Obstetric Disorders and Critical Illness

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KEYWORDS

• Obstetric critical care • Postpartum hemorrhage • Hypertensive disorders of pregnancy
• HELLP syndrome • Acute fatty liver of pregnancy • Peripartum cardiomyopathy
• Amniotic fluid embolism • Pulmonary embolism

KEY POINTS

- Pregnant women may become critically ill due to obstetric or nonobstetric illness. The intensivists caring for them must have a fundamental understanding of maternal physiology.
- The most common obstetric-related conditions that lead to critical illness include postpartum hemorrhage; the hypertensive disorders of pregnancy; hemolysis, elevated liver enzymes, and low platelets syndrome; acute fatty liver of pregnancy; amniotic fluid embolism; and peripartum cardiomyopathy.
- Two nonobstetric conditions that cause life-threatening illness in pregnant women include pulmonary embolism and Covid-19.
- An understanding of the physiology and best management of these conditions is essential for providing best care to one's patients. We provide presentations, physiology and management of these conditions in this review.

INTRODUCTION

Pregnant and postpartum women rarely need the involvement of intensivists in their care.When they do, it is crucial for their critical care physicians to be prepared to provide the best, most well-informed care by an interdisciplinary team including the patient's obstetrician, maternal–fetal medicine (MFM) specialist, obstetric anesthesiologist, and other relevant specialties.

There are over 3.5 million live births per year in the United States,[1] and UNICEF estimates over 130 million annual births worldwide. Globally, maternal mortality shows a great variation among countries, but it approaches 216 per 100,000 births.[2] Similarly, severe maternal morbidity (SMM) also varies greatly between more- and less-resourced regions. In the United States, maternal mortality has been on the rise, nearing 17.4 per 100,000 live births, with significant ethnic and racial variability[3] and cardiovascular diseases as the most common causes.[4] Maternal mortality is higher in the United States than in all other developed countries and is justifiably considered a crisis, hence the need to act swiftly to identify causes for this rise and educate providers on the care of pregnant women. There are clear racial discrepancies in maternal morbidity and mortality in the United States. Black women in this country have a maternal mortality rate 2.5 times that of white women.[5] Black women are also more likely to be readmitted with severe morbidity in the postpartum period than white women.[6] This warrants particular awareness and recognition of structural and intrinsic biases when assessing patients for ICU admission and care and ongoing work to eliminate these disparities.

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Abbreviations	
ICU	intensive care unit
IM/IV	intramuscular/ intravenous
ARDS	acute respiratory distress syndrome
DIC	disseminated intravascular coagulation
SBP	systolic blood pressure
DBP	diastolic blood pressure
BP	blood pressure
LDH	lactate dehydrogenase
AST	aspartate transaminase
ALT	alanine transaminase
PT	prothrombin time
PTT	partial thromboplastin time
APTT	activated partial thromboplastin time
ECMO	extracorporeal membrane oxygenation
INR	international normalized ratio
TTE	transthoracic echocardiogram
TEE	transesophageal echocardiogram
ECMO	extracorporeal membrane oxygenation
RV	right ventricle
VA	venoarterial
IF	insulin-like growth factor
CHEST	the official publication of the American College of Chest Physicians
NIH	National Institutes of Health
UNICEF	United Nations International Children's Emergency Fund
WHO	World Health Organization

Obstetric patients may become critically ill due to either obstetric or non-obstetric illness. The most common causes for pregnant and peripartum women to be admitted to an ICU—with variations depending on the robustness of health care systems and resources available therein—include postpartum hemorrhage (PPH), hypertensive disorders of pregnancy (HDP), sepsis, and pulmonary embolism (PE).[7–10] A fundamental knowledge of obstetric critical illness and specific aspects of maternal care and physiology is essential.

In this article, we will discuss some of the more common obstetric-related conditions that can lead to critical illness and require management in an ICU. We will also discuss PE and Covid-19. Despite not being specific to obstetric patients, PE is a common, life-threatening diagnosis in pregnancy with particular risks and management aspects. Covid-19 does not seem to occur with higher frequency in pregnant women, but it does lead to higher rates of ICU admissions and mechanical ventilation in pregnant women than in their nonpregnant peers.[11] Its prevalence during our current global pandemic makes it important to discuss in this article.

PHYSIOLOGIC CHANGES IN PREGNANCY MOST RELEVANT TO CRITICAL CARE

This section highlights physiologic changes most relevant to the assessment and care of critically ill obstetric patients—specifically, those affecting hemodynamic and respiratory states—and is not intended as a comprehensive review.

Hemodynamics

Pregnancy is associated with profound hemodynamic changes. **Table 1** illustrates some of these.[12–14] Blood volume increases by approximately 50% above baseline,[13,15] reflecting increases in both plasma volume and erythrocytes. As a result, there is an ability to tolerate 500 to 1000 mL rapid blood loss without significant hemodynamic compromise.[16,17] This may lead to a

Table 1
Hemodynamic changes in normal pregnancies

	Direction of Change in Pregnancy	% Change
Blood volume	↑	40%–50%
Cardiac output	↑	30%–50%
Heart rate	↑	15%–20%
Blood pressure	↓	—
Systematic vascular resistance	↓	20%–30%

false assessment of the severity of blood loss in a pregnant patient if judging by the hemodynamic state.

In the supine position, by mid-pregnancy, the enlarging uterus compresses the aorta and vena cava. This leads to decreased venous return and a drop in maternal cardiac output. To counter this, critically ill gravid patients should typically be positioned with a left lateral tilt to 15° to 20°, displacing the uterus laterally and offsetting the aortocaval compromise.[18] This is particularly true in instances of clinically significant hemodynamic compromise.

