Focused Review

CME Sepsis and Acute Renal Failure in Pregnancy

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The unique physiology of pregnancy poses several problems for clinicians charged with caring for critically ill pregnant patients. This focused review summarizes two problems encountered in critically ill pregnant patients: pregnancy-related sepsis and acute renal failure. Common causes, and the effects of pregnancy on diagnosis and treatment are discussed.

(Anesth Analg 2009;108:572–5)

The critically ill pregnant patient poses unique challenges for clinicians involved in critical care. Pregnancy increases the risk of specific critical diseases (e.g., pulmonary embolism), which may complicate diagnosis and the patient's ability to fight the disease, yet rarely alters therapy. Hemorrhage, embolic events, hypertensive disorders, and respiratory distress remain the most common reasons for admission to the intensive care unit (ICU) among pregnant women.[1–6] In 2007, the Confidential Enquiry into Maternal and Child Health in the United Kingdom published 10 key recommendations aimed at improving child health and reducing maternal mortality.[5] These recommendations highlighted the importance of early recognition and management of severely ill pregnant women, routine use of early warning scoring systems to be used for obstetric patients and development and implementation of guidelines for the management of sepsis in pregnancy.[5] The goal of this focused review is to summarize the latest recommendations for two potentially catastrophic conditions: pregnancy-related sepsis and acute renal failure.

Fetal Assessment

Fetal assessment is important in the care of critically ill pregnant patients. A general principle for pregnant patients in the ICU from the second trimester onwards is attention to uterine displacement owing to the enlarged uterus and aorto-caval compression in the supine position. This assessment can easily be accomplished by placing a rolled blanket or hip roll under the right thorax and flank, facilitating lateral tilting to the left. Fetal assessment and contingency planning for a possible emergency cesarean delivery should be established for fetuses that have reached a point of maturity that would make survival after an emergency delivery possible. Many institutions have surgical equipment in close proximity in preparation for emergency cesarean delivery; some institutions are equipped to perform bedside operative deliveries in the ICU.

Decisions regarding antepartum testing during critical illness should be made in consultation with a maternal-fetal medicine specialist. In most centers in the United States, the fetus is considered viable after 24 wk gestation. For gestations <24 wk, assessment is usually limited to Doppler auscultation to document fetal heart tones with the understanding that documentation of a fetal heart rate (FHR) does not ensure viability. At 26 wk, current recommendations suggest bi-weekly testing with one of the following: fetal movement assessment, contraction stress test, nonstress test, biophysical profile or umbilical artery Doppler velocimetry.[7–9]

Continuous FHR monitoring involves assessing the FHR in relationship to changes in uterine activity. Since FHR variability does not usually occur until after 28 wk gestation, monitoring is not mandatory for all critically ill pregnant patients and should only be used if clinical decisions are to be made based on this information.[7,9] The false positive rate for predicting adverse fetal outcomes with electronic FHR monitoring is high; nevertheless, during the labor of patients with high-risk conditions, FHR should be monitored continuously.[9] The biophysical profile combines information from FHR monitoring and ultrasonography to determine the quality of breathing movements, heart rate variability, amniotic fluid volume, fetal tone, and gross body movements. This technique usually does not provide useful information until after 32 wk gestation.[7]

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Accepted for publication September 5, 2008.

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DOI: 10.1213/ane.0b013e3181937b7e

Studies are conflicting about the value of information obtained from fetal monitoring to make treatment decisions. A multidisciplinary approach is best taken with input from obstetricians, neonatologists, maternal-fetal medicine experts, and specialized nursing staff. In particular, each institution should establish protocols with regard to who will be responsible for fetal assessment in an ICU setting. Options include continuous monitoring by a trained obstetric nurse in the ICU, remote telemetry to a site where fetal monitoring can be observed (such as a labor and delivery unit), or intermittent FHR assessment at regular intervals. Moreover, if a hospital does not have the capacity to provide obstetric care or emergency delivery, consideration should be given to transportation of the critically ill pregnant patient to an appropriate tertiary care facility.

Sepsis

Sepsis, although rare, is a leading cause of maternal and perinatal mortality worldwide.[6,10] Sepsis is a complex, multifaceted clinical problem, and in pregnant patients, no single definition is sufficient.[11] In 2001, a consensus conference concluded that sepsis in nonpregnant patients is a clinical syndrome manifested by infection and a systemic inflammatory response,[12] defined by the presence of at least two of the following: temperature higher than 38°C or <36°C, heart rate more than 90 bpm, tachypnea more than 20/min or a $Paco_2$ <32 mm Hg, and a white blood cell count more than 12,000/mm^3 or <4000/mm^3 or <10% band forms.[12] Applying these criteria to pregnant patients is problematic due to the physiological changes associated with pregnancy. White blood cell counts increase throughout pregnancy and maternal temperature may increase during neuraxial labor analgesia.[13–16] Diagnosis of sepsis during labor can be particularly challenging, since heart rate and respiratory rates increase significantly with exertion and the stress of labor.[10]

