Maternal Sepsis and Septic Shock

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KEYWORDS

• Pregnancy • Sepsis • Severe sepsis • Septic shock

KEY POINTS

- Sepsis and septic shock are leading causes of intensive care unit admission as well as maternal and fetal morbidity and mortality.
- Early identification and management can be facilitated by various scoring systems.
- Physiologic changes of pregnancy and fetal oxygenation must be considered during resuscitation and management.
- The sites of infection as well as the organisms responsible for sepsis evolve throughout pregnancy, delivery, and postnatal intervals.
- Although not specifically developed for the pregnant patient, the Surviving Sepsis guidelines provide a useful paradigm for management.

INCIDENCE AND MORTALITY

Sepsis is the leading cause of death in the intensive care unit (ICU) and a common cause of morbidity and mortality worldwide.[1,2] Sepsis is also recognized as one of the major factors accounting for admission of pregnant patients to the ICU and for maternal death. Multiple studies over the years have documented an increase in the awareness of the precipitating factors and risks for sepsis in this special population.[3–10] The causative organisms, timing, prophylactic methods, and preventive strategies have been reviewed. Factors associated with the progression from severe sepsis to septic shock have also been identified. For pregnant women, there is a rapid progression from initial recognition of sepsis via defining parameters to development of severe sepsis and shock. In

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this regard, the normal underlying physiologic changes during pregnancy can critically alter hemodynamic stability when overlapped with sepsis. In concert with the most recent Surviving Sepsis campaign,[11] emphasis remains on timely recognition of sepsis and early administration of fluids and antibiotics. Sepsis accounted for 10.7% of maternal deaths from 2003 to 2012 according to the World Health Organization systematic analysis on the global causes of maternal death.[12] Trends of maternal mortality worldwide have been falling, but in the most recent report from the Centre for Maternal and Child Enquiries Mission statement in the United Kingdom, sepsis secondary to genital infections has become the leading cause of death, particularly from group A streptococcus (GAS).[9] There was an increase in maternal deaths related to sepsis from 0.85 of 100,000 pregnant women in 2003 to 2005 to 1.13 of 100,000 in 2006 to 2008.[9] Similarly, in a review of 2 tertiary referral maternity hospitals in Dublin, Ireland from 2005 to 2012 that included more than 150,000 pregnant women, the sepsis rate was 1.81 per 1000 pregnant women, of which 17% of the episodes occurred antenatally, 36% occurred intrapartum, and 47% occurred postpartum.[10] In a retrospective review on 74 patients admitted to the ICU, the rates of systemic inflammatory response syndrome (SIRS), severe sepsis, and septic shock are 59%, 24%, and 3%, respectively.[13] In a prospective study of 298 obstetric patients admitted to a tertiary referral ICU in Brazil, 14.2% of the admissions were caused by sepsis.[14] This increase may be attributed to women becoming pregnant after age 35 and presenting with higher rates of comorbidities.[15] Sepsis led to a high perinatal mortality as well as preterm delivery.[10] In the United States, similar trends have been observed. The incidence of pregnancy-associated severe sepsis (PASS) has increased by 236% over the last decade according to a study on 4,060,201 pregnancy-associated hospitalizations and 1077 PASS hospitalizations from 2001 to 2010.[16] The Centers for Disease Control and Prevention's Pregnancy Mortality Surveillance System recorded an increase in the number of reported pregnancy-related deaths in the United States. The pregnancy-related mortality ratio was 17.8 deaths per 100,000 live births according to the data from 2011, and 14% of the deaths were attributed to infection or sepsis, which was among the top 3 leading causes of pregnancy-related deaths (**Fig. 1**). As stated earlier, sepsis is also a major cause for admission of pregnant women to the ICU, together with hemorrhage, abortion, and complications of hypertension.[17]

DEFINITION

The definitions of SIRS, sepsis, severe sepsis, and septic shock for the nonpregnant patient are delineated in **Table 1**. However, there is currently no standard definition for severe sepsis for pregnant and peripartum women. There are multiple physiologic changes that occur in an obstetric patient during the antepartum and postpartum periods, which can mask some of the objective findings required to identify SIRS. Also, the accepted SIRS definition to identify patients with sepsis may be flawed. A recent study used data from 172 ICUs in Australia and in New Zealand that reviewed 1,171,797 patients admitted from 2003 to 2011 and found that using the current SIRS definition failed to identify up to 15% of patients with similar infections, organ failure, and risk of death.[18]

Accordingly, investigators have attempted to define severe sepsis, particularly for the pregnant patient. Barton and Sibai[15] defined a different set of parameters for severe sepsis and septic shock among obstetric patients that included a heart rate greater than 110 beats/min and respiratory rate greater than 24 breaths/min.

