Obstetric Disorders in the ICU

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KEYWORDS

- Pre-eclampsia • Eclampsia • Pulmonary edema
- Amniotic fluid embolism • Venous thromboembolism
- Ovarian hyperstimulation syndrome • HELLP
- Acute fatty liver of pregnancy

Maternal mortality in the developed world, even in patients admitted to intensive care units (ICUs), is rare. Unfortunately, mortality rates in the developing world are much higher. Recent statistics have shown that the lifetime risk of dying in pregnancy is 1 in 65 in Asia and parts of Africa, whereas that same risk is 1 in 8700 in Switzerland. Risks for mortality during pregnancy and childbirth include lack of education, single marital status, multiparity, lack of prenatal care, and non-Hispanic black race. The lowest rate of mortality is seen in non-Hispanic whites in the developed world. Traditional customs, social bias, and cultural factors also may affect mortality rates. Most maternal deaths (up to 70%) occur antepartum, whereas 27% of mothers who die do so in the first 6 weeks postpartum.

Obstetric disorders account for 55% to 80% of admissions to the ICUs in the obstetric population.[1,2] Despite this, medical conditions are emerging as the leading cause of maternal mortality, partly because of marked improvement in surgical and obstetric care in the developed world. The rise in maternal mortality related to medical conditions can be explained by multiple factors: (1) medical care is improved and women with chronic illnesses are reaching childbearing years, (2) many women in the western world are older at the time of their first pregnancy, (3) reproductive technologies have improved significantly in the past 20 years (consequently, older women and women with chronic illnesses are more likely to successfully conceive), and (4) severe medical conditions may be exacerbated by the physiologic changes of pregnancy,[3] leading to a sicker pregnant population.

The lower mortality associated with obstetric disorders may be explained by the fact that in many cases, delivery or surgical intervention is associated with quick reversal of the underlying pathology and clinical improvement. Risk factors for critical illness and consequent ICU admissions were suggested in a 14-year study of 1023 admissions to the ICU.[4] Risk factors include age older than 35 years (OR = 1.4, CI 1.05–1.81; $P = .02$), black race (OR = 1.8, CI = 1.38–2.30; $P < .001$), race other than black or white (OR = 5.9, CI = 2.60–12.77; $P < .001$), treatment in a minor teaching hospital (OR = 2.0, CI = 1.48–2.60; $P < .001$), and transfer to a higher level hospital (OR = 2.5, CI = 1.23–5.14; $P = .01$). Overall, the proportion of pregnant women admitted to nonobstetric ICUs is small, which makes the exposure of the average intensivist to pregnancy-related issues limited. The focus of this article is to review the most frequent disorders leading to ICU admissions in the obstetric population.

PRE-ECLAMPSIA

Pre-eclampsia (PEC) is an idiopathic multisystemic disorder that is specific to human pregnancy and the puerperium. It is essentially a placental disorder because complete molar pregnancies

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that contain no fetal tissue have been associated with PEC. PEC and eclampsia were the second most likely cause of maternal mortality in a study published in 1988[5] and accounted for 15% of maternal deaths. More recent statistics from the confidential enquiry into maternal mortality in the United Kingdom found hypertensive disorders to directly cause 14 deaths per 1 million maternities (**Tables 1** and **2**).[6] Fortunately, maternal mortality rates related to PEC have declined significantly over the past two decades,[6,7] but PEC-associated infant mortality remains elevated and was reported to be 47.2 per 1000 births.[7]

The development of PEC has been thought to be secondary to abnormal placentation, which suggests that PEC is determined at an early stage in gestation. Failure of the second phase of trophoblast invasion results in the lack of destruction of the muscularis layer of the spiral arterioles. Persistence of this layer hinders the ability of those arterioles to vasodilate and accommodate the increase in blood flow.[8] Subsequently, placental hypoperfusion and hypoxia lead to the release of factors in the maternal circulation that are thought to be responsible for endothelial dysfunction, hypertension, and other manifestations of PEC. Endothelial dysfunction is thought to occur in part as a result of a functional defect in vascular endothelial growth factor, related to elevated levels of vascular endothelial growth factor antagonists such as s-Flt1 and endoglin. However, other factors are involved in the pathogenesis.

Clinically, the most conservative definition of PEC is blood pressure of 140/90 mm Hg or more in a previously normotensive woman and proteinuria more than 300 mg/dL or 2+ or more on a urine dipstick with or without peripheral edema. This definition has been used in most clinical studies. The Canadian Society of Obstetrics and However, gynecology recently issued a report that accepted the diagnosis of PEC in the absence of proteinuria (http://www.sogc.org/guidelines/documents/gui206CPG0803_001.pdf9) (**Table 3**).[9] PEC occurs in 8% to 10% of pregnancies, but in most cases it is mild to moderate and does not necessitate critical care services. It is increased in frequency in patients with a prior history of PEC, a family history in a first-degree relative, underlying renal disease, thrombophilia, secondary hypertension, or systemic lupus erythematosis. A few life-threatening complications of PEC may require an ICU admission.