Most obstetric patients who develop bacteremia do not develop sepsis. Conversely, bacteremia is not necessary to develop sepsis because local infection can initiate an inflammatory response.[10,17] The microbiology of sepsis is distinct in pregnancy; endotoxin-producing Gram-negative rods such as *E. coli* are common etiologic agents, whereas Gram-positive bacteria are common culprits in nonpregnant patients with sepsis.[10,17] In many cases, polymicrobial causes are identified. *E. coli*, enterococci, *Klebsiella* species, *Staphylococcus aureus* and β-hemolytic streptococci are the most frequently recovered organisms in bacteremic pregnant patients with sepsis.[18,19]

Pyelonephritis, caused in part by the reduction in renal concentrating ability, bladder flaccidity, and ureteral dilation during pregnancy, is a frequent precipitating illness, and urosepsis in pregnancy can be fatal.[20] The most common risk factor for maternal sepsis is cesarean delivery.[10] The decreased pH and increased glycogen in the vaginal epithelium during pregnancy contribute to an increased incidence of chorioamnionitis and septic abortion. Pneumonia can lead to sepsis and the risk of respiratory failure may be increased due to elevation of the diaphragm by the uterus and compromised pulmonary mechanics. The leading causes of sepsis in pregnant patients are listed in Table 1.

Table 1. Leading Causes of Sepsis in Pregnant Patients

Pyelonephritis[a]
Renal calculi
Chorioamnionitis
Endomyometritis
Septic abortion
Necrotizing fasciitis
Episiotomy infections
Postpartum endometritis
Septic pelvic thrombophlebitis

Data from (10–11).

[a] Most common cause of septic shock.

The benefits of goal-directed therapy and the tenets of the Surviving Sepsis Campaign have been reviewed extensively elsewhere and, unfortunately, no evidence-based recommendations are specific for the septic pregnant patient.[10,20,21] Goal-directed therapy for severe sepsis, including the use of steroids and activated protein C, has not been studied extensively in pregnant patients. In nonpregnant patients, maintenance of central venous pressure in the range of 8–12 mm Hg, urine output more than 0.5 mL · kg^{-1} · h^{-1}, $ScvO_2$ more than 70%, and SaO_2 more than 93% have been shown to decrease in-hospital mortality from 46.5% in groups assigned to early goal-directed therapy compared to 30.5% in groups treated with standard therapy.[10,22] Application of goal-directed therapy in pregnant patients is challenging because normal physiologic changes in pregnancy can be confounding. For instance, during normal pregnancy the central venous pressure may be increased up to 10 mm Hg in the third trimester, the mean arterial blood pressure is decreased, the heart rate is usually increased, and the $ScvO_2$ may be as high as 80%.[10]

Early antibiotic administration and aggressive source control are mandatory for both nonpregnant and pregnant patients.[21] Many institutions administer meropenem and vancomycin for broad empiric coverage until antibiotics can be tailored according to information gained from culture and sensitivity results. In pregnant patients, the pelvis is a common site of infection and these infections are usually amenable to surgical or medical interventions. Hence, early consultation with infectious disease specialists is recommended and surgeons and interventional radiologists should be actively engaged for aggressive source control.[10] Imaging modalities, including ultrasound, magnetic resonance imaging and even ionizing radiation, are not contraindicated in pregnancy if needed for diagnostic purposes.

Table 2. Risk of Renal Failure, Injury to Kidney, Failure of Kidney Function, Loss of Kidney Function, and End-Stage Renal Failure (RIFLE) Criteria

	GFR criteria	Urine output criteria	Sensitivity/specificity
Risk	↑ Cr 1.5× baseline Or GFR ↓ >25%	UO <5 mL · kg^{-1} · h^{-1} × 6 h	High sensitivity
Injury	↑ Cr 2× baseline Or GFR ↓ >50%	UO <0.5 mL · kg^{-1} · h^{-1} × 12 h	High sensitivity
Failure	↑ Cr 3× baseline with GFR ↓ by 75% Or Cr >4.0 mg/dL	UO <0.3 mL · kg^{-1} · h^{-1} × 24 h Or Anuria × 12 h	High sensitivity
Loss	Persistent acute renal failure (loss of kidney function for at least 4 wk)	Persistent acute renal failure (loss of kidney function for at least 4 wk)	High specificity
ESKD	End stage kidney disease (complete loss of renal function for at least 3 mo)	End stage kidney disease (complete loss of renal function for at least 3 mo)	High specificity

Cr = serum creatinine; UO = urine output; GFR = glomerular filtration rate; ESKD = end stage kidney disease. (From Abosaif et al.,[29]).