In addition, SIRS criteria may overlap with normal hemodynamic and other parameters during pregnancy and the peripartum period.[19] Those investigators conducted a

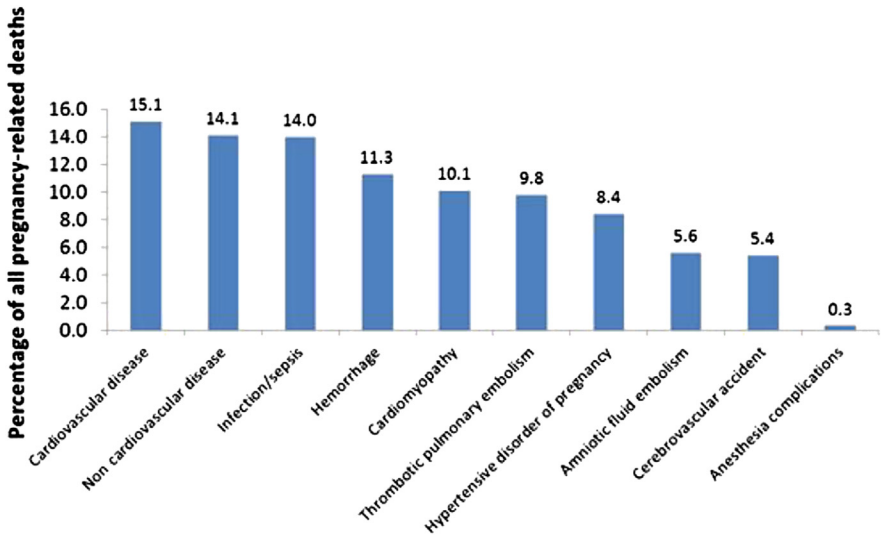

Fig. 1. Cause of pregnancy-related death in the United States: 2011. Note: The cause of death is unknown for 5.9% of all pregnancy-related deaths. (*From* CDC Pregnancy Mortality Surveillance System. Available at: http://www.cdc.gov/reproductivehealth/MaternalInfantHealth/PMSS.html.)

meta-analysis on 8834 healthy pregnant women, which revealed an overlap of 2 standard deviations above current SIRS criteria of heart rate, respiratory rate, and white blood cell count with the normal physiologic parameters during the second trimester, third trimester, and during labor, suggesting that other criteria may be needed to define maternal sepsis.[19]

PATHOPHYSIOLOGY OF SEPSIS

Sepsis is a complex, generalized, and overexpressed response by the host to an infection. On recognition of bacterial cell wall components and bacterial products such as endotoxins and exotoxins, the immune system initiates a cascade of events, including the release of pro-inflammatory mediators, release of cytokines by macrophages, recruitment of additional inflammatory cells, and activation of complement. These events lead to widespread cellular injury with ischemia, mitochondrial dysfunction, apoptosis, immunosuppression, multiple organ dysfunction, and death.[11] The response is modified by the patient's age, health status, and ability to compensate for the changes induced by the inflammatory response. Physiologic changes during pregnancy can contribute to an exaggerated septic response.

Immunologic Changes During Pregnancy

During pregnancy, there are immune response changes to protect the fetus from maternal inflammatory response. There is downregulation of cell-mediated immunity, with decreased T-cell activity secondary to a decrease in numbers or reduction in the CD4/CD8 ratio, with an intact or upregulated humoral response to balance this change. Because of this, there is a predisposition to certain infections, including *Listeria monocytogenes*, and more severe manifestations of some viral and fungal infections.[20]

Table 1
Definitions and parameters of systemic inflammatory response syndrome, severe sepsis, and septic shock