Airways and Ventilation

Functional residual capacity decreases by about 20% in pregnancy. By approximately 12 weeks gestational age, ligamental relaxation leads to widening of the rib cage, pulling the diaphragm upward.[19] As the fetus grows, the enlarging uterus creates cephalad pressure on the diaphragm with resultant further elevation of the diaphragm,[19] and the chest wall becomes less compliant.[20] At the same time, oxygen demand increases due to increases in both metabolic rate and oxygen consumption.[21] As a result, the tolerance for hypoventilation and apnea in pregnancy is reduced as compared with nonpregnant patients.[22]

Endotracheal intubation in pregnant patients is challenging. Rates of failed intubation are eight times higher than in the general population.[23] The intolerance of hypoventilation or apnea, combined with airways that are difficult in pregnancy due to airway edema and hyperemia, necessitates that intubation be performed by the most experienced provider available. Preoxygenation is essential.

Laboratory differences in pregnancy must be factored into the assessments of patients. Arterial blood gases (ABGs), commonly used in the assessment of critically ill patients, normally indicate mild respiratory alkalosis in pregnancy, with a physiologic PaCO2 of 28 to 32 mm Hg. In compensation for this, the serum bicarbonate level falls to 18 to 21 meq/L.

Some of the conditions requiring ICU admission in pregnant women may be specific to or worsen in pregnancy, whereas others are not. Here, we focus primarily on the obstetric-specific conditions associated with high maternal mortality that lead to ICU admissions.

POSTPARTUM HEMORRHAGE

PPH is the leading cause of maternal death worldwide. It accounts for 27.1% of maternal fatalities and occurs with a much higher frequency in developing countries.[24] Between 1993 and 2014, the United States had a precipitous 4- to 5-fold rise in the rate of PPH.[25] This coincided with the

- Leading cause of maternal death worldwide
- Etiologies: the 4 Ts—tone, trauma, tissue, and thrombin
- Management:
  - Uterotonics
    - Oxytocin 10 IU IM/IV for all births, can repeat up to 40 IU for continued hemorrhage
    - Secondary agents such as methylergonovine
  - Transexamic acid (TXA) 1g in 10 mL IV, can repeat if ongoing bleeding after 30 minutes
  - Removal of retained tissues
  - Repair of trauma
  - Transfusion of blood and blood products, using a massive transfusion protocol where appropriate and available

- Most frequent nonhemorrhagic diagnoses requiring ICU admission in pregnancy/peripartum
- HDP can present de novo postpartum
- Gestational hypertension: blood pressure greater than 140/90 mm Hg at greater than 20 weeks gestational age in a patient without prior hypertension
- Hypertensive emergency: systolic blood pressure greater than 160/110 mm Hg for greater than 15 minutes
- Preeclampsia: hypertension with proteinuria or other measures of organ dysfunction
- Eclampsia: preeclampsia plus seizures or coma
- Management:
  - Antihypertensives
    - Initial management with nifedipine, labetalol, or hydralazine (suggested dosing in Table 2)
    - Refractory management with nicardipine, labetalol, esmolol, or sodium nitroprusside (suggested dosing in Table 3)
  - Magnesium for seizure prophylaxis, 4–6 g IV loading dose, and then 1–2 g/h continuous infusion
  - Delivery

increased rates of cesarean deliveries, leading both to increased obstetric interventions and instrumentation, but also to increased risk for intra-abdominal scar tissue and abnormal placentation, leading in turn to the increased risk of PPH in future pregnancies.[26]

PPH is defined differently by various national obstetric societies, but most recently the American College of Obstetrics and Gynecology (ACOG) defines it as cumulative blood loss of 1000 mL or more, or blood loss associated with clinical evidence of hypovolemia, regardless of route of delivery.[27]

Risk factors for PPH include advanced maternal age, grand multiparity, previous cesarean delivery, suspected or proven placental abruption, placenta previa, and preeclampsia or gestational hypertension. Uterine fibroids, multiple pregnancy, fetal macrosomia, instrumental vaginal delivery, cervical laceration, and uterine rupture also increase risk of PPH.[28]

Etiologies can be categorized according to the "4 Ts" mnemonic by order of frequency: tone (uterine atony, accounting for 70% of all cases), trauma, tissue (retained tissue, invasive placenta), and thrombin (coagulopathies).[27] Because of the prevalence of uterine atony as a cause, the World Health Organization (WHO) recommends prophylactic administration of oxytocin 10 IU IM or IV for all births during the third stage of labor to stimulate uterine contraction.[29]

Uterine atony can be managed medically, mechanically, or failing those conservative measures, surgically. This management is mainly led by the obstetric team. The initial management of hemorrhage due to uterine atony includes bimanual uterine massage and the routine administration of oxytocin. Further dosing of oxytocin, not to exceed 40 IU, can be infused at a rate necessary to control uterine atony. Following that, a secondary uterotonic agent can be administered, often methylergonovine. If these measures fail, mechanical attempts to control atony-related hemorrhage may include balloon tamponade of the uterus, placement of an internal uterine suction device,[30] or uterine compression sutures. If these methods are unsuccessful, surgical interventions, including bilateral uterine artery ligation, internal iliac ligation, or ultimately hysterectomy, can be lifesaving procedures for the mother.[27]

The uterus must be inspected for retained placental tissue, with evacuation as needed. The uterus and genital tract are inspected for trauma, with repair of any lacerations.

The mainstays of management by the ICU team are achieving hemostasis and transfusion support, including the utilization of a massive transfusion protocol. The administration of large volumes of clear fluids has been associated with more severe deterioration of coagulation parameters, suggesting that restrictive fluid resuscitation in women with PPH is advisable.[31] Blood and blood products should be administered at ratios based on local and institutional thresholds and massive transfusion protocols. There are no clear obstetric guidelines on a recommended ratio of administration of packed red blood cells, fresh frozen plasma, and platelets. These data have been extrapolated from trauma literature,[32,33] and institutions develop their own massive transfusion protocols. As with all bleeding, the indication for transfusion may be guided by targeting certain laboratory values (ie, hemoglobin > 7, platelets >50, INR >1.5) or by the clinical scenario. Lack of hemodynamic instability may be misleading, as mentioned previously. Thromboelastography or rotational thromboelastometry, where available, may be beneficial in helping guide blood and blood products' administration.[34]

Table 2
Suggested initial management for severe intrapartum or postpartum Hypertension

If SBP ≥ 160 mm Hg or BBP ≥ 110 mm Hg, start fetal surveillance if undelivered and the fetus is viable
If this degree of hypertension is maintained for >15 min, start...