Intensive insulin therapy, which has been shown to decrease mortality, ventilator days and time in the ICU for nonpregnant patients, has not been evaluated in critically ill pregnant patients.[19] Pregnant patients are resistant to insulin and are also predisposed to developing fasting hypoglycemia; the impact of intensive insulin control in this population remains to be determined.

Although not contraindicated in pregnancy, the administration of steroids is controversial. In the largest randomized study investigating the potential benefit of hydrocortisone in nonpregnant patients with septic shock, no survival advantage was found; however, some authors recommend empiric therapy for pregnant patients.[10,23] If preterm delivery of a viable fetus is likely, antenatal corticosteroid administration with betamethasone or dexamethasone has been shown to confer a survival benefit for the fetus.[24]

The use of other adjunctive agents such as recombinant human activated protein C is controversial in pregnant patients. Activated protein C is an endogenous protein that promotes fibrinolysis and regulates coagulation and inflammation associated with severe sepsis.[25] Even though this agent has been shown to improve mortality in nonpregnant patients at high risk for death with sepsis, recombinant human activated protein C increases the risk of bleeding and is relatively contraindicated due to the risk of hemorrhage during labor or cesarean delivery.[10]

Acute Renal Failure

Pregnancy has a minimal effect on renal function and is usually not associated with postpartum deterioration or development of end-stage renal disease. Acute renal failure during pregnancy is rare in the developed world with an incidence of approximately 1:15,000, but access-to-care problems, even in the United States, contribute to a low renal recovery rate.[26,27] In general, there is no consensus on a definition for renal failure during pregnancy, and definitions range from a creatinine level above 0.8 mg/dL to the requirement for dialysis.[26] Mild renal insufficiency has generally been defined as a serum creatinine level of 0.9 to 1.4 mg/dL moderate renal insufficiency as a creatinine of 1.5–2.9 mg/dL, and severe renal insufficiency as a creatinine level more than 3.0 mg/dL.[28] The Acute Dialysis Quality Initiative developed the RIFLE diagnostic scheme for renal failure; this scheme was designed for nonpregnant patients and has been shown to have prognostic utility in this population (Table 2).[29]

Dilation of the renal collecting system, combined with hormonally induced ureteral smooth muscle relaxation, is a normal change in pregnancy. Renal vascular resistance decreases, while the glomerular filtration rate increases. Proteinuria <300 mg in 24 h is normal in pregnancy, as is mild glycosuria. The respiratory alkalosis (Pco_2 28–30 mm Hg) and decreased serum bicarbonate (18–20 mEq/L) that accompanies normal pregnancy physiologically explains the inability of a pregnant patient's kidneys to swiftly compensate for a renal insult.

The pathophysiology of renal failure in pregnancy can be categorized according to anatomical pathology, hemodynamic changes, abnormal substrate handling or acid-base abnormalities. The most common cause of renal failure in pregnancy is preeclampsia, but only 1.5%–2% of preeclamptic patients develop failure.[26] While the glomerular filtration rate decreases in preeclampsia, acute renal failure usually occurs only when another obstetrical complication such as hemorrhage or abruption is present. Approximately 4%–14% of preeclamptic patients develop the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets); these patients have an increased risk of developing renal failure.[26] Other pregnancy-specific causes include acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, amniotic fluid embolism, infection, sepsis, intravascular volume depletion, obstruction or idiopathic etiologies.

The initial management of renal failure in pregnancy commences with treatment of underlying causes. Nephrotoxins, specifically aminoglycosides or radiocontrast agents, should be avoided. Drug dosing, with particular attention to magnesium therapy, should be adjusted using serum levels for guidance. Following these measures, judicious fluid management is the foundation for successful treatment.[26]

Renal perfusion should be restored and maintained so as to prevent further ischemic changes and invasive monitoring may be required to meet these goals.[27] Low-dose dopamine has not been found to be effective and is not recommended.[30] Although diuretics have not been shown to reduce mortality, they are useful in conditions associated with detrimental intravascular volume overload such as hypoxemia and heart failure.[31] Furosemide and mannitol are class B drugs in pregnancy whereas thiazides are class C. Prompt initiation of dialysis seems to be safe and beneficial when indicated; however, some studies in nonpregnant patients have indicated that morbidity may be increased in patients receiving dialysis more frequently.[13,16,32,13] Indications for dialysis include intravascular volume overload, hyperkalemia refractory to medical management, metabolic acidosis or symptomatic uremia.[26]

CONCLUSION

Since pregnant patients with sepsis and acute renal failure are typically younger and have fewer comorbidities, the morbidity and mortality rate is usually far less than the nonpregnant population. As more women continue to bear children at an advanced maternal age, it is conceivable that these conditions might become more prevalent. Knowledge of the pathophysiology and treatment of these disorders, as well as knowledge of how the physiologic changes in pregnancy affect these disorders, is a prerequisite for successful management and survival.

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