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock (Dellinger, 2012[11])			Clinical and Laboratory Findings of Severe Sepsis and Septic Shock (for Obstetric Patients) (Barton, 2012)
Infection	The invasion of normally sterile tissue by organisms		—
Bacteremia	Presence of viable bacteria in the blood		
SIRS	Two or more abnormalities in temperature, heart rate, respiration, or white blood count	General variables • Fever (>38.3°C) • Hypothermia (core temperature <36°C) • Heart rate >90/min^{-1} or more than 2 SD above the normal value for age • Tachypnea • Altered mental status • Significant edema or positive fluid balance (>20 mL/kg over 24 h) • Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes Inflammatory variables • Leukocytosis (WBC count >12,000 μL^{-1}) • Leukopenia (WBC count <4000 μL^{-1}) • Normal WBC count with >10% immature forms • Plasma C-reactive protein more than 2 SD above the normal value • Plasma procalcitonin more than 2 SD above the normal value Hemodynamic variables • Arterial hypotension (systolic blood pressure [SBP] <90 mm Hg, MAP <70 mm Hg, or an SBP decrease >40 mm Hg in adults or less than 2 SD below normal for age) Organ dysfunction variables • Arterial hypoxemia (Pao_2/Fio_2 <300) • Acute oliguria (urine output <0.5 mL/kg/h for at least 2 h despite adequate fluid resuscitation) • Creatinine increase >0.5 mg/dL or 44.2 μmol/L • Coagulation abnormalities (INR >1.5 or aPTT >60 s) • Ileus (absent bowel sounds) • Thrombocytopenia (platelet count <100,000 μL^{-1}) • Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L) Tissue perfusion variables • Hyperlactatemia (>1 mmol/L) • Decreased capillary refill or mottling	Signs and symptoms of severe sepsis and septic shock • Fever • Temperature instability (>38°C or <36°C) • Tachycardia (HR >100 bpm), tachypnea (RR >28/min) • Diaphoresis • Clammy/mottled skin • Nausea/vomiting • Hypotension/shock • Oliguria • Pain (location based on site of infection) • Altered mental status (confusion, decreased alertness) Laboratory findings in severe sepsis and septic shock • Leukocytosis or leukopenia • Hypoxemia • Thrombocytopenia • Metabolic acidosis ◦ Increased serum lactate ◦ Low pH ◦ Increased base deficit • Elevated liver enzymes • Disseminated intravascular coagulopathy • Elevated serum creatinine

Sepsis	The presence (probable or documented) of infection together with systemic manifestations of infection	—
Severe sepsis	Sepsis plus sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)	Sepsis-induced hypotension • Lactate above upper limits laboratory normal • Urine output <0.5 mL/kg/h for more than 2 h despite adequate fluid resuscitation • Acute lung injury with Pao_2/Fio_2 <250 in the absence of pneumonia as infection source • Acute lung injury with Pao_2/Fio_2 <200 in the presence of pneumonia as infection source • Creatinine >2.0 mg/dL (176.8 μmol/L) • Bilirubin >2 mg/dL (34.2 μmol/L) • Platelet count <100,000 μL • Coagulopathy (international normalized ratio >1.5)
Sepsis-induced hypotension	SBP <90 mm Hg or MAP <70 mm Hg or an SBP decrease >40 mm Hg or less than 2 SD below normal for age in the absence of other causes of hypotension	
Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation (infusion of 30 mL/kg of crystalloids)	
Multiple organ dysfunction syndrome	Progressive organ dysfunction in an acutely ill patient, such that hemostasis cannot be maintained without intervention	

Abbreviations: aPTT, activated partial thromboplastin time; HR, hazard ratio; INR, international normalized ratio; RR, relative risk; WBC, white blood cell count.

Adapted from Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39(2):165–228; and Barton JR, Sibai BM. Severe sepsis and septic shock in pregnancy. Obstet Gynecol 2012;120(3):689–706; with permission.

IDENTIFICATION/SCORING SYSTEMS

There are several scoring systems that have been used to identify patients at risk for sepsis and septic shock, including the Modified Early Warning Score (MEWS) and REMS score (Rapid Emergency Medicine Score). The MEWS has been used for emergency admissions to identity patients at risk for ICU admission and death. Lappen and colleagues[21] evaluated 913 chorioamnionitis patients using both SIRS and MEWS scores and found that neither can adequately identify patients at risk for sepsis, ICU transfer, or death. One of the reasons for failure of this scoring system to identify risk of morbidity in the obstetric population may be related to failure to take into account the normal physiologic changes seen in pregnancy, as described above (**Table 2**).

The Modified Early Obstetric Warning Score (MEOWS) is a tool designed specifically for the obstetric population, with a high sensitivity in predicting morbidity (89%) and reasonable specificity (79%) supporting its use for obstetric patients in predicting morbidity.[22] A validation study of the Confidential Enquiry into Maternal and Child Health Report (CEMACH) recommended modified early obstetric warning system (MEOWS). It is currently being used in the United Kingdom as recommended by the most recent CEMACH report,[9] but has not been widely used in North America.