Eclampsia

Eclampsia is defined as seizures or coma in the setting of PEC without any evidence of other neurologic disorders. The cause of the convulsions is thought to be related to cerebral vasospasm with local ischemia, hypertensive encephalopathy, vasogenic edema, or endothelial damage. Approximately half the cases of eclampsia occur before term (< 37 weeks' gestation), with more than 20% occurring before 31 weeks' gestation. Most seizures are self-limited and last 3 to 4 minutes at most, and most usually occur before the patient even has intravenous access, which makes it difficult to properly compare the therapeutic effects of drugs. It is thought that seizure prophylaxis and control are best achieved with magnesium sulfate ($MgSO_4$) infusions, however. Benzodiazepines also may be used, and they control the seizures in most cases within 5 minutes; however, use of benzodiazepines close to delivery may be associated with severe respiratory depression in the newborn, so if they are required for seizure control it is recommended that a neonatologist be present for delivery. When comparing $MgSO_4$ to phenytoin and benzodiazepines, the eclampsia trial collaborative group showed that $MgSO_4$ is superior to

Table 1
Numbers of direct deaths attributed to eclampsia and pre-eclampsia and mortality rates per 100,000 maternities, United Kingdom: 1985–2005

Triennium	Number	Rate	95% CI	
1985–1987	27	1.19	0.82	1.73
1988–1990	27	1.14	0.79	1.66
1991–1993	20	0.86	0.56	1.33
1994–1996	20	0.91	0.59	1.41
1997–1999	16	0.75	0.46	1.22
2000–2002	14	0.70	0.42	1.16
2003–2005	18	0.85	0.54	1.35

Data from Lewis G, editor. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer. 2003–2005. The seventh report on confidential enquiries into maternal deaths in the United Kingdom. London: CEMACH; 2007.

both drugs in the prevention of recurrent eclamptic seizures.[10] $MgSO_4$ was also shown to be associated with 8% lower likelihood of ICU admission and need for ventilatory support when compared with phenytoin.[10] Patients treated with magnesium infusion should have patellar reflex monitoring and monitoring of respiratory rate and urine output. Respiratory arrest caused by magnesium toxicity can be reversed with calcium. Blood pressure control is also essential in the setting of eclampsia.

Pulmonary Edema

Pulmonary edema complicates 0.05% of low-risk pregnancies and 2.9% of all cases of PEC (**Fig. 1**).[11] Starling forces dictate the capillary–interstitial fluid exchange that occurs in the lungs, and the development of pulmonary edema is governed largely by the plasma colloid oncotic pressure-pulmonary capillary wedge pressure gradient.[12] Pulmonary edema in patients with PEC can be either cardiogenic or noncardiogenic and may be caused by various mechanisms. First, plasma colloid oncotic pressure falls during normal pregnancy from 23.2 mm Hg in the first trimester to 21.1 mm Hg at term[13] to 16 mm after delivery. The fall is even more pronounced in cases of PEC.[14] This significant drop in colloid oncotic pressure in PEC can be explained by renal albumin losses and impaired liver synthesis. The precipitous drop in the postpartum period can be explained further by blood loss, fluid shifts from the extravascular to the intravascular space, and excessive crystalloid infusions. Second, increased capillary wedge pressure may be related to left ventricular dysfunction, intravenous fluids, or the phenomenon of autotransfusion observed with uterine contractions in labor. In fact, 300 to 500 mL of blood are pumped from the uterine circulation into the systemic circulation with every contraction. Third, capillary endothelial damage can occur because pulmonary edema has been observed in the setting of normal colloid oncotic pressure–wedge gradient and normal wedge pressure. Finally, left ventricular dysfunction, which may be either systolic or diastolic, can be present. Pulmonary edema secondary to systolic dysfunction may occur in patients with severe hypertension, leading to a sudden increase in afterload or underlying heart disease, such as peripartum cardiomyopathy or cardiomyopathy predating the pregnancy related to various causes.[15] The development of pulmonary edema in these cases is facilitated by the drop in the oncotic-hydrostatic pressure gradient. Diastolic dysfunction has been described in obese, chronically hypertensive women with superimposed PEC.

Table 2
Number of deaths from pre-eclampsia or eclampsia, United Kingdom: 2003–2005

	Cerebral					Pulmonary				Hepatic			
Triennium	Intracranial Hemorrhage	Subarachnoid	Infarct	Edema	All	ARDS	Edema	Other	All	Rupture	Failure/ Necrosis	Other	All	Total
1985–1987	11	0	0	0	11	9	1	2	12	0	1	3	4	27
1988–1990	10	2	2	0	14	9	1	0	10	0	1	2	3	27
1991–1993	5	0	0	0	5	8	3	0	11	0	0	4	4	20
1994–1996	3	1	0	3	7	6	2	0	8	2	1	2	5	20
1997–1999	7	0	0	0	7	2	0	0	2	2	0	5	7	16
2000–2002	9	0	0	0	9	1	0	0	1	0	0	4	4	14
2003–2005	10	0	2	0	12	0	0	0	0	0	2	4	6	18

Abbreviation: ARDS, adult respiratory distress syndrome.
Data from Lewis G, editor. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer. 2003–2005. The seventh report on confidential enquiries into maternal deaths in the United Kingdom. London: CEMACH; 2007.