Choice of initial medication	IV labetalol (intermittent)	IV hydralazine	Oral nifedipine
	Labetalol 10–20 mg IV over 2 min	Hydralazine 5–10 mg IV over 2 min	Immediate-release nifedipine capsules, 10 mg orally
Repeat BP in ...	10 min	20 min	20 min
If SBP still ≥160 mm Hg or DBP ≥110 mm Hg....	Labetalol 40 mg IV over 2 min	Hydralazine 10 mg IV over 2 min	Immediate-release nifedipine capsules, 20 mg orally
Repeat BP in ...	10 min	20 min	20 min
If SBP still ≥160 mm Hg or DBP ≥ 110 mm Hg....	Labetalol 80 mg IV over 2 min	Labetalol 20 mg IV over 2 min	Immediate-release nifedipine capsules, 20 mg orally
Repeat BP in ...	10 min	10 min	20 min
If SBP still ≥ 160 mm Hg or DBP ≥ 110 mm Hg....	Hydralazine 10 mg IV over 2 min	Labetalol 40 mg IV over 2 min consult MFM internal medicine, anesthesia, or critical care subspecialists	Labetalol 20 mg IV over 2 min and consult MFM, internal medicine, anesthesia, or critical care subspecialist
Repeat BP in ...	20 min		
If SBP still ≥ 160 mm Hg or DBP ≥ 110 mm Hg....	Consult MFM, internal medicine, anesthesia, or critical care subspecialists		

- Variant of severe preeclampsia
- Women may have any or all of the elements of the triad of HELLP syndrome
- Differential diagnosis: idiopathic thrombocytopenic purpura (ITP), acute fatty liver of pregnancy (AFLP), hemolytic uremic syndrome (HUS), thrombotic thrombocytopenia purpura (TTP), and systemic lupus erythematosus (SLE)
- Management
  - Delivery
  - Corticosteroids for fetal lung maturity if < 34 weeks gestational age, and it is felt safe to defer immediate delivery
- Complications:
  - DIC, hepatic infarction, subcapsular hematomas, hepatic intraparenchymal hemorrhage, intracranial hemorrhage, placental abruption, acute renal failure, pulmonary edema, and seizures

TXA inhibits the breakdown of fibrinogen and fibrin clots. In 2017, the WHO recommended its use within 3 hours of delivery in women diagnosed with PPH in addition to standard care.[35,36] The recommended dose is 1g in 10 mL (100 mg/mL) IV at 1 mL/min, with a second dose of 1g IV given if bleeding continues after 30 minutes (WHO). There is a reduction in benefit of TXA with time from delivery, with no benefit in its administration after 3 hours from birth.

SMM due to PPH remains a significant problem worldwide, with patients developing multisystem organ failure, shock, ARDS, and DIC. Management of each of these is unchanged from their management in non-obstetric patients, and intensivists' expertise managing those patients who progress to severe illness after PPH is invaluable.

HYPERTENSIVE DISORDERS OF PREGNANCY: HYPERTENSIVE EMERGENCIES, PREECLAMPSIA, AND ECLAMPSIA

The HDP are the most frequent nonhemorrhagic diagnoses requiring ICU admission in pregnant

Table 3
Suggested secondary management for severe intrapartum or postpartum hypertension

Choice of Initial Infusion Medication	Labetalol (Continuous Infusion)	Nicardipine	Esmolol	Sodium Nitroprusside
Starting dose	1–2 mg/min	5 mg/h	Bolus: 500 μg/kg Maintenance: 50 μg/kg/min	0.25 μg/kg/min
Titration dose and frequency	Increase by 1-mg/min every 10 min as needed	Increase by 2.5 mg/h every 5–15 min as needed	Increase by 50 μg/kg/min every 4 min as needed	Increase by 0.25–0.5 μg/kg/min every 2–3 min as needed
Maximum dose	300 mg/d IV	15 mg/h	300 μg/kg/min	5 μg/kg/min * potential risk for cyanide/thiocyanate toxicity if used for >4 h

and peripartum women.[7,37] They are the second-leading cause of maternal death worldwide.[24]

Gestational hypertension is defined as a blood pressure greater than 140/90 at greater than 20 weeks gestational age in a woman who was not hypertensive before 20 weeks. Preeclampsia is the same degree of hypertension but with the additional finding of proteinuria and/or any of the features listed in **Box 1**.[38–40] Those other features, or a severely elevated blood pressure (greater than 160/110 mm Hg on at least two separate assessments) with proteinuria or the listed findings, define preeclampsia with severe features. Eclampsia is the disease state when preeclampsia is accompanied by seizures or coma. The syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLPs) is considered a variant of HDP and will be discussed separately.

Box 1
Preeclampsia

Preeclampsia: SBP $\geq$ 140 mm Hg and/or DBP $\geq$ 90 mm Hg after 20 weeks gestation in a woman without chronic hypertension, accompanied by proteinuria ($\geq$300 mg protein/24 h urine collection; protein: creatinine $\geq$ 0.3 mg/dL; or urine dipstick reading of 2+ if quantitative measures are unavailable) or any of the features listed below.

