.⁶⁷,⁶⁸ Magnesium sulfate is currently the most effective antiepileptic drug in patients with preeclampsia with severe features, reducing the rate of seizures from 3.4% to 0.3%.⁶⁷,⁷⁰,⁷¹ Accumulation of excess magnesium at neuromuscular junctions competes with calcium at acetylcholine binding sites, and thus inhibits presynaptic acetylcholine release and postsynaptic membrane excitability.⁵³,⁷² Magnesium therapy may also cause sedation, neuromuscular weakness, hypotension, uterine atony, postpartum hemorrhage, pulmonary edema, and respiratory depression.⁵³,⁶⁷ Magnesium has been designated as a high-alert medication due to potential toxicity and has been implicated in cases of iatrogenic harm to mothers.⁷³ Patients on magnesium therapy should be assigned appropriate nursing ratios to ensure close, regular monitoring with vital signs, deep tendon reflexes, levels of sedation, and urine output; magnesium levels should be checked for patients with impaired renal function or concern for magnesium toxicity based on clinical signs. Calcium gluconate or carbonate should be readily available to treat patients with magnesium toxicity.⁷³,⁷⁴

**Peripartum cardiomyopathy**

PPCM is a rare (1 in 2000 US births⁷⁵) complication that presents in late pregnancy through the early postpartum period.⁷⁶,⁷⁷ PPCM is characterized by left ventricular systolic dysfunction (left ventricular ejection fraction (LVEF) <45%) that develops in patients without preexisting cause for heart failure. In 2010 the European Society of Cardiology (ESC) revised the prior diagnostic timeline set out in the 1990s by the US National Heart, Lung, and Blood Institute—heart failure that develops in the last month of pregnancy or up to 5-months postpartum—to be less restrictive and to include patients who would otherwise meet diagnostic criteria for PPCM.⁷⁶,⁷⁸,⁷⁹ The cause of PPCM is not entirely understood; however, research suggests a multifactorial etiology that includes genetics, hormone-mediated vascular dysfunction, or the intersection of the two.⁸⁰,⁸¹ Risk factors for PPCM include Black ancestry, advanced maternal age, preeclampsia, and multiple gestation pregnancy.⁷⁶ With pharmacologic treatment, more than half of women suffering from PPCM will recover to a normal systolic function within the first 6 months to a year; those who are left with chronic cardiomyopathy may require mechanical support or heart transplantation.⁷⁶,⁸¹–⁸³

Patients with PPCM present with classic heart failure symptomatology: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, chest pain, lower extremity
edema, and fatigue. These symptoms commonly overlap with those of normal pregnancy and this may delay diagnosis. For some patients, the diagnosis of PPCM will follow a catastrophic presentation of acute, severe respiratory distress, and cardiogenic shock. Regardless of presentation, postpartum patients with new respiratory distress should be evaluated for PPCM. BNP levels have been shown to be reliable and predictive of short- and long-term outcomes in pregnant women with PPCM.

**Postpartum hemorrhage**

PPH is a leading cause of maternal mortality worldwide and occurs in about 6% of all childbirths. Approximately 3% of all postpartum patients require a blood product transfusion, whereas greater than 50% of patients with PPH require a transfusion—often massive transfusions (ie, >10 units in 24 hours). Transfusion-related acute lung injury (TRALI) and transfusion-associated cardiac overload (TACO) are significant complications associated with blood product transfusion and resuscitation. TRALI is a specific manifestation of acute respiratory distress syndrome (ARDS). The incidence of TRALI, while decreasing since 2006, is approximately 1 per 5000 units of transfused blood product. TRALI is the most common lethal posttransfusion complication at 30% to 40% with a mortality rate of 5% to 10%. TRALI presents with rapidly deteriorating hypoxemia, bilateral pulmonary edema, and hemodynamic instability within 6 hours of transfusion in patients without a history of pulmonary trauma or alternative etiology for acute lung injury. TRALI is a diagnosis of exclusion and the differential should include alternative causes of ARDS, TACO, cardiogenic shock, venous thromboembolism, and AFE. If a postpartum patient presents with acute, rapid respiratory decompensation after receiving a blood transfusion TRALI must be considered, and appropriate supportive therapies initiated to minimize morbidity.