Table 3
Classification of the hypertensive disorders of pregnancy

Primary Diagnosis	Definition of Pre-Eclampsia[a]
Pre-existing hypertension	
With comorbid conditions[b]	
With pre-eclampsia → (after 20 weeks' gestation)	Resistant hypertension or new or worsening proteinuria or one or more adverse conditions
Gestational hypertension	
With comorbid conditions[b]	
With pre-eclampsia → (after 20 weeks' gestation)	New proteinuria or one/more adverse conditions[c]

Women may be classified into more than one subgroup.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

[a] Severe pre-eclampsia corresponds to pre-eclampsia with onset before 34 weeks' gestation, with heavy proteinura (3–5 g/d according to other international guidelines) or with one or more adverse conditions.

[b] Comorbid conditions, such as type I or II diabetes mellitus, renal disease, or an indication for antihypertensive therapy outside pregnancy.

[c] Other adverse conditions consist of maternal symptoms (persistent or new/unusual headache, visual disturbances, persistent abdominal right upper quadrant pain, severe nausea or vomiting, chest pain, or dyspnea), maternal signs of end-organ dysfunction (eclampsia, severe hypertension, pulmonary edema, or suspected abruptio placentae), abnormal maternal laboratory testing (elevated serum creatinine [according to local laboratory criteria]; elevated AST, ALT or LDH [according to local laboratory criteria] with symptoms; platelet count <100 × 109/L; or serum albumin <20 g/L); or fetal morbidity (oligohydramnios, intrauterine growth restriction, absent or reversed end-diastolic flow in the umbilical artery by Doppler velocimetry, or intrauterine fetal death [www.sogc.org/guidelines]).

From von Dadelszen P, Magee L. What matters in preeclampsia are the associated adverse outcomes: the view from Canada. Current Opin Obstet Gynecol 2008;20:111; with permission.

A confounding factor suggested in the literature as a possible cause for the development of pulmonary edema is intravenous administration of $MgSO_4$ for seizure prevention in pre-eclampsia.

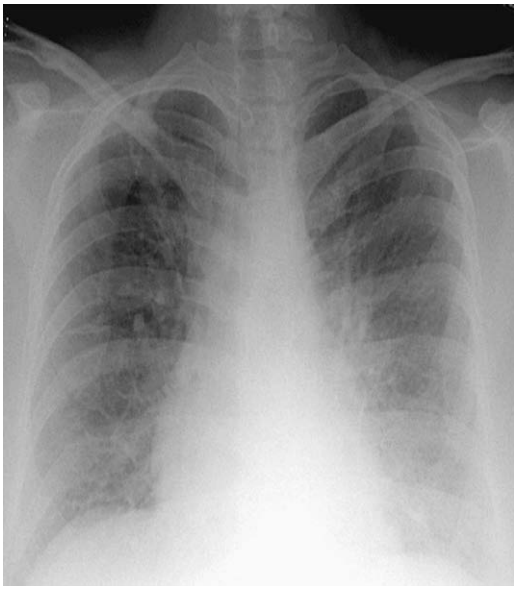

Fig. 1. 44-year-old G1P0 with pre-eclampsia and cardiogenic pulmonary edema.

In a study of 294 patients who received $MgSO_4$ for the prevention of pre-eclamptic seizures, however, only 4 patients developed pulmonary edema,[16] which makes this causative relationship less likely.

Pulmonary edema develops most commonly (70%–80% of cases) in the postpartum period.[11,14] It can be explained by the postpartum changes that include a significant drop in colloid oncotic pressure and the increase in preload that occurs with uterine contractions, the relief of vena caval obstruction after delivery of the conception products, and the mobilization of extravascular fluid that occurs in the initial 24 to 72 hours postpartum. Diseased kidneys are also commonly incapable of handling this rapid increase in intravascular volume. On the other hand, the small proportion of patients who experiences pre-eclampsia and develop pulmonary edema in the antenatal period is usually multiparous and older and has chronic hypertension.[11]

Hemodynamic profiles of patients with severe PEC/eclampsia vary in the literature from an elevated cardiac output and a normal systemic vascular resistance in the preclinical stage to an elevated cardiac output and elevated systemic vascular resistance or an elevated systemic vascular resistance with a depressed cardiac output

or even normal systemic vascular resistance.[17–21] Variations in the data may depend partly on the methods used to measure hemodynamics[20] but also may suggest the presence of different hemodynamic profiles in PEC. It is not entirely clear whether patients may progress from one profile to the other. In a study that followed serial hemodynamic measurements in an obstetric population using a finger arterial pressure waveform registration device, patients with PEC without fetal growth restriction were found to have a higher cardiac output at different stages in pregnancy than patients with PEC with fetal growth restriction.[22] For those reasons, hemodynamic monitoring may be necessary in patients with severe, complicated PEC who do not respond to initial therapy to help clarify the hemodynamic profile and tailor therapy accordingly.

Treatment of pulmonary edema is basically unchanged compared with the general population and should be modified depending on whether pulmonary edema is thought to be cardiogenic or noncardiogenic in nature. Pregnant women generally respond to lower doses of diuretics than nonpregnant women, and most patients respond to 10 mg of furosemide administered intravenously. Afterload reduction and blood pressure control may be achieved with administration of intravenous hydralazine or labetolol.

Hypertensive Emergency

PEC may present with severe hypertension with a potential for end-organ damage, including retinal hemorrhage, papilledema, pulmonary edema, severe headache, and renal failure. Acute cerebral complications (eg, intracranial hemorrhage, massive cerebral edema) are particularly worrisome because they account for more than 75% of maternal deaths secondary to PEC. The goal of treatment is to prevent end-organ damage while still maintaining adequate uteroplacental perfusion.