The Sepsis in Obstetrics Score (S.O.S.) is another model that has been developed by Albright and colleagues to identify patients at high risk for admission to the ICU, specifically in an obstetric population group. A retrospective cohort study evaluated 850 women and compared S.O.S. with validated emergency department sepsis scoring systems, MEWS (cutoff of 5) and REMS (cutoff of 6), results of which are included in **Table 2**.

Risk Factors

Antepartum risk factors predisposing to perinatal sepsis include nonwhite ethnicity, obesity, lack of prenatal care, malnourishment, impaired glucose tolerance and diabetes mellitus, anemia, and impaired immunity. Patients with sickle cell disease or trait struggle to eliminate encapsulated bacteria due to poor splenic function. Immunosuppression due to HIV/AIDS compounded by opportunistic infections, such as tuberculosis, greatly increases the risk of severe postpartum infections.[4] History of group B streptococcal colonization or infection[7]; invasive procedures performed during pregnancy, such as sampling of chorionic villous, cervical cerclage, or amniocentesis[7,23,24]; black or minority ethnic origin, primiparous, pre-existing medical problems, febrile illness, and use of antibiotics in the 2 weeks before presentation also increased the odds of severe sepsis.[25]

Intrapartum risk factors include protracted active labor, especially in the nullipara, and prolonged rupture of membranes. More than 5 vaginal examinations increase

Table 2
Efficiency of scoring systems to predict sepsis

Scoring System	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
S.O.S.	88.9	99.2	16.7	99.9
REMS	77.8	93.3	11.1	99.7
MEWS	100	77.6	4.6	100

Data from Albright CM, Ali TN, Lopes V, et al. The Sepsis in Obstetrics Score: a model to identify risk of morbidity from sepsis in pregnancy. Am J Obstet Gynecol 2014;211:39.e1–8.

risk, together with perineal manipulation during the second stage of labor, as well as instrumentation at delivery.[13,23] Antibiotic prophylaxis for cesarean section is another risk. Finally, unscheduled cesarean section is the single most important risk factor for sepsis. Women who underwent cesarean section have a 5- to 20-fold greater risk for severe infections such as endometritis or wound infection compared with those who have a vaginal birth.[26]

Postpartum risk factors include retained placental fragments, cracked nipples, and operative delivery.[23] Operative vaginal delivery, prelabor cesarean section, and cesarean section after onset of labor also have increased odds of postpartum sepsis.[25] Risk factors associated with progression of sepsis include age greater than 25 years, high school education or less, public or no health insurance, and primary or repeat cesarean section.[4] Risk factors associated with progression to severe sepsis/septic shock include black, Asian, or Hispanic race, public or no health insurance, diabetes mellitus, chronic hypertension, delivery in a low-volume hospital (<1000 births/year), primiparity, multiple pregnancy, and postpartum hemorrhage.[4] In particular, multiple pregnancy and GAS as a causative organism have been associated with increased odds of progression to septic shock.[4,25]

Obesity is a significant emerging factor, and interestingly, the rates of both cesarean section and obesity have increased worldwide.[4] Poverty is still the most important determinant of maternal mortality from sepsis in developing countries. An avoidable risk factor in both high- and low-income countries is the failure to recognize severity of an infection by mothers, family members, birth attendants, and hospital staff (**Box 1**).

PREVENTION

Special Considerations: Maternal Cardiopulmonary Physiology and Fetal Oxygenation

An in-depth description of the dynamics of maternal physiology throughout pregnancy and the peripartum interval, as well as mechanisms of oxygen delivery to the fetus, is beyond the scope of this article, and the reader is referred to standard authorities on these topics. However, perturbations of these systems induced by severe sepsis can

Box 1
Techniques to prevent infections in pregnancy

1. Identify risks of contact with young children and individuals with recent pharyngitis
2. Perineal hygiene and hand washing
3. Prompt treatment of infections of other sites
4. Shower with antiseptic agent before surgery
5. Avoid smoking within 30 d of surgery
6. Glycemic control
7. Antimicrobial prophylaxis
8. Antenatal prophylaxis for premature rupture of membranes less than 37 weeks
9. Antibiotics for premature rupture of membranes greater than 37 weeks
10. Antibiotic prophylaxis for cesarean section
11. Broad spectrum antibiotics for obstetric and anal sphincter repair (3rd to 4th degree (Pelvic, laceration)

have profound effects on fetal and maternal viability. Accordingly, some aspects of maternal and fetal physiology that are likely to be affected during sepsis are summarized. Fig. 2 depicts representative maternal and fetal physiologic issues.