**Amniotic fluid embolism**

AFE is a rare (2–8 cases per 100,000 deliveries) but serious obstetric complication that can present with an abrupt cardiopulmonary collapse, although AFE presentation can vary considerably and no diagnostic criteria have been developed to date. The syndrome can occur during labor, delivery, or early postpartum (up to 48 hrs) and is characterized by symptoms including hypoxia, hypotension, generalized seizures, and disseminated intravascular coagulopathy (DIC). The etiology remains largely unknown. AFE is thought to be caused by the introduction of amniotic components (amniotic fluid, fetal cells, hair, or other debris) into the maternal circulation triggering an abnormal immunologic response sometimes called the “anaphylactoid syndrome of pregnancy.” Although a rare cause of postpartum respiratory depression, maintaining high clinical suspicion for AFE can increase the likelihood of early detection and effective treatment; see Table 5 for cardiopulmonary symptoms associated with AFE.

**Sepsis and acute respiratory distress syndrome**

Sepsis is a life-threatening medical condition defined by acute organ dysfunction that is the result of abnormal host response to infection. Sepsis and septic shock are major, preventable causes of maternal morbidity and mortality. Historically, in the preantibiotic era, nearly half of maternal deaths were due to infection; now, an estimated 4 to 10 in 10,000 live births are complicated by sepsis. Early recognition and treatment are essential to improve maternal outcomes. The Sequential Organ Failure Assessment (SOFA) score is used to help identify patients at risk for sepsis/septic shock. Varied parameters assessing respiratory,
coagulation, hepatic, cardiovascular, central nervous, and renal system dysfunction are scored.113 The quick SOFA (qSOFA) is a set of 3 clinical criteria that can be used for bedside assessments with 2 or more positive criteria that suggest an increased risk of adverse sepsis-related outcomes.112 A significant overlap exists between these sepsis criteria cutoffs and normal maternal physiologic parameters, as such the Society of Obstetric Medicine Australia and New Zealand (SOMANZ) introduced modified guidelines and SOFA parameters for the obstetric population in 2017 (Table 6).112,114

As suggested by its inclusion in the SOFA and qSOFA scoring systems, respiratory compromise is an important but variable manifestation of sepsis. Studies of the recent respiratory virus pandemics (2009 H1N1 and 2019 SARS-CoV-2) provide a unique insight into sepsis, ARDS, and respiratory failure in the obstetric population.115–118

In a prospective cohort study of 675 women that presented for delivery in 3 New York City hospitals, Prabhu and colleagues reported that women with COVID-19 were more likely to deliver via a cesarean section and have an increased risk of postpartum complications. One in 10 women admitted tested positive for SARS-CoV-2 (10.4%; 78.6% were asymptomatic.) The rate of cesarean delivery in women with symptomatic COVID-19 (46.7%) was significantly higher than those without COVID-

### Table 5

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<tr>
<th>Cardiovascular</th>
<th>Pulmonary</th>
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<tr>
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<tr>
<td>Tachycardia</td>
<td>Cough</td>
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<td>Arrhythmia</td>
<td>Hypoxemia</td>
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<tr>
<td>Right heart failure</td>
<td>Pulmonary edema/ARDS</td>
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<tr>
<td>Left heart failure</td>
<td>Acute pulmonary hypertension</td>
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<tr>
<td>Cardiogenic shock</td>
<td>V:Q mismatch</td>
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→ **Cardiac arrest**

→ **Respiratory arrest**

Abbreviation: ARDS, acute respiratory distress syndrome.


### Table 6

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<th>Quick Sequential organ failure assessment (qSOFA) score</th>
<th>General Population</th>
<th>Obstetric Population</th>
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<tr>
<td>Systolic blood pressure</td>
<td>&lt;100 mm Hg</td>
<td>&lt;90 mm Hg</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>&gt;22 breaths per minute</td>
<td>&gt;25 breaths per minute</td>
</tr>
<tr>
<td>Altered Mental Status</td>
<td>Present</td>
<td>Present</td>
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19 (30.9%) and historical national averages (31.7%, 2019). Although the rate of postpartum complications, defined as fever, hypoxia, and readmission, was 3 times higher in the COVID-19 cohort (12.9% vs 4.5%) none of the women in the study required mechanical ventilation. Similar findings have been reported by others.