Optimal blood pressure goals in the management of severe PEC are controversial. There is a general consensus that blood pressure of more than 180 mm Hg (systolic) or 110 mm Hg (diastolic) should be treated urgently in all cases and that patients who present with evidence of end-organ damage benefit from treatment of blood pressure more than 160 mm Hg (systolic) or 100 mm Hg (diastolic). In patients with no evidence of end-organ damage, no data suggest a clear benefit from treating blood pressure less than 180 mm Hg systolic or 110 mm Hg diastolic. Because PEC is a disorder characterized by diffuse vasospasm, many experts believe that allowing blood pressure to run in the moderate to severe range is the safest approach for avoiding worsening of ischemia and maintaining an adequate uteroplacental flow.

If urgent lowering of blood pressure is required, intravenous labetalol or intravenous hydralazine may be used. Some evidence suggests that labetalol may be the better choice,[23] but studies comparing one antihypertensive to another are limited.[24] Short-acting nifedipine is also a reasonable alternative and begins to work within 30 minutes when given orally. Previous reports of nifedipine drug interactions with magnesium seem to be ill founded, and calcium channel blockers and magnesium may be used concurrently.[25] Nitroglycerin has been used for many indications in pregnancy, such as acute blood pressure control, acute coronary syndrome, and uterine relaxation. It seems to be safe in pregnancy, but data are limited. Nitroprusside has been associated with a risk of cyanide accumulation in the fetus.

Oliguric Renal Failure

Renal failure in the setting of PEC is usually rapidly reversible. For patients with oliguria and rising creatinine, treatment with small fluid boluses (250 mL) may improve urine output. Fluids should be given with caution because pregnant women with PEC are at risk for pulmonary edema, which is more likely to be associated with poor obstetric outcomes than mild renal failure. Less commonly, acute tubular necrosis or cortical necrosis may occur, especially if significant hypotension has occurred, which may be the case with placental abruption or disseminated intravascular coagulation–related hemorrhage. Prolonged oliguria is unusual in cases of PEC. If renal function deteriorates rapidly, other diagnoses, such as hemolytic uremic syndrome and thrombotic thrombocytopenic purpura, should be considered.

HEMOLYSIS, ELEVATED LIVER ENZYMES, AND LOW PLATELETS

Hemolysis, elevated liver enzymes, and low platelets (HELLP) is a constellation of findings that includes hemolysis with a microangiopathic blood smear, elevated liver function tests, and thrombocytopenia. HELLP complicates 1 in 1000 pregnancies but is much more common in patients with severe PEC, occurring in up to 20% of patients.[26] In the same series, HELLP was diagnosed antenatally in up to 70% of patients,[26] and most patients were diagnosed before 37 weeks' gestation. It is not clear whether HELLP is a manifestation of PEC or an independent entity altogether. Although maternal mortality is in the range of 1% in patients with HELLP, perinatal mortality associated with

this syndrome ranges between 7% and 20%.[27] It is important to differentiate HELLP from thrombotic thrombocytopenic purpura/hemolytic uremic syndrome because the distinction has an impact on prognostic and therapeutic factors. Complications should be sought if liver enzymes are significantly elevated, which suggests hepatic infarction or congestion (**Fig. 2**), or if severe abdominal pain is present, which may suggest a subcapsular hematoma.

Delivery is the ultimate treatment for HELLP syndrome; however, the timing and urgency of delivery depend on fetal maturity, fetal well-being, and the severity of maternal disease. The decision to deliver should be made in conjunction with maternal fetal medicine specialists. The use of corticosteroids has been controversial. A Cochrane review of randomized and quasi-randomized clinical trials concluded that there were insufficient data to determine whether corticosteroid use in HELLP had any significant effect on maternal and fetal morbidity and mortality.[28] A subsequent large study by Fonseca and colleagues[29] that randomized patients to receive therapy with either dexamethasone or placebo found no difference in recovery of platelet number, lactate dehydrogenase, or aspartate aminotransferase. There was no difference in the duration of hospitalization, need for transfusion, or maternal complications.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy is a complication unique to human pregnancy that occurs in the second half of pregnancy, usually in the third trimester. This condition affects 1 in 13,000 pregnancies but is usually associated with a high mortality. Acute fatty liver of pregnancy is characterized by the deposition of microvesicular fat in the hepatocytes; the clinical presentation may include fulminant hepatic failure with coagulopathy, coma, and renal failure. In 50% of cases, acute fatty liver of pregnancy was associated with PEC at one point in the course of the disease.[30] Diagnosis is made definitively by a liver biopsy; however, because of the invasive nature of this test, it is not always performed. Delivery should be contemplated as soon as the diagnosis of acute fatty liver of pregnancy is made. The condition tends to improve with early recognition and delivery. Transfer to a liver unit may be necessary in severe cases, and some patients may require liver transplantation. It is important to counsel patients regarding the potential for recurrence in subsequent pregnancies.