As pregnancy progresses, there is a progressive increase in maternal blood volume of up to 150% by 32 weeks. Although red cell mass increases, expansion of plasma volume is greater, resulting in a modest decrease of hemoglobin, the "anemia of pregnancy."[27,28] Cardiac output and stroke volume also increase to 30% to 50% above prepregnancy values with a decrease in systemic vascular resistance.[29–35] Positional changes of the mother also modify venous return with obstruction of the vena cava by the gravid uterus.[36] Lateral decubitus or sitting posture improves venous return and hemodynamic parameters. During labor, cardiac output and arterial pressure increase, and each uterine contraction may be associated with an increase of 300 to 500 mL of venous return.[37,38] After delivery, there is an autotransfusion of up to 500 mL of blood from the uterus as well as removal of the gravid uterus as a source of vena caval obstruction. These changes may help offset blood loss during delivery. Fluid shifts from the extravascular fluid volume (ECF) to the vascular volume occur postpartum that may be augmented by intravenous fluids given during delivery. Serum proteins decline during pregnancy with a modest decrease of colloid osmotic pressure (COP) that may be further reduced by the ECF alterations cited above, hemorrhage, or administration of crystalloidal fluid. Further decreases of COP may be induced by alterations of vascular permeability by sepsis, increasing the risk of edema. Blood pressure returns to prepregnant values shortly after delivery, although increases in cardiac output and stroke volume may persist for a few weeks.[31,39–41] Although respiratory rate remains unchanged during pregnancy, there is an increase in tidal volume and minute ventilation. Maternal arterial blood gases reflect a modest respiratory alkalosis, with $Paco_2$ values of approximately 32 mm Hg induced in part by progesterone.[42–44] However, if $Paco_2$ values decrease to less than 30 mm Hg, there may be reductions of uterine blood flow. Renal blood flow is augmented during pregnancy, although during periods of stress, renal perfusion may be preferentially compromised with risk of acute renal injury.[29] In addition to the mild anemia of pregnancy cited earlier, there may be modest thrombocytopenia, which may be confused with or accentuated by sepsis.[29] Pregnancy is a procoagulant state, with up to a 4-fold increased risk of thromboses.[45] In addition, decreases in fibrinolytic activity during pregnancy may be further compromised by sepsis.

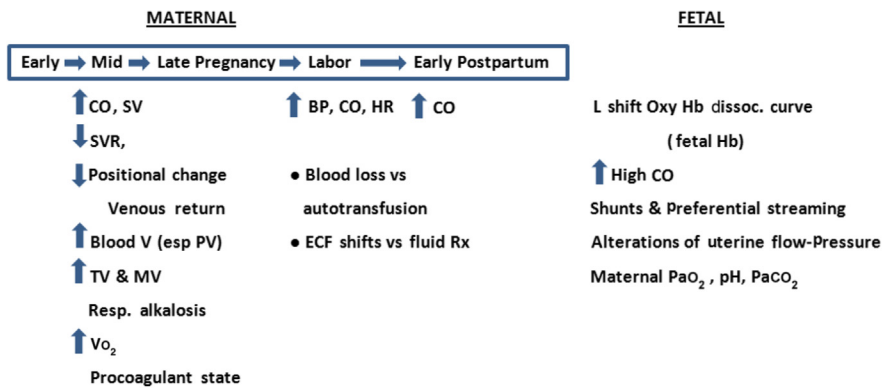

Fig. 2. Compilation of maternal and fetal physiologic dynamics potentially altered by sepsis. Blood V, blood volume; BP, arterial pressure; CO, cardiac output; MV, minute ventilation; PV, plasma volume; SV, stroke volume; TV, tidal volume; Vo_2, oxygen uptake–consumption.

Fetal transport and utilization of oxygen are complex processes and involve maternal pulmonary oxygenation and ventilation, uterine blood flow and pressure, maternal and fetal hemoglobin concentrations, as well as the oxygen tension gradient across the placenta. These changes are augmented by the left-shifted fetal oxyhemoglobin dissociation curve (ODC), maternal blood pH and $Paco_2$ umbilical blood flow, shunts and preferential streaming of blood within the fetus, together with the hyperdynamic fetal cardiovascular system.[46–48] Any or all of these components may be adversely affected during sepsis.