In the event of more serious infections and severe ARDS, women may require mechanical ventilatory support or ECMO. In a systematic review of case reports, Ong and colleagues found approximately 40% of ECMO deployments in the peripartum or postpartum patient are for respiratory failure; more than 90% of these cases are due to ARDS. The remaining 60% of ECMO cases are for cardiovascular indications of which 23.7% were cases of pulmonary embolism and 16.9% were due to PPCM. A retrospective observational study by Nair and colleagues looked at the use of ECMO support in twelve critically ill pregnant and postpartum patients with ARDS in Australia and New Zealand during the 2009 H1N1 pandemic. In their review, they found that most patients required veno-venous (VV) ECMO. Bleeding was the most common complication and the use of ECMO for severe ARDS in this population was associated with a 66% survival rate (comparable to 63%–75% survival rate for ECMO patients overall). Similarly, in their case series published in 2021, Barrantes and colleagues report on the 9 pregnant and peripartum patients with severe COVID-19 ARDS who required ECMO support. In this patient subset, the survival rate was 100% and these patients also suffered minor bleeding but did not otherwise suffer any significant ECMO complications. Moore and colleagues reviewed all cases of ECMO use during pregnancy between 1991 and 2007 (n = 45) and found an overall maternal survival rate of 78%. The review by Ong and colleagues included the use of ECMO in both pregnant and postpartum patients between 1972 and 2017 (n = 97) with an increase in the maternal survival rate to 91%.

Even with these reassuring reports on the effectiveness of ECMO as a rescue treatment for obstetric patients with severe ARDS, the treatment modality remains a limited resource that is not available or feasible for all patients. This is especially concerning given the findings of the retrospective study by Callaghan and colleagues that used ICD-9CM diagnosis codes and data from the National Inpatient Sample to study trends in maternal morbidity and mortality between 1998 and 2009. The study made several sobering observations over the 10-year span:

- The rate of ARDS increased 75% during delivery hospitalizations and 181% during postpartum hospitalizations.
- 8 in 100,000 women died during their delivery hospitalization (0.008%, n = 4012/48,346,974).
  - Of these deaths:
    - 60.6% required mechanical ventilation (n = 2430/4012) and
    - 33.2% were diagnosed with ARDS (n = 1332/4012).
- 2 in 1000 women died during their postpartum hospitalizations (0.2%, n = 1592/738,124).
  - Of these deaths:
    - 76.5% required mechanical ventilation (n = 1218/1592) and
    - 53.3% were diagnosed with ARDS (n = 848/1592).

**Peripartum medications**

**Neuraxial opioids**

Neuraxial opioid analgesia is the bedrock of obstetric anesthesia due to its effectiveness for postoperative analgesia and favorable risk-benefit profile for pregnant and lactating women. Most parturients receive epidural or intrathecal opioids via single injection, continuous or intermittent infusions and, of those who do not, many will receive systemic
opioids. As such the exposure to opioids, and the associated risk of opioid-induced respiratory depression as described above, is present for many postpartum patients.

Respiratory drive originates in the brainstem and is a culmination of inputs from central and peripheral chemoreceptors and the cerebral cortex. Opioid receptors are present throughout the respiratory control centers. Respiratory rhythm generation in the brainstem (medulla and pons) is the most sensitive to the effects of opioids with changes in the respiratory pattern seen at lower doses than those required to manifest changes in tidal volume. With higher opioid doses, the reduction in tidal volume is thought to be caused by a decrease in tonic inputs from opioid-sensitive chemoreceptors—both centrally and peripherally. In conjunction, opioids can cause respiration to slow and become irregular resulting in hypercapnia and hypoxemia.