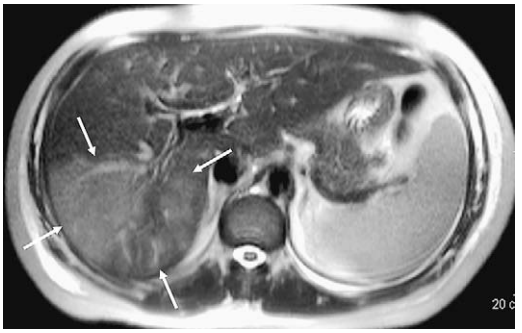

Fig. 2. 34-year-old G1P0 with pre-eclampsia and HELLP and transaminases >1000. Axial T2-weighted MRI of the liver demonstrates geographic increased signal intensity in the posterior right hepatic lobe (*arrows*) due to hepatic congestion.

TOCOLYTIC-INDUCED PULMONARY EDEMA

Preterm birth is defined as birth before 37 weeks' gestation. Preterm birth—with its many consequences—is by far the leading cause of infant mortality in the United States. Preterm labor occurred in 12.5% of births in 2005, but in general, 30% of cases of preterm labor remit spontaneously.[31] A significant number of patients require medical intervention to delay labor with the intention of either having enough time to administer glucocorticoids to help with fetal organ/lung maturity or to prolong the pregnancy in the case of a treatable risk factor for preterm labor.

The main agents used in the treatment of preterm labor include beta-adrenergics, $MgSO_4$ or calcium channel blockers. Tocolytic-induced pulmonary edema is a potential complication of these agents; however, recent data suggest that the incidence of pulmonary edema associated with beta-adrenergic agents is 0.3%.[32] Among beta-agonists, ritodrine is the only drug that is approved by the US Food and Drug Administration for the treatment of PTL; however, this drug is not manufactured in the United States any longer. Terbutaline is the most commonly used beta-adrenergic. The development of pulmonary edema with betasympathomimetics may be multifactorial. Increased plasma volume encountered in pregnancy is a predisposing factor.[33] Fluid overload related to the release of antidiuretic hormone, renin, angiotensin, and aldosterone by beta-agonists leading to increased salt and water retention likely plays a role.[34] The administration of additional fluid may worsen the fluid balance. Decreased diastolic filling time related to tachycardia is another important factor, especially in women with underlying heart disease. The administration of multiple tocolytics was found to be present in all identified cases of tocolytic-induced pulmonary edema in one large series.[35]

Pulmonary edema is occasionally related to increased vascular permeability, especially in the setting of an infectious process leading to preterm labor or superimposed PEC. Pulmonary edema also has been described with the use of nifedipine for tocolysis. The data are not convincing, however, either because the pulmonary complication may not be pulmonary edema based on the case description[36] or because the co-administration of other tocolytics, glucocorticoids, or intravenous fluids makes the association less potent.[37]

$MgSO_4$ has been associated with the development of pulmonary edema, with an incidence of 6.3% in one study.[38] Risk factors for the development of pulmonary edema include higher magnesium and intravenous infusion rates. Other causes, such as the concomitant use of other tocolytics, less concentrated infusions, and large net positive fluid balances, were also described as risk factors in that study.[38] These conditions likely represent risk factors for the development of pulmonary edema of any cause rather than being specific to magnesium-induced pulmonary edema. The use of $MgSO_4$ in PEC for seizure prevention also was not shown to be associated with a higher rate of pulmonary edema than that in the general population with pre-eclampsia.[16]

Indomethacin is another drug used for the treatment of preterm labor. This drug carries a black box warning against the increased incidence of cardiovascular events because of a risk of premature narrowing or closure of the patent ductus arteriosus with prolonged use. Atosiban is a tocolytic that is used commonly in Europe but is not available in the United States. Atosiban is a potential alternative because it has not been associated with any cardiovascular complications.

Treatment of tocolytic-induced pulmonary edema involves the withdrawal of the offending agent and treatment with supplemental oxygen as needed, fluid restriction, and diuresis. Minimizing the risk of tocolytic-induced pulmonary edema can be achieved by administering the lowest possible infusion rates and minimizing the duration of the infusion while monitoring heart rate.

AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism (AFE) is a rare but potentially catastrophic obstetric complication. The incidence of AFE varies significantly in the literature from 1 in 8000 to 1 in 80,000 live births.[39–41] Despite a low incidence, morbidity and mortality remain significant, with mortality reports ranging from 26% to 86%.[42,43] Survivors of the initial event and the cardiopulmonary collapse are likely to develop serious complications, such as disseminated intravascular coagulation and adult respiratory distress syndrome, and neurologic complications related to a hypoxic injury. In an analysis of a national registry, Clark and colleagues[40] found that neurologic sequelae in survivors of AFE occur in more than 80% of cases.