Any of the following criteria in the setting of preeclampsia with severe features:

- SBP $\geq$160 mm Hg and/or DPB $\geq$110 more than 4 hours apart (unless antihypertensive therapy has begun)
- Thrombocytopenia (plt < 100,000 $\times$ 10^9/L)
- Transaminases >2X upper limit of normal
- Severe right upper quadrant or epigastric pain without an alternative diagnosis
- Serum creatinine greater than 1.1 mg/dL or twice baseline, without other kidney disease
- Pulmonary edema
- New-onset headache unresponsive to acetaminophen and without other diagnosis or visual symptoms

The presence of acute, severe hypertension (>160/110 mm Hg) measured accurately more than 15 minutes apart is a hypertensive emergency, with the greatest risk to the mother of a central nervous system injury. Pregnant women with severe systolic or diastolic hypertension, or both, require urgent therapy.[39] ACOG has published guidelines for the emergency management of acute, severe hypertension during pregnancy and the postpartum period.[38]

The definitive treatment of preeclampsia and eclampsia is delivery of the fetus. When hypertension is associated with severe features at or beyond 34 weeks gestational age, delivery is recommended. At earlier gestational ages, expectant management may be considered, with guidance available from ACOG.[38]

These recommendations include the choice of IV labetalol, IV hydralazine, or oral nifedipine when IV access is unavailable. The target blood pressure should be an initial range of 140 to 150/90 to 100 mm Hg. There is no single accepted first line agent, but see **Table 2** for first-choice options and suggested dosing and intervals.[38,39,41–43]

Guidance is less clear on medications to use when the initial antihypertensive therapies fail. See **Table 3** for alternatives, dosing and intervals.[41,42]

Table 4
Mississippi and Tennessee criteria for hemolysis, elevated liver enzymes, and low platelet syndrome

Tennessee Criteria	Missisippi-Triple Class System
• Evidence of hemolysis on a peripheral smear • Decreased haptoglobin • Increased serum bilirubin ($\geq$20.5 μmol/L or) or $\geq$ 1.2 mg/100 mL) • Elevated LDH (>600 units/L_ • Platelets $\leq$ 100 $\times$ 10^9/L • AST $\geq$ 70 IU/L (ref)	Class 1 • LDH $\geq$ 600 IU/L • ALT or AST $\geq$70 IU/L • platelets $\leq$50 $\times$ 10^9/L
	Class 2 • LDH $\geq$ 600 IU/L • ALT or AST $\geq$ 70 IU/L • platelets $\geq$ 50 $\times$ 10^9/L but $\leq$ 150 $\times$ 10^9/L
	Class 3 • LDH $\geq$ 600 IU/L • ALT or AST $\geq$ 40 IU/L • platelets $\geq$ 100 $\times$ 10^9/L but $\leq$ 150 $\times$ 10^9/L

- More true hepatic dysfunction than HELLP, evidenced by hypoglycemia, coagulopathies, and encephalopathy
- Many women have coexisting preeclampsia
- Management:
  - Delivery
  - Supportive care—close monitoring, transfusions as needed, mechanical ventilation if needed
- Most patients recover within 1 to 2 weeks after delivery
- Evaluation for orthotopic liver transplantation, though rarely needed, is indicated if liver failure is severe or progressive.

Magnesium is also recommended for seizure prophylaxis, and per ACOG guidelines should be started in a pregnant or postpartum patient with gestational hypertension with severe features, preeclampsia with severe features, or those with eclampsia.[38] For the first two, it is more effective than other agents in reducing the risk of eclampsia.[44] A suggested regimen is a loading dose of 4-6g IV of magnesium sulfate followed by 1-2 g/h maintenance infusion.[38]

If the patient requires induction of general anesthesia and endotracheal intubation, blood

Box 2
Diagnostic criteria for acute fatty liver of pregnancy

Swansea criteria

Six or more of the following, without an alternative etiology, are needed for a diagnosis of AFLP:

- Nausea/vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- Ascites or "bright-appearing" liver on ultrasound
- Hyperbilirubinemia (>14 μmol/L or >0.82 mg/dL)
- Hypoglycemia (<4 mmol/L or <72 mg/dL)
- Hyperuricemia (>340 μmol/L or >5.7 mg/dL)
- Leukocytosis (>11 $\times$ 10/L)
- Transaminitis (AST or ALT >42 IU/L)
- Hyperammonemia (>47 μmol/L or 66 μg/dL)
- Renal dysfunction (creatinine >150 μmol/L or >1.7 mg/dL)
- Coagulopathy (PT > 14 sec or APTT> 34 sec)
- If liver biopsy is performed, +microvesicular steatosis

pressure monitoring and management are critical, as induction and intubation themselves can raise blood pressures dramatically.

It is also important to recognize that approximately 1/3 of eclampsia develops postpartum. A postpartum patient with hypertension accompanied by headaches and/or vision changes is at high risk of serious complications. Half of intracerebral hemorrhage caused by preeclampsia occurs postpartum.[40] Last, patients with preeclampsia tend to have baseline intravascular depletion and do not tolerate the same degree of blood loss as patients without preeclampsia.

HEMOLYSIS, ELEVATED LIVER ENZYMES, AND LOW PLATELETS (HELLP SYNDROME)

- Presents with a clinical triad of dyspnea and/or hypoxia; cardiovascular collapse; DIC
- Management
  - Supportive, including clearly cardiopulmonary resuscitation (CPR) in event of cardiac arrest
  - Fetal delivery (if not already delivered) within 5 minutes of starting CPR if there has been no return of spontaneous circulation
  - Vasopressors are preferred over crystalloid fluid infusions for BP support
  - Pulmonary vasodilator such as inhaled nitric oxide
- Patients with refractory heart or lung failure should be considered for ECMO
- Differential diagnosis includes PE, high spinal anesthesia, and magnesium toxicity

The HELLP syndrome is characterized by the triad of HELLPs. There is no consensus for specific laboratory values, and women may have one, two, or all three components of the syndrome.