The incidence of respiratory depression following neuraxial opioid administration in the nonobstetrical population is also poorly defined. Opioid-induced respiratory depression more broadly is well summarized by Gupta and colleagues in their 2018 systematic review and metaanalysis in which they report the incidence of ORID as 0.04% to 0.5% using naloxone administration as the clinical indication of ORID and 23%–41% using hypoxemia or bradypnea. In the same review, Gupta and colleagues reported on the prevalence of certain underlying comorbidities in patients with OIRD:

- Cardiac disease 45%124–126
- Diabetes mellitus 23%125–127
- Respiratory disease 17%124,126,127
  - COPD 81%124–127
- OSA 18%124–128
- Renal disease 17%124,126,127

Similarly, Ramachandran and colleagues reported the presence of underlying cardiac or respiratory disease was independently associated with an increased risk of respiratory complications postoperatively and a closed claims analysis by Lee and colleagues found OSA or suspected OSA in 24% of patients with postoperative OIRD.

The low incidence of adverse events reported in the literature with modern, ultralow, and low-doses of neuraxial morphine for postcesarean delivery analgesia suggest a high-degree of safety and efficacy in most obstetric patients. For the selected comorbidities and conditions acquired in pregnancy that we have reviewed here, obstetric anesthesiologists should undertake careful consideration of the patient's unique risks and benefits. In particular, neuraxial opioid use in combination with other medications that depress respiration should be avoided to the extent possible, and careful postpartum monitoring strategies should be used. More research is needed to better understand and elucidate safe practices to optimize the postcesarean delivery analgesic options and monitoring strategies for patients at greater risk of postpartum respiratory depression and adverse events (see Fig. 1).

**Sedatives**

Many analgesic adjuncts, sedatives, anxiolytics, and antiemetics can compromise respiratory drive. These agents when used in combination with opioids can potentiate respiratory depression and should be used judiciously. Some common medications associated with respiratory depression used by obstetric patients are summarized in Table 3.

**Anesthetic complications**

In addition to the effects of opioids, neuraxial analgesia can result in respiratory depression or failure in the event of a “high” or “total” spinal level blockade (spread
of local anesthetic that affects spinal nerves above T4). A “high spinal” causes paralysis of the muscles involved in active exhalation (abdominals, intercostals) leading to reduced expiratory reserve volume, peak expiratory flow, and maximum minute ventilation. This can manifest as dyspnea in parturients with normal pulmonary function but, in patients with underlying obstructive pulmonary disease, the loss of accessory respiratory muscle function can be significant. Further, although rare, a “total spinal” to a cervical level can compromise the phrenic nerve and preganglionic sympathetic nerves resulting in diaphragm paralysis, hypotension, bradycardia, and subsequent hypoperfusion of the medullary respiratory center (central apnea). This results in profound respiratory failure that requires prompt intubation and supportive positive pressure ventilation as well as circulatory support.

Despite the aforementioned risks of respiratory depression with neuraxial analgesia, it is held to be the preferred anesthetic technique for cesarean delivery. General anesthesia is avoided when possible due to an increased risk for aspiration, bleeding, failed intubation, and intraoperative awareness. A general anesthetic for cesarean delivery can also increase a patient’s risk of postpartum respiratory depression due to depressant effects of anesthetic agents, residual neuromuscular blockade (NMB), and intravenous opioids.

NMB is a risk factor for postoperative respiratory compromise in the postpartum patient just as in the general population. In some cases, the risk may be even more significant and weight-based dosing of neuromuscular blockade agents should be carefully considered. Total body weight (TBW), lean body weight (LBW), and ideal body weight (IBW) are all mass measurements used in the dosing of anesthetics. In normal-weight persons, LBW and IBW are similar; however, in obese persons, the LBW increases with increasing TBW. Commonly, an obstetric patient’s TBW (and LBW) will increase throughout pregnancy and remain increased during the postpartum period while their IBW remains constant. Weight-based dosing during this dynamic time can result in inconsistent responses to medications. A small study by Gin and colleagues examining the duration of rocuronium neuromuscular blockade in recently postpartum patients found that dosing by TBW resulted in a prolonged block when compared with control (and similar block duration when dosed by LBW.) Additionally, the use of agents known to prolong neuromuscular blockade, such as magnesium sulfate, is common in the obstetric population. Hypermagnesemia is desirable in situations of preterm delivery and in patients with preeclampsia for its neuroprotective qualities; however, the subsequent administration of nondepolarizing NMB in the event of cesarean delivery under general anesthesia can result in profoundly deep and prolonged neuromuscular blockade. Notably, magnesium sulfate therapy itself has been associated with respiratory depression at a rate of 0% to 8.2%. There has been little research to guide the use of sugammadex for the antagonism of NMBs in obstetric and lactating patients, as such their use has been limited in this population. Sugammadex seems to be safe for use in term and postpartum lactating women and its use should not be withheld when it may improve maternal safety. The Society for Obstetric Anesthesia and Perinatology issued a statement on its use in these populations in 2019.