The pathogenesis of AFE is poorly understood. Risk factors such as the use of oxytocin, uterine tetany, male fetus, multiparity, and advanced maternal age have been debated in the literature.[40,43] The inciting event to the development of acute cardiopulmonary collapse was thought to be the presence of fetal debris and fetal squamous cells in the pulmonary vasculature, leading to a mechanical obstruction or stimulating an immunohumoral cascade that leads to the cardiovascular collapse. Later studies showed fetal squamous cells to be present in the pulmonary vasculature of patients who died of anesthetic complications and not AFE.[44] Hemodynamic changes associated with AFE support a humoral cause rather than an obstructive one in the pathogenesis of AFE.[45]

Hypoxia, one of the hallmarks of the disease, occurs early in the presentation. It is thought to be related to either an acute ventilation perfusion mismatch that results from the embolic event or the development of cardiogenic pulmonary edema secondary to left ventricular dysfunction. Hypoxia persists in the course of the disease and is thought to be secondary to a profound alveolar capillary membrane damage and noncardiogenic pulmonary edema. Hypotension is another manifestation of AFE. Human data are scarce on hemodynamic changes in the early phases. Case reports describe elevated right-sided pressures with right ventricular failure.[46,47] Animal studies show an increase in pulmonary artery pressure shortly after an AFE bolus.[48] After the initial transient vasospasm and rise in pulmonary artery pressures, blood pressure drops precipitously. With echocardiography and pulmonary artery catheters, left ventricular dysfunction has been shown to be present in the early and late phases of this syndrome.[49–52] Later in the course of the disease, a distributive ‘‘septic shock-like’’ physiology occurs with the development of noncardiogenic pulmonary edema.[53]

Disseminated intravascular coagulation may occur in 80% of patients and may be the first manifestation of AFE. Hemorrhage as a consequence of disseminated intravascular coagulation also may occur but rarely causes hypovolemic or hemorrhagic shock. This is likely related to the physiology of pregnancy, in which plasma volume is increased by nearly 50%, and the autotransfusion and redistribution of extravascular fluid that occurs during labor and delivery and the postpartum period.

The diagnosis of AFE is based on a high degree of suspicion and recognition of the constellation of signs and symptoms under the right circumstances. The presence of fetal squamous cells in the pulmonary vasculature is not a specific finding.[44] Although serologic assays and immunohistochemical staining using the monoclonal antibody TKH-2 to detect a common fetal antigen seem to have a high sensitivity for AFE,[54,55] these methods are not fully validated and cannot be recommended in routine practice. Treatment of AFE after the initial resuscitative effort is supportive. Goals of therapy should be early oxygenation, hemodynamic support, improving oliguria, and close monitoring for the development of coagulopathy.

OVARIAN HYPERSTIMULATION SYNDROME

Ovarian hyperstimulation syndrome (OHSS) is a rare but potentially life-threatening condition that tends to occur most commonly in association with assisted reproductive technologies but rarely occurs in association with spontaneous pregnancies. OHSS presents at approximately 3 to 8 weeks' gestation with ascites, dyspnea, severely enlarged polycystic ovaries, electrolyte imbalance, hemoconcentration, and hypercoagulability. OHSS occurs in 0.2% to 1% of all cycles that occur in assisted reproduction according to the World Health Organization estimates, but higher estimates have been reported in the literature.[56]

Luteinized granulosa cells express the mRNA of vascular endothelial growth factor among other factors.[57,58] Current findings suggest that vascular endothelial growth factor plays the most prominent role in increased vascular permeability and the development of hemoconcentration, fluid shifts, and electrolyte imbalance.[59] Vascular endothelial growth factor levels seem to correlate with disease severity.[60,61] Other factors, such as insulin-like growth factor and angiotensin-II, have been implicated in the pathophysiology.[56] Venous thromboembolism in patients with OHSS is thought to be caused by factors such as high serum estrogen levels and hemoconcentration. Some coagulation factors also may be affected in OHSS,[58,62] possibly predisposing patients to the development of thromboembolism. There have been multiple case reports of subclavian and internal jugular venous thrombosis in patients with OHSS.

The practice committee of the American Society of Reproductive Medicine[61] recognizes the difficulty in categorizing patients with OHSS according to severity because symptoms and signs represent a continuum that defies attempts at classifications of severity. Symptoms can vary from mild nausea, vomiting, and diarrhea to hemodynamic instability, acute renal failure, and acute respiratory distress syndrome. Ovarian torsion leading to an acute abdomen should not be missed because that risk increases with enlarged ovaries.

Patients with OHSS should be monitored frequently for worsening severity with daily weights and periodic laboratory measurements of electrolytes, analysis of renal and hepatic function, complete blood counts, and physical examinations. This follow-up is especially important if they are pregnant because the rising levels of human chorionic gonadotropic hormone may contribute further to the hyperstimulation. Intravenous fluids are needed to expand the intravascular volume, keeping in mind the increase in vascular permeability. Repeated paracenteses and thoracenteses are frequently needed in more severe cases. Thromboprophylaxis with anticoagulants such as unfractionated heparin or low molecular weight heparin and compression stockings or pneumatic compression should be strongly considered. Mechanical ventilation, invasive hemodynamic monitoring, and short-term hemodialysis are occasionally required. Treatment with dopamine of patients who have severe oliguric OHSS has been shown to dilate renal vessels and increase renal blood flow without significantly affecting blood pressure or heart rate.[63]

Some authors have recommended early termination of pregnancy in patients with critical complications of OHSS.[64] This decision should be made on an individual basis and with a multidisciplinary team, and it should be encouraged only if the termination is thought to positively impact the patient's condition.

PULMONARY EMBOLISM

Although not an obstetric disorder, pulmonary embolism (PE) remains the leading cause of nonobstetric maternal mortality in many countries around the world. Although mortality in the obstetric population from venous thromboembolism (VTE) is decreasing in some parts of the world,[65,66] PE continues to be a major cause of mortality in many other parts.[67,68] Therefore, a brief discussion of the salient features of this disorder in this population will be included.