Maternal respiratory alkalosis favors the left-shifted ODC, affecting fetal oxygen loading as well as transport of CO_2 from fetus to the maternal circulation. Metabolic or respiratory acidosis of the mother may therefore adversely affect O_2 and CO_2 diffusion across the placenta. There must be a gradient of CO_2 tension from fetus to mother to eliminate fetal CO_2. Transient changes of these values are well usually well tolerated, but prolonged or severe disturbances of maternal pH, or $Paco_2$, may lead to fetal distress.[48–50] All of these factors are in turn affected by uterine blood flow and pressure. During pregnancy, maternal Pao_2 is normal, but fetal oxygen tensions are much lower with levels in the umbilical circulation of approximately 35 mm Hg and a corresponding saturation of 81%.[47,51] Hence, fetal oxygen delivery and utilization are dependent on a high fetal cardiac output, umbilical flow, shunts, and streaming of blood within the fetal circulation. Maternal hypoxemia can therefore have disastrous results on fetal oxygen delivery.

INFECTIONS DURING PREGNANCY AND THE PUERPERIUM: COMMON SITES THAT MAY LEAD TO SEPSIS AND ETIOLOGIC ORGANISMS

Infections of the genitalia or other sites can occur throughout pregnancy. The pregnant woman may develop similar infections as acquired during nonpregnant conditions, but there is a decrease in cell-mediated immune response in pregnancy, which may lead to greater predispositions for certain infections and a more severe response. There are also alterations of chest and abdominal cavities that may also lead to adverse outcomes for pneumonia.[52] In addition, the development of hydronephrosis as well as urinary reflux and high levels of progesterone is associated with a greater incidence of urinary infections. During labor and delivery, chorioamnionitis and endometritis may develop, particularly after extended labor, ruptured membranes, prior lower genital tract infections, and frequent vaginal examinations.[53] Therefore, most serious infections occurring during pregnancy affect the genitourinary systems. The evolution of etiologic agents during pregnancy, the intrapartum interval, and postnatal period is shown in **Table 3**.

PREGNANCY-ASSOCIATED GROUP A STREPTOCOCCAL INFECTIONS

GAS or *Streptococcus pyogenes* is a very virulent organism that can produce exotoxin, with extensive and rapidly developing tissue necrosis and maternal death.[54,55] The introduction of penicillin and antiseptic practice reduced the incidence of GAS,[56] but these infections re-emerged in 1980 with an annual incidence of 6 per 100,000 live births in the United States.[57] Compared with nonpregnant patients postpartum, women have a 20-fold increase in the incidence of GAS.[58] The increase may be related to breaches of mucosal barriers, alterations of vaginal pH, and decreased cellular immunity during pregnancy.

GAS presents with abdominal pain, fever, and tachycardia. Hypotension usually heralds the development of toxic shock syndrome and may be associated with up to 60% mortality, particularly if coupled with the development of renal failure.[56] Early diagnosis is thus crucial to prevent complications. Leukocytosis with marked

Table 3
Evolution of infectious organisms during pregnancy, intrapartum, and postnatal intervals

Organism	Antenatal	Intrapartum	Postnatal
E coli	55%	22%	42%
Group B streptococcus	4.2%	43%	9.2%
Anaerobes	8.5%	8%	8.5%
Staphylococcus	8.5%	5%	9.2%
Enterococcus	4.2%	5%	4.6%
G	0	2%	7.6%
Klebsiella	2%	2%	1.5%
H influenzae	6.4%	1%	0
Other	11.2%	11%	11.2%
Total, n	47	99	130

Data from Knowles SJ, O'Sullivan NP, Meenan AM. Maternal sepsis incidence, etiology and outcome for mother and fetus: a prospective study. BJOG 2015;122(5):663–71.

increases of immature white blood cells, together with fever and abdominal pain, should alert the clinician to consider GAS. Blood, urine, and endometrial aspiration should be performed, together with additional testing that may include computed tomographic (CT) imaging. Abdominal ultrasound may also be helpful. Aggressive and early resuscitation, antibiotics, and source control are keys to successful management. Penicillin G, together with Clindamycin, is the treatment of choice. Vancomycin may also be an alternative.[59] Duration of antibiotic therapy should be at least 14 days for patients with bacteremia or necrotizing fasciitis.