HELLP syndrome is considered a variant of severe preeclampsia, though it can occur in women with normal blood pressure. It is rare, occurring in 0.2% to 0.9% of all pregnancies[45–47] and 10% to 20% of women with severe preeclampsia.[47] The diagnosis carries an increased risk of complications for both mother and fetus,[45,46] and its recognition and appropriate management are therefore paramount.

There are two classification systems for HELLP, the Tennessee criteria and the Mississippi Triple Class System, as shown in **Table 4**, which define and classify HELLP based on degrees of hemolysis, thrombocytopenia, and degree of liver dysfunction.

The differential diagnosis of HELLP is broad as mentioned above. ITP is not more common in or exacerbated by pregnancy, and even with quite low platelet counts, the incidence of maternal or fetal morbidity or mortality is low.[48] HUS and TTP are thrombotic microangiopathies with some similar features to HELLP syndrome. HUS, when present in peripartum patients, tends to develop postpartum and presents with symptoms of renal failure.[47] TTP is exceedingly rare in pregnancy but presents with neurologic dysfunction, fever, abdominal pain, and bleeding.[47] SLE can affect multiple organ systems, but patients with lupus nephritis may present with clinical and laboratory findings similar to patients with severe preeclampsia.[47]

If HELLP manifests at $\geq$34 weeks gestational age, or if there are concerning and potentially dangerous additional findings in the mother including multiorgan dysfunction, DIC, liver hemorrhage or infarction, renal failure, suspected placental abruption, or nonreassuring fetal status, there is general consensus to deliver the fetus.[46,49,50]

In pregnancies less than 34 weeks gestational age, glucocorticoids are used for fetal lung maturity if it is felt to be safe to delay delivery. Glucocorticoids have no benefit in regard to maternal morbidity/mortality or perinatal or infant death.[51]

Decisions regarding timing of delivery will necessarily be made in close collaboration with the patient's obstetrician and MFM specialists.

Potential complications include DIC, hepatic infarction, subcapsular hematomas, hepatic intraparenchymal hemorrhage, intracranial hemorrhage, placental abruption, acute renal failure, pulmonary edema, and seizures.[47,52–54]

Particular mention is warranted of the complication of hepatic rupture, as it can be catastrophic. Abdominal pain, particularly in the epigastric or right upper quadrant and/or radiating to the right shoulder, with either hypertension or shock, should trigger consideration of prompt abdominal imaging with ultrasound or CT if the patient is stable enough to allow it.[52–54] Treatment may include conservative management with aggressive support of coagulation, transfusion of blood products, and prophylactic antibiotics if the hematoma is contained.[52] Embolization may also be considered at that point. Hemodynamic instability should trigger either hepatic artery embolization, surgical packing of the liver, or a combination of these therapies.[52–54]

ACUTE FATTY LIVER OF PREGNANCY

This is a relatively rare but potentially fatal complication of pregnancy characterized histologically by microvesicular fatty infiltration of hepatocytes. It demonstrates more true hepatic dysfunction than preeclampsia or HELLP, which manifests clinically as hypoglycemia as well as coagulopathies, encephalopathy, and DIC.[55]

The diagnosis is often clinical, based on symptoms and laboratory values. Liver biopsy is the gold standard for diagnosis but is rarely performed. The clinical and laboratory findings included in the diagnosis are combined in the Swansea criteria, as shown in **Box 2**.

Treatment is primarily supportive, including transfusions, ICU monitoring, and mechanical ventilation if indicated. Delivery of the fetus is critical. Most patients' liver function returns to normal after delivery, typically within 1 to 2 weeks.

In rare cases, orthotopic liver transplantation is pursued.[56,57] A small review of patients referred to a UK liver transplant center between 1997 and 2008 with severe pregnancy associated liver dysfunction from AFLP or HELLP revealed that elevated lactate and the presence of hepatic encephalopathy were the only admission parameters predictive of death or need for liver transplant. King's college criteria did *not* predict outcome.[56]

AMNIOTIC FLUID EMBOLISM

- Presents in late pregnancy or postpartum with symptoms of HF or more rarely with catastrophic complications
- Management
  - Standard therapy for HF, with modifications for fetal and breastfeeding safety
  - Anticoagulation
  - Ventricular assist devices or ECMO for severe decompensated HF
  - Consideration of wearable defibrillators while awaiting possible cardiac recovery
  - Consideration of implantable cardioverter/defibrillators (ICDs) for prolonged, severe LV dysfunction

Amniotic fluid embolism (AFE) is a rare entity, with a wide range of reported incidence based on different reporting methodologies. It carries a high morbidity and mortality ranging between less than 20% to more than 60%. The pathophysiology seems to be a combination of fetal components entering the maternal circulation and an abnormal, anaphylactoid, immune response to those fetal components. Fetal components can be found in the maternal circulation of pregnant and postpartum women without AFE; the immune response is a key component of the clinical syndrome.[58,59]

AFE classically encompasses a triad of dyspnea and/or hypoxia followed by cardiovascular collapse and severe coagulopathy, with significant oozing and frank bleeding at suture lines, vaginal tears, and venipuncture sites. Patients may also demonstrate neurologic changes that include altered mentation and seizures. These physical signs and symptoms typically occur during labor and delivery, cesarean delivery, dilation and evacuation, or immediately postpartum without an alternative explanation. There also seems to be a version of AFE that presents as isolated DIC and hemorrhage, without or with only minimal maternal hypoxia or hemodynamic instability or collapse.[60]

Physiologically, there is a transient initial period of pulmonary and systemic hypertension, with intense pulmonary vasoconstriction leading to hypoxia and right heart failure (HF).[61] This is followed by profound depression of left ventricular (LV) function with normal PA pressures. The myocardial dysfunction may be due to myocardial ischemia from hypoxia due to lung injury or cardiac arrest imposed by AFE or there may be myocardial ischemia due to coronary artery spasm.[58]