Epidemiology

Pregnancy is an independent risk factor for venous thromboembolism (VTE), and retrospective cohort studies suggest that the incidence of VTE is 5 to 12 per 10,000 pregnancies in the antenatal period and 3 to 7 per 10,000 deliveries in the postpartum period[69–71] compared with an age and

sex-adjusted incidence of 1.6 per 10,000 women and 0.2 per 10,000 women, respectively, in comparable time frames.[69] Hypercoagulability in pregnancy is a result of increased levels of procoagulant factors (increased factor V and VIII levels) and decreased fibrinolytic and anticoagulant activity (decreased protein S levels and increased activated protein C resistance).[72] Venous stasis is not only related to vascular compression by the gravid uterus but is also a consequence of progesterone, which starts rising early in the first trimester.[73] The risk of VTE in pregnancy is further increased in patients with additional risk factors, including prolonged bed rest,[74] advanced maternal age,[75] family history of thrombosis,[76] multiparity, previous thrombosis, thrombophilia, previous superficial phlebitis, pre-eclampsia, tobacco use, or operative delivery.[77]

Clinical Predictors

For the past two decades, clinical assessment has been used to stratify patients into risk categories using either clinical decision tools[78–81] or experienced clinician's assessment.[82] Because pregnancy is an independent risk factor for thrombosis, however, it is difficult to know how models of clinical prediction of PE would apply to a pregnant population. Clinical prediction is also complicated by the fact that physiologic dyspnea and an increase in heart rate occur commonly in pregnancy. It is likely that the distribution of physical findings, such as the presence of left leg swelling, may be more predictive of VTE in pregnant women than right leg swelling (because left-sided DVTs are much more common in pregnancy). Historical risk factors that include personal history of VTE or thrombophilia may be important determinants of pretest probability in the obstetric population. The performance of clinical assessment is more complicated in this subpopulation.

Diagnostic Tests

Some of the physiologic changes of pregnancy contribute to the diagnostic challenges in PE. For instance, alveolo-arterial gradient was found to be normal in more than 50% of pregnant patients diagnosed with a PE.[83] The need to make an accurate diagnosis and adequately treat PE certainly outweighs the risk of fetal radiation exposure that diagnostic testing for VTE entails. All of the imaging tests that involve ionizing radiation expose the fetus to a radiation dose that falls within the limits of what is considered "acceptable" in pregnancy. Protocol modifications may be used in a way that would limit radiation exposure without affecting diagnostic accuracy. Ventilation/perfusion scans have the advantage of having some outcome data in the pregnant population but are limited by small numbers of patients and are retrospective.[84,85] The predictive value of ventilation perfusion scans depends heavily on the clinical presentation, and the positive predictive value ranges between 56% and 98% in nonpregnant patients with low versus high clinical suspicion.[82] Given the poor predictive value of the clinical presentation in pregnancy, the interpretation of ventilation perfusion scans is limited to some extent. Accuracy data of ventilation/perfusion scans are lacking in pregnancy. One of the major advantages of this test in pregnancy compared with the general population is the fact that the rate of intermediate/nondiagnostic scans is much lower in pregnancy—in the range of 3% to 25%.[84,86]

On the other hand, CT pulmonary angiograms (CTPAs) carry the advantage of exposing the fetus to a lower amount of radiation than ventilation/perfusion scans,[87] and they offer a different diagnosis (**Fig. 3**). The disadvantages of CTPAs are the amount of maternal breast radiation exposure, which is in the range of 2 to 5 rad.[88] Breast radiation may be minimized by the use of breast shields without significantly affecting image resolution.[88,89] Another disadvantage of CTPAs in pregnancy is the fact that plasma volume, cardiac output, and heart rate are increased, which dilute the contrast dye and result in a higher proportion of technically limited studies.[90] Accuracy and outcome data are lacking in pregnancy, but outcome trials are ongoing. One retrospective study that reviewed 78 patients with negative, technically adequate CTPAs found that 2 of 78 of those patients had concomitant positive ultrasound studies.[91] Iodinated contrast crosses the placenta, so there is a theoretic risk of fetal thyroid dysfunction.

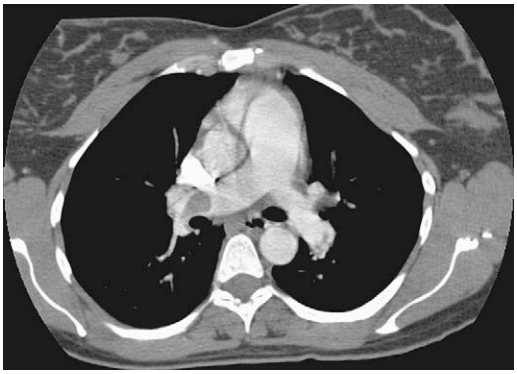

Fig. 3. 39-year-old G4P3 with mild chest discomfort and no hemodynamic instability. CTPA shows a large right pulmonary artery embolus.

Guidelines from the Contrast Media Safety Committee of the European Society of Urogenital Radiology released in 2005[92] stated that there is a paucity of information in the literature and encouraged the collection and publication of results of neonatal thyroid function results. After this statement, a small study by Atwell and colleagues[93] found no neonatal thyroid function abnormalities in newborns of 21 patients exposed to iodinated contrast during pregnancy. Larger studies are needed to shed light on this issue.