BACTERIAL PNEUMONIA

Similar microorganisms are generally recovered during pregnancy as for the nonpregnant patient. Although respiratory complications are frequently encountered, bacterial pneumonia occurs in only 0.1% to 0.2% of pregnancies.[60] Nevertheless, pneumonia is a major cause of maternal and fetal mortality[61] and is often misdiagnosed. It is also important to exclude and promptly treat viral causes of pneumonia.

An infectious agent can be isolated in 40% to 60% of patients with pneumonia.[61] Risk factors as well as signs and symptoms are similar to nonpregnant patients, although asthma is more common during pregnancy and may predispose to the development of pneumonia.[62]

Therapy for a healthy pregnant woman with uncomplicated community-acquired pneumonia is usually a macrolide. Doxycycline should be avoided and is contraindicated in pregnancy. Complicated or severe pneumonia should be managed with a macrolide plus a β-lactam.[63] Fluoroquinolones such as Levofloxacillin can also be considered a safe alternative[64] and are also effective against Legionella. Vancomycin can be added if *Staphylococcal pneumoniae* is suspected.

In addition to major complications such as septic shock and multiorgan failure, pneumonia during pregnancy is associated with a high incidence of preterm labor and delivery.[65]

PYELONEPHRITIS

Pyelonephritis is one of the more common severe infections during pregnancy and occurs in up to 2% of patients.[66] Because of compression of the gravid uterus,

pyelonephritis predominately affects the right kidney. Etiologic organisms are usually similar to those in nonpregnant patients, with *Escherichia coli* a major pathogen. Other organisms, such as *Klebsiella* or *Proteus*, may also be recovered on culture, as well as more virulent organisms such as *Pseudomonas*. Patients who have underlying anatomic obstructive changes, instrumentation, or prior infections may also present with a variety of other organisms, although gram-positive and anaerobic organisms are seen less frequently in this population. For reasons that are not clear, acute respiratory distress syndrome occurs in up to 7% of pregnant patients with pyelonephritis.[20,67,68]

For patients with pyelonephritis who require hospitalization, therapy should include parenteral ceftriaxone.[69] Patients with severe or resistant infections should receive combination therapy that may include an aminoglycoside. Urine and blood cultures can guide selection for patients with uncommon or resistant organisms.

CHORIOAMNIONITIS

Chorioamnionitis (intra-amniotic infection) is a serious obstetric infection and is associated with increased risk of premature delivery and neonatal sepsis.[70] There is infection of the amniotic fluid, membranes, and placenta. Clinical infection complicates 1% of term pregnancies but may be more frequent with preterm delivery.[53,71] The route of infection is usually migration from the cervicovaginal area, with progression to the amnion, decidua, and amnionic fluid.[72] The infection is typically polymicrobial with a predominance of genital *Mycoplasma*, as well as *Streptococcus agalactiae* (*Streptococcus B*) and *E coli*.[73] Risk factors include prolonged labor, membrane rupture, digital vaginal examinations, presence of genital trace pathogens, young age, and alcohol use.[74] The patient presents with sepsis, uterine tenderness, and purulent discharge. Fever is present in almost all instances and is essential for diagnosis.[70] Bacteremia occurs in up to 10% of cases, especially with *E coli* and group B *Streptococcal* infection. Diagnosis can be confirmed with Gram stain and culture of amniotic fluid.

Empiric antibiotic coverage against anaerobes and aerobes should be initiated. One regimen includes Ampicillin with Gentamycin; Clindamycin can be added in patients undergoing cesarean section.[15,75] There is no benefit to continued oral antibiotics after parenteral therapy.[76]

Delivery will provide source control and prevent neonatal complications, but time to delivery does not appear to impact outcome.[71] Cesarean delivery is not indicated and should be reserved for the usual obstetric indications.

ENDOMETRITIS

In parallel with increases in the utilization of cesarean section, there has been a corresponding increase in the occurrence of endometritis, which remains a potentially life-threatening complication of abdominal delivery.[72] Postpartum endometritis is typically a polymicrobial infection that includes anaerobes in up to 40% of instances, together with a mixture of gram-positive and gram-negative facultative anaerobes.[77] Serious infections that are prone to lead to sepsis are caused by GAS, Staphylococci, and Clostridium species. Prolonged labor, cesarean section delivery, prolonged rupture of membranes, and multiple cervical examinations are risk factors.[78,79]

The patient presents with fever, tachycardia, and lower abdominal pain. Gram stain and culture of the uterine cavity is used to confirm the diagnosis and guide antibiotic therapy. Although ultrasound examination and CT scans can be used, the diagnosis is usually based on clinical features.