In women who suffer cardiac arrest from AFE, all three of the lethal dysrhythmias have been described—ventricular fibrillation, pulseless electrical activity, and asystole. These likely reflect different physiologic mechanisms of arrest: hypoxia, direct myocardial depression, and exsanguination.[62] Survivors of cardiac arrest often develop multisystem organ failure, including hypoxic brain injury.[58]

The differential diagnosis includes PE, anaphylaxis, aortic dissection, septic shock, air or fat embolism, eclampsia, adverse reaction to medications, and hemorrhagic shock, among others.[63] In classic AFE, ABGs will reflect hypoxemia but are not specific enough to really aid in diagnosis. Chest x-rays are also nonspecific, often appearing consistent with pulmonary edema. PT/INR/PTT and fibrinogen should be evaluated. For patients with suspected AFE who experience hemodynamic collapse, bedside echocardiogram (TTE or TEE if an experienced provider is immediately available) can be useful in demonstrating RV failure, though this may not help differentiate between AFE and some of the alternative diagnoses, particularly PE. The presence of the acute, often

profound, coagulopathy seen in AFE can help differentiate between these two diagnoses. Various serum markers have been examined as clues to the diagnosis, including C1 esterase inhibitor and IGF, but do not seem particularly useful in acute diagnosis and management. The diagnosis is a clinical one.

Other diagnoses in the differential include high spinal anesthesia, which can complicate spinal or epidural anesthesia and can present with dyspnea or apnea, profound hypotension, and bradycardia. It is managed with aggressive fluid resuscitation, hemodynamic and respiratory support, and intralipid. Magnesium toxicity is also in the differential as it can present with hemodynamic collapse. It is treated with IV calcium.

The management of AFE is supportive. CPR is indicated in the event of cardiac arrest, and delivery is indicated within 5 minutes if there is no response to CPR or if non-reassuring fetal status remains despite correction of maternal hypoxia.

Blood pressure support with vasopressors is recommended over volume expansion (excepting blood and blood products to manage hemorrhage)

- One of the leading causes of maternal deaths in the United States
- Pregnant women have a significantly higher incidence of thromboembolic disease than their nonpregnant peers, with highest risk postpartum
- Management:
  - Anticoagulation
  - Systemic or catheter-directed thrombolysis
  - Surgical thrombectomy
  - Salvage therapy with ECMO should be considered for patients with circulatory collapse or refractory hypoxemia

due to the presence of acute right HF. Inotropic support and pulmonary vasodilators may also be indicated.[64] Patients with refractory HF should be evaluated for VA ECMO.[65]

Transfusion of blood and blood products is indicated for the coagulopathy and secondary hemorrhage that develop.[66] Recombinant factor VIIa has been associated with worse outcomes compared with blood and blood products alone; thus, it is not a recommended therapy.[67] Experimental therapies include administration of C1 esterase inhibitor concentrate,[68,69] TXA, aminocaproic acid, and aprotinin. They remain investigational and are not currently recommended therapies, and aprotinin is no longer on the market.

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy (PPCM) is defined as "an idiopathic condition with LV systolic dysfunction (ejection fraction [EF] <45%) toward the end of pregnancy or following delivery, when no other cause of HF is found."[70]

The incidence varies greatly in different studies, with variability between different populations. Of note, women of African descent have a much higher incidence of PPCM than white women.[71–73] There is also a strong association between the HDP and PPCM.[74–76] Risk factors for PPCM include African ancestry, preeclampsia and hypertension, multiparity, and advanced maternal age[70,77–79].

The pathophysiology of PPCM is unclear and likely multifactorial. It does not seem to be a response to the physiologic hemodynamic demands of pregnancy. For most patients, presenting symptoms of PPCM include the symptoms of HF, which can unfortunately overlap with some of the symptoms—particularly dyspnea—typically seen in pregnancy. A minority of patients may present in cardiogenic shock or with arrhythmias or complications of thromboembolism.[80] There are no specific laboratory markers for this condition, but the B-type natriuretic peptide is markedly elevated in PPCM and is not elevated in typical pregnancy, which makes this a useful test in this diagnosis.[81–83] Echocardiography reveals a reduced EF and may demonstrate left and right ventricular dilatation and/or dysfunction, valvular dysfunction, left or bi-atrial enlargement, or pulmonary hypertension.[80]

Mortality in this diagnosis can be due to arrhythmias and thromboembolic disease as well as decompensated HF.

Management includes the management of decompensated HF; diuresis, beta blockade, and sometimes inotropes, all with the caveats of taking medication safety in pregnancy and breastfeeding into account. There is a high reported incidence of LV thrombosis and thromboembolism,[84,85] so anticoagulation has been recommended from diagnosis through 6 to 8 weeks after delivery.[86] Both the American Heart Association and the European Society of Cardiology suggest anticoagulation in PPCM with EF < 30 or 35%, respectively,[87–89] but there are no published guidelines to determine therapeutic versus prophylactic anticoagulation. Prolactin inhibition has been studied, specifically with the use of

- Pregnant women with Covid-19 have higher rates of ICU admission, need for mechanical ventilation, and death than their nonpregnant peers.
- Management of critically ill pregnant women with Covid-19 pneumonia and ARDS should include:
  - Latest medical therapies in accordance with infectious disease guidelines
  - Neuromuscular blockade, prone positioning, and inhaled nitric oxide should all be considered for refractory hypoxemia
  - Prone positioning can be safely performed even in later stages of pregnancy
  - For truly refractory hypoxemia, hypercarbia, or cardiopulmonary failure, patients should be evaluated for ECMO

bromocriptine, but it remains experimental, especially given a concern for increased risk of thrombosis with bromocriptine and the importance of retaining the ability to breastfeed.[80,90]

The increased risk of thrombosis and thromboembolism are thought to be due to a combination of factors, including hemostasis in a poorly contracting ventricle, the hypercoagulable state of pregnancy, and relative immobility for many patients (particularly those recovering from cesarean sections or complicated vaginal deliveries).