SUMMARY

The peripartum period is a vulnerable time for many patients. Several of the conditions discussed here in the context of respiratory depression can have far-reaching ramifications including disability and death. Postpartum respiratory depression is a complex, multifactorial issue that encompasses a patient’s baseline preexisting conditions, certain pregnancy-specific conditions, or complications, as well as the iatrogenic...
effects of medications given during the peripartum period. Importantly, while the etiologies of postpartum respiratory depression/failure are numerous, certain patients are more vulnerable than others to respiratory compromise. The detection of respiratory compromise in these patients can be complicated by the significant overlap between or confounding by normal maternal physiologic changes. For this reason, it is important to modify or develop specific alert criteria and algorithms for the obstetric population.

The use of opioids, specifically neuraxial morphine, for postcesarean delivery analgesia at modern, ultra-low, and low dosages is safe and effective, and carries a low risk of respiratory depression for most obstetric patients. For those patients at higher risk for respiratory depression given select co-morbidities or conditions, careful consideration of each patient’s unique risks and benefits should be undertaken before the administration of neuraxial morphine or any other drug that may depress respiration, and further research is needed to better elucidate these risk factors.

Over the last decade, there has been an increase in the incidence of severe peripartum pulmonary complications resulting in ARDS and severe respiratory failure. The recent, novel H1N1 and COVID-19 viral respiratory pandemics have taken this to an extreme and, in the process, helped to demonstrate the value and safety of mechanical ventilatory support, including ECMO, in pregnant and postpartum patients.

Ultimately, each patient and pregnancy is unique. The care of each postpartum patient should be individualized and consider their specific risk factors and their risk for postpartum respiratory depression.

**CLINICS CARE POINTS**

- Pre-existing diseases such as obstructive sleep apnea, obesity hypventilation syndrome, and cardiopulmonary diseases may interact with conditions acquired during pregnancy or postpartum, or with drugs administered peripartum, to compound the risk of respiratory compromise in vulnerable patients.

- When pregnancy physiology is superimposed on the pathophysiology of obesity, significant respiratory compromise can result.

- Neuraxial morphine is an effective form of post-cesarean delivery analgesia and should not be withheld from obese women out of concern for respiratory depression if ultra-low or low doses are utilized with multi-modal analgesia, along with appropriate monitoring strategies and care plans.

- Obstetrical patients with obstructive sleep apnea should be carefully monitored, and non-invasive ventilation should be continued in hospital and adjusted as needed; sedating medications should be avoided when possible and used judiciously with appropriate monitoring when unavoidable as in the case of magnesium.

- Restrictive lung disease is a risk factor for hypoxic or hypercapnic respiratory failure in pregnancy and the postpartum period and may manifest varied pathology during the peripartum period.

- While all patients are at risk for bronchospasm with the administration of carboprost, patients with a history of asthma are more likely to suffer severe or life-threatening reactions.

- Patients who chronically use or abuse opioids are at risk for opioid tolerance and may require higher doses of opioids—increasing their risk of respiratory depression—to achieve the same degree of analgesia.

- Magnesium has been designated as a high-alert medication due to potential toxicity, and has been implicated in cases of iatrogenic harm to mothers.

- BNP levels have been shown to be reliable and predictive of short- and long-term outcomes in pregnant women with peripartum cardiomyopathy.
If a postpartum patient presents with acute, rapid respiratory decompensation after receiving a blood transfusion TRALI must be considered, and appropriate supportive therapies initiated to minimize morbidity.

DISCLOSURE

The authors have nothing to disclose.

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