Many authors suggest the use of leg ultrasounds as an initial test in the evaluation of PE despite the negative data that suggest low sensitivity even in the general population (23%–52%)[94–97] and the fact that this approach is not validated in the pregnant or nonpregnant population. The positive predictive value of leg ultrasounds in patients without signs or symptoms of DVT is thought to be low. Leg ultrasounds are helpful as an adjunctive test to chest imaging studies in the evaluations of PE in pregnancy but cannot be recommended as initial tests.

MRI seems like an attractive alternative to ventilation/perfusion scans or CTPA because it does not involve any ionizing radiation. Most commonly used techniques involve the use of gadolinium, which is known to cross the placenta and has produced limited data in human pregnancies. Techniques such as real-time MRI do not necessitate the use of contrast agents. Real-time MRI is gated to a patient's respiration and shows clots on T2-weighted images. Further studies are needed before this test can be recommended for use in this population. Other diagnostic techniques such as D-dimers have not been studied sufficiently in pregnancy, and the fact that those levels rise during gestation complicates their use. The use of D-dimers is further complicated by the fact that they should be used in conjunction with clinical models of pretest probability, which are not yet validated in pregnancy.

Pregnant women with PE are treated with unfractionated heparin or low molecular weight heparin, neither of which crosses the placenta. Warfarin is rarely used in pregnant women because of its teratogenic effects. Compared with unfractionated heparin, low molecular weight heparin has the advantage of a lower rate of heparin-induced thrombocytopenia, less painful injection site, and a lower rate of osteopenia.[98] Heparin requirements are usually increased in pregnancy and bioavailability is reduced, likely in relation to pregnancy-related pharmacokinetics. Patients on low molecular weight heparin are best monitored with periodic anti-Xa levels given the weight changes in pregnancy and the possible changes in medication redistribution. Pregnant patients on therapeutic anticoagulation should have a detailed labor and delivery plan to minimize the risk of bleeding during vaginal or cesarean deliveries; however, this discussion is outside the scope of this article.

Thrombolysis has been described in more than 170 cases in pregnant patients worldwide. When these cases are combined, the maternal mortality rate is 1.2%, the bleeding rate is 8.1%, and the incidence of fetal loss is 5.8%.[99] Streptokinase at therapeutic doses was not associated with a fibrinolytic effect in cord blood, and neither streptokinase nor urokinase seems to be teratogenic. Hemorrhagic complications mostly occur intrapartum or postpartum when fibrinolytic therapy has been given near delivery. Tissue plasminogen activator is more frequently used, is not teratogenic, and is likely the safest fibrinolytic drug in pregnancy. Indications for the use of thrombolysis are not different in the pregnant population, and thrombolytic drugs should be strongly considered in the presence of a life-threatening PE remote from delivery.

PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy is a dilated cardiomyopathy of uncertain cause. The true incidence is unknown, with reported rates ranging from 1 in 1500 to 1 in 15,000. This wide variation may reflect differences in geographic regions, referral bias, and individual practice patterns. Diagnostic criteria for peripartum cardiomyopathy have been established by the National Heart, Lung and Blood Institute:

- Development of cardiac failure in the last month of pregnancy or within 5 months after delivery
- The absence of a determinable cause of cardiac failure
- The absence of demonstrable heart disease before the last month of pregnancy
- Left ventricular dysfunction as demonstrated by echocardiography[100]

Risk factors for peripartum cardiomyopathy include advanced maternal age, multiple gestation, pre-eclampsia, gestational hypertension, and African descent. Several possible causes have been proposed, including myocarditis, abnormal immune response to pregnancy, maladaptive response to the hemodynamic stress of pregnancy, stress-activated cytokines, and prolonged tocolysis. There have also been some reports of familial peripartum cardiomyopathy.

Medical treatment of peripartum cardiomyopathy is similar to the treatment of other forms of congestive heart failure. Although no studies have compared therapeutic approaches, standard therapy with sodium restriction, diuretics, and vasodilators should be initiated. Loop diuretics seem to be safe in pregnancy and may be used in breastfeeding mothers. Angiotensin-converting enzyme inhibitors are contraindicated in pregnancy because of teratogenicity, but some are compatible with breastfeeding and should be initiated immediately after delivery. Hydralazine and nitrates are safer alternatives in pregnancy. Beta blockers may be useful primarily in the postpartum period for women who continue to have symptoms and left ventricular dysfunction despite more than 2 weeks of standard heart failure therapy. Anticoagulation should be considered in patients with peripartum cardiomyopathy because of a high rate of thromboembolic disease, especially in women with an ejection fraction less than 35%, atrial fibrillation, or mural thrombus.[101] The higher likelihood of thromboembolic disease is likely secondary to the hypercoagulable state of pregnancy and stasis of blood in the left ventricle. In the United States, mortality estimates from peripartum cardiomyopathy range from 25% to 50%. Approximately 50% of women recover to baseline ventricular function within 6 months of delivery. The other 50% of women have varying degrees of persistent dysfunction ranging from mild, compensated heart failure to deterioration and death, with most deaths occurring in the first 3 months postpartum.

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