Patients with severe HF due to PPCM may require mechanical support with ventricular assist devices or cardiopulmonary support with ECMO.[91–93]

For patients who present with PPCM while still pregnant, the planning for labor and delivery should be multidisciplinary, involving obstetricians, cardiologists, MFM specialists, obstetric internists, anesthesiologists, nursing, pharmacologists, and social workers.

Many patients demonstrate recovery in their LV function, often within the first 6 months, with a significantly higher likelihood of recovery in those patients whose EF is greater than 30% at their time of diagnosis.[94] Because of frequent recovery of cardiac function, ICDs are generally not recommended initially, though there may be a consideration of wearable defibrillators.[74,95] There are no clear guidelines on when, or in which patients, ICDs should be considered. These decisions should be guided by the patient's cardiologist as they are followed after initial diagnosis.

PULMONARY EMBOLISM

PE is one of the leading causes of death in the United States, accounting for 9.5% of

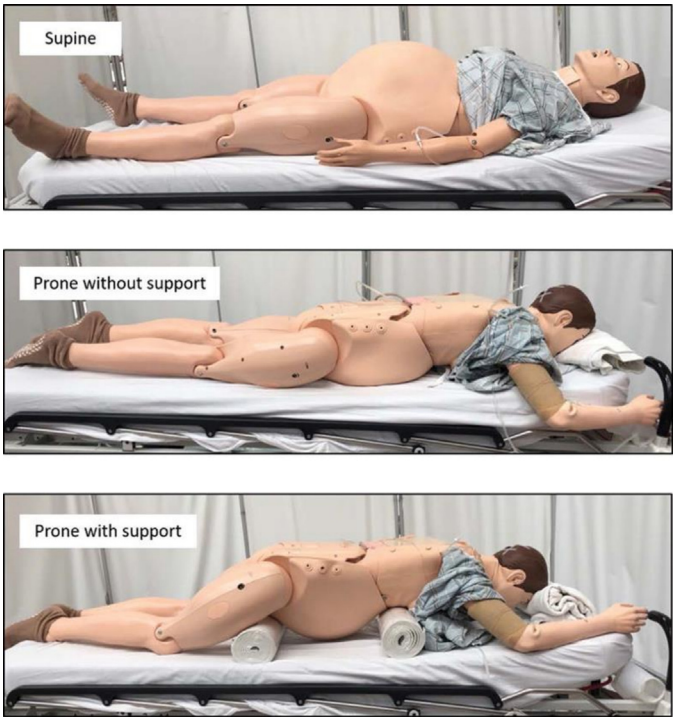

Fig. 1. Prone positioning of the pregnant patient with key areas of support. (*From* Oxford-Horrey C, Savage M, Prabhu M, Abramovitz S, Griffin K, La-Fond E, Riley L, Easter SR. Putting It All Together: Clinical Considerations in the Care of Critically Ill Obstetric Patients with COVID-19. Am J Perinatol. 2020 Aug;37(10):1044-1051.)

pregnancy-related deaths there.[5,96,97] During pregnancy, there are increases in procoagulant factors, resistance to activated protein C, and decreases in circulating protein S,[98] with simultaneous decreases in fibrinolysis, leading to a state of hypercoagulability. Pregnancy yields a triad of this hypercoagulability, venous stasis, and vascular injury[99] that together significantly increase the incidence of PE in pregnant women compared with their nonpregnant peers.[100–102]

We focus here on the acute management of high-risk submassive and massive PEs. The mortality rate for untreated submassive and massive PEs is high in the general population.[103–105] Treatment with anticoagulation reduces the mortality risk, and at minimum, this should be started in all patients without a contraindication[106–108] as soon as the PE is diagnosed. With high-risk submassive and massive PEs, however, consideration should be given to the more aggressive therapies, including systemic or catheter-guided thrombolysis, surgical or catheter-based thrombectomy or fragmentation, and support with ECMO.[106,107,109–111] Evidence-based data supporting one management strategy over another are exceedingly limited, with most of the literature encompassing limited case series. There is also a concern for publication bias suggesting a higher than actual success rate. Despite those caveats, we present what is known of the therapeutic options for these potentially catastrophic PEs.

The 2016 CHEST guidelines on antithrombotic and thrombolytic therapy in the general population recommend thrombolysis for treatment of a PE with hypotension (SBP<90 mm Hg), but pregnancy is included as a relative contraindication.[107] However, a 2020 systematic review of thrombolysis in pregnancy and the immediate puerperium concluded that there was in fact *not* a prohibitive risk to thrombolytic therapy for PE in pregnancy.[112] The risks of hemorrhage in thrombolysis are higher in pregnant and particularly postpartum patients than in the general population, but the risks of morbidity and mortality from massive PE outweigh the risks from thrombolysis, making this a justifiable intervention.[109,110,112]

Although data are limited, the theoretic decreased risk of bleeding with catheter-guided lysis,[113,114] due to its two-third dose reduction compared with systemic lysis,[115] makes this an attractive option to explore further. CHEST guidelines still recommend reserving catheter-guided lysis for patients at increased risk of bleeding complications, with no specific comment on pregnant patients. The very limited case reports on patients for whom catheter directed therapy was used in massive and submassive PEs in pregnant women seem to show good outcomes with few complications.[116,117].

In cases of refractory hypoxemia or circulatory collapse, pregnant women with massive or submassive PE may be evaluated for VV or VA ECMO. This is a promising strategy under scrutiny in the general population, with data supporting its consideration.[118–120] Data on its use in pregnant women are quite limited, but they have been reported with favorable outcomes.[121–124]

COVID-19 AND ARDS MANAGEMENT

Covid-19 is clearly not an obstetric disease. Nevertheless, given its current prevalence around the world and the increased risk for severe illness that pregnant women face from the SARS-CoV2 virus, a brief section on severe Covid-19 in pregnant women is included in this article.