The choice of antibiotics should consider the polymicrobial nature of the infection: one regimen includes an aminoglycoside and clindamycin. Second- or third-generation cephalosporins, together with metronidazole, can also be used.[72,77] Duration of therapy should be guided by the clinical response; there is usually no need for extended oral therapy after response to parenteral antibiotics.[80]

MANAGEMENT

The guidelines developed by the Surviving Sepsis program can be used as a basis for the treatment of the pregnant woman with severe sepsis and septic shock, although the obstetric population was not specifically considered during the establishment of the guidelines and does not have provisions that consider the physiologic changes during pregnancy.[11] The clinician should also assess fetal viability as resuscitation and definitive management proceed.

Early recognition of sepsis is associated with improved mortality and outcome. However, in the young, otherwise healthy pregnant patient, delays in identification of sepsis may occur. Therefore, warning signs that may alert to severe sepsis include fever or hypothermia, tachycardia, tachypnea, diarrhea, vaginal discharge, leukopenia or leukocytosis, elevated lactate, metabolic acidosis, thrombocytopenia, or other manifestations of coagulopathy.[54] Utilization of a rapid response protocol that can detect early signs of sepsis and initiate additional evaluation with early and appropriate antibiotics and resuscitation has been linked to survival.[81,82]

Early goal-directed therapy (EGDT) aims to restore perfusion and tissue oxygenation by achieving physiologic targets during the early phases of resuscitation, including measurements of mean arterial pressure (MAP), central venous pressure (CVP), mixed venous oxygen saturation (SVO_2), and clearance of blood lactate.[83] EGDT has become a widely accepted standard of care in the management of severe sepsis and septic shock and has been applied to treatment of sepsis during pregnancy.[84] However, a recent study not involving pregnant patients did not observe a mortality benefit of EGDT resuscitation compared with usual care of patients with suspected sepsis in the emergency department.[85] In addition, some of the target values of the Rivers EGDT are different in pregnancy, such as cardiac output and SVO_2, which reflect a hyperdynamic state in pregnancy. In addition, by the third trimester, MAP is higher in the pregnant woman, together with a lower CVP and higher SVO_2.

Invasive hemodynamic monitoring using pulmonary artery flow-directed catheters has been used in pregnancy.[30] However, there are insufficient data to determine if invasive hemodynamic monitoring alters outcome during severe sepsis in pregnancy. If invasive hemodynamic monitoring is considered, the use of such devices and interpretation of hemodynamic parameters should be restricted to clinicians skilled in these techniques.[34] A variety of noninvasive techniques are now emerging to assess hemodynamic variables in the unstable patient.[29,31–34,39,86] Bedside ultrasound may be useful to guide fluid management, with assessment of inferior vena cava (IVC) size and collapse to various maneuvers, to estimate status of vascular volume and fluid responsiveness.[87] However, use of IVC changes to guide fluid resuscitation in pregnant patients has not been well studied, and positional effects as well as correlations with vascular volume may differ from the nonpregnant state.[36] A combination of invasive and noninvasive techniques is therefore recommended to achieve a functional approach to monitoring the unstable patient.[88] Once severe sepsis is suspected, restoration of perfusion should take priority by initiating antibiotics as well as fluid infusion. Using guidelines suggested above, an initial bolus of approximately 30 mL/kg should be given rapidly, using physiologic salt solution or lactated Ringer

solution.[89] The choice of additional fluid remains controversial, but may include albumin. Synthetic colloidal solutions are not recommended.[90–92] Volume overload and pulmonary edema are potential hazards of vigorous volume resuscitation.

Vasoactive agents and additional blood products may be used if perfusion is not restored. Norepinephrine is typically the initial choice of a vasoactive agent, which may be augmented by epinephrine or vasopressin infusion.[93] Dopamine may be used for the patient with bradycardia. Dobutamine should be considered when an increase of cardiac output is a goal. Corticosteroids are currently recommended if the patient has refractory septic shock. The benefit of a random serum cortisol has been questioned.[94]

SUMMARY

Sepsis remains a major cause for admission of pregnant women to the ICU and is a leading cause of maternal morbidity and mortality. The Surviving Sepsis guideline continues to serve as a cornerstone for the diagnosis and management of sepsis, and many aspects of the management of severe sepsis are similar to that for the nonpregnant patient. However, both maternal and fetal morbidity and mortality are affected by the effectiveness of resuscitation and definitive therapy.

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