Pregnant women with Covid-19 have higher rates of ICU admission, need for mechanical ventilation, need for ECMO, and death than their age-matches, nonpregnant peers.[11,125] In pregnant and recently pregnant women with Covid-19 compared with pregnant and recently pregnant women without Covid-19, all-cause mortality and ICU admission rates were significantly higher in the patients with the disease. Some of the speculated reasons for this include physiologic changes of pregnancy such as increased heart rate and oxygen consumption, decreased lung capacity, increased risk for thromboembolic disease, and changes in immunity[11] but this remains unclear.

The management of severe Covid-19 and Covid ARDS in pregnancy has few differences from nonpregnant patients, but providers need to account for some of the physiologic changes of pregnancy and remain mindful of that higher acceptable oxygenation threshold to allow adequate fetal oxygenation.

The Covid-19 Treatment Guidelines Panel of the NIH recommends that “potentially effective treatment for Covid-19 should not be withheld from pregnant women because of theoretic concerns related to the safety of therapeutic agents in pregnancy.”[126] Included in these guidelines, dexamethasone is strongly recommended for patients who require hospitalization and supplemental oxygen.[126] Given the ongoing research and frequently updated guidelines, other specific recommendations for treatment are not included here, but the NIH states that “In general, the recommendations for managing Covid-19 in nonpregnant patients also apply to pregnant patients.”

In the event that a patient’s Covid-19 progresses to ARDS, some reminders for

management of ARDS in pregnancy are included. Maternal oxygenation should be maintained at a PaO2 greater than 70, corresponding to an oxygen saturation of ≥95%, to maintain adequate fetal oxygenation. A recent study suggested that an SpO_2 of 93% is normal in pregnancy and may be a reasonable acceptable threshold,[127] but this has not yet been widely adopted.

The acceptable range for pCO_2 in permissive hypercapnia is also altered, with allowance of pCO_2 rising only to 60 mm Hg out of concern for decreased placental perfusion at higher ranges.[128] This contrasts with much higher accepted ranges of pCO_2 in nonpregnant patients with ARDS.

For refractory hypoxemia, neuromuscular blocking agents should be added to sedatives to facilitate lung-protective ventilation, and inhaled pulmonary vasodilators such as inhaled nitric oxide and epoprostenol should be considered for hypoxemia that is refractory to standard management.[129] Prone positioning in ARDS has a demonstrated mortality benefit[130] and has been widely used to improve gas exchange in patients with Covid-19 ARDS. Accordingly, this strategy should also be used in pregnant patients with Covid-19 ARDS when indicated. Prone positioning can be challenging in later stages of pregnancy given the gravid uterus, but with proper support (**Fig. 1**), it can be achieved and provide benefit.[131,132]

For truly refractory hypoxemia and/or hypercarbia, pregnant women with Covid ARDS should be evaluated for ECMO by an experienced ECMO team.[121,122,133,134] There may be cannulation challenges in later stages of pregnancy related to the degree of uterine enlargement, which will require close communication and coordination with the ECMO team.

SUMMARY

Pregnant and peripartum women rarely require the care of intensivists. However, they may need ICU level care for a variety of conditions—some unrelated to pregnancy, and some that are directly related to pregnancy. We have discussed the diagnosis and management of these obstetric critical illnesses here, as they may be somewhat less familiar to medical intensivists than the nonobstetric indications for ICU admission (septic shock, for example) and also a few non-obstetric conditions that create significant morbidity and mortality in pregnant patients. Although the care of critically ill pregnant and peripartum women should remain a collaborative effort between the intensivists, obstetricians, MFM, and other relevant specialists involved with a given patient, our hope is that this article has provided a framework to guide more informed, medically sophisticated conversations among all participants in the care team.

CLINICS CARE POINTS

- Maternal physiology in a normal, healthy pregnancy includes changes in blood volume, heart rate, cardiac output, blood pressure, and systemic vascular resistance.
- Airways and ventilation change as well, with a decrease in functional residual capacity and an increase in oxygen demand. The tolerance for hypoventilation and apnea is decreased in pregnant women as compared to nonpregnant patients.
- Postpartum hemorrhage is the leading cause of maternal death in the world. Management recommendations include prophylactic oxytocin for all births, with further medical, mechanical, and surgical management options if it develops despite the oxytocin.
- The hypertensive disorders of pregnancy are the most common nonhemorrhagic ICU-requiring diagnoses in pregnancy and the peripartum period. Management includes antihypertensive medications, magnesium, and for refractory conditions, delivery.
- HELLP syndrome is a variant of preeclampsia. If it manifests at 34 weeks gestational age or the mother develops dangerous adverse effects from this syndrome, delivery is recommended.
- Acute fatty liver of pregnancy is managed with delivery and with supportive care, with rare referrals for orthotopc liver transplantation.
- Amniotic fluid embolism is a rare entity, though with high morbidity and mortality, that is managed supportively but must be recognized immediately for appropriate management.
- Peripartum cardiomyopathy is managed similarly to decompensated heart failure and is best managed in close collaboration with cardiologists.-Pulmonary embolism is one of the leading causes of maternal deaths in the United States. It is most often managed with anticoagulation, but other treatment options, depending on the clinical picture, include thrombolysis, thrombectomy, or salvage therapy with ECMO.
- Covid-19 does not infect pregnant women more than others, but does convey a higher risk of ICU admission, need for mechanical

ventilation, and death than in nonpregnant patients. Management of Covid-19 ARDS in pregnant women is similar to management in nonpregnant patients, with some alterations based on the physiologic changes of pregnancy, including a higher threshold of acceptable PaO2 to allow adequate fetal oxygenation.

- The care of critically ill pregnant women is best managed by a multidisciplinary team that includes intensivists, obstetricians, maternal-fetal-medicine specialists, and other relevant specialists depending on the specific situation.

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The authors have nothing to disclose.

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