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SMFM Consult Series #47: Sepsis during pregnancy and the puerperium

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Maternal sepsis is a significant cause of maternal morbidity and mortality and is a preventable cause of maternal death. The purpose of this guideline is to summarize what is known about sepsis and to provide guidance for the management of sepsis in pregnancy and the postpartum period. The following are SMFM recommendations: (1) we recommend that sepsis and septic shock be considered medical emergencies and that treatment and resuscitation begin immediately (GRADE 1B); (2) we recommend that providers consider the diagnosis of sepsis in pregnant patients with otherwise unexplained end-organ damage in the presence of an infectious process, regardless of the presence of fever (GRADE 1B); (3) we recommend that empiric broad-spectrum antibiotics be administered as soon as possible, ideally within 1 hour, in any pregnant woman in whom sepsis is suspected (GRADE 1B); (4) we recommend obtaining cultures (blood, urine, respiratory, and others as indicated) and serum lactate levels in pregnant or postpartum women in whom sepsis is suspected or identified, and early source control should be completed as soon as possible (GRADE 1C); (5) we recommend early administration of 1−2 L of crystalloid solutions in sepsis complicated by hypotension or suspected organ hypoperfusion (GRADE 1C); (6) we recommend the use of norepinephrine as the first-line vasopressor during pregnancy and the postpartum period in sepsis with persistent hypotension and/or hypoperfusion despite fluid resuscitation (GRADE 1C); (7) we recommend against immediate delivery for the sole indication of sepsis and that delivery should be dictated by obstetric indications (GRADE 1B).

Key words: maternal sepsis, pregnancy-associated sepsis, sepsis

Maternal sepsis is a significant cause of maternal morbidity and mortality. Nearly one half of all maternal deaths in the preantibiotic era were due to infection.[1,2] Recent US data report that maternal sepsis complicates 4−10 per 10,000 live births.[3-5] Sepsis continues to be associated with significant mortality, and the most recent triennial Confidential Enquiries into Maternal Deaths and Morbidity in the United Kingdom reported that sepsis accounted for one quarter of all maternal deaths. In 63% of maternal sepsis deaths, independent reviewers found substandard care, most often a delay in recognition or management and most often on the obstetric unit.[6]

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The rate of sepsis appears to be increasing. A detailed analysis of pregnancy-associated sepsis during a delivery hospitalization in Texas demonstrated a temporal increase in pregnancy-associated severe sepsis, doubling from 6 per 10,000 in 2001 to 12 per 10,000 in 2010. When abortions and fetal demises were included, the incidence of pregnancy-associated severe sepsis increased from 11 per 10,000 pregnancies in 2001 to 26 per 10,000 in 2010. There was a 9.1% annual increase in sepsis as the maternal cause of death from 2001 to 2010.[7] Similarly, an evaluation of the Nationwide Inpatient Sample between 1998 and 2008 demonstrated a 10% per year increase in maternal severe sepsis and sepsis-related death in the United States.[8]

Nulliparity, black race, and public or no insurance have been identified as risk factors for pregnancy-associated sepsis. In addition, obstetric risk factors, including cesarean

delivery, assisted reproductive technologies, and multiple gestation also play a role.[9,10] More than 50% of the women who die from sepsis have 1 or more chronic comorbid conditions, including chronic renal disease, chronic liver disease, and congestive heart failure.[7,10]

Sepsis is increasingly recognized as an important preventable cause of maternal death. The purpose of this guideline is to summarize what is known about sepsis and to provide guidance for the management of sepsis in pregnancy and the postpartum period.

How is sepsis defined and what are the clinical features?

Sepsis is not a specific illness; rather it is a syndrome that encompasses a still uncertain pathobiology. In 2016, The Third Internal Consensus Definitions for Sepsis and Septic Shock Task Force defined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[11]

Organ dysfunction may be objectively defined as an acute increase of 2 or more points in the Sequential Organ Failure Assessment (SOFA) score (Table 1). In individuals with no baseline disease, the initial SOFA score should be zero. Although multiple definitions for septic shock have been used, septic shock was defined by Singer et al[11] as a "subset of sepsis in which underlying circulation and cellular/metabolic abnormalities are profound enough to substantially increase mortality." Although multiple definitions of septic shock are currently in use, septic shock can be identified within a clinical construct of sepsis with persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥65 mm Hg and a serum lactate level >2 mmol/L despite adequate volume resuscitation.[11]

The present definition of sepsis emphasizes signs of organ dysfunction rather than signs of infection. To assist in the evaluation of suspected sepsis, a brief bedside assessment tool known as the quick SOFA score (qSOFA) has been introduced into clinical practice. The qSOFA score evaluates the presence of 3 clinical criteria: systolic blood pressure ≤100 mm Hg, respiratory rate ≥22 per minute, and altered mental status. If 2 or more of these criteria are present, the patient is at increased risk for poor sepsis–related outcomes, and these signs should prompt the physician to

TABLE 1
Sequential Organ Failure Assessment score

	Score				
Organ system	**0**	**1**	**2**	**3**	**4**
Respiratory					
PaO_2/F_IO_2	≥400 mm Hg (53.3 kPa)	<400 mm Hg (53.3 kPa)	<300 mm Hg (40 kPa)	<200 mm Hg (26.7 kPa) with respiratory support	<100 mm Hg (13.3 kPa) with respiratory support
Coagulation					
Platelets	≥150 × 10^3/ μL	<150	<100	<50	<20
Hepatic					
Bilirubin	<1.2 mg/dL (20 μmol/L)	1.2–1.9 mg/dL (20–32 μmol/L)	2.0–5.9 mg/dL (33–101 μmol/L)	6.0–11.9 mg/dL (102–204 μmol/L)	>12 mg/dL (204 μmol/L)
Cardiovascular					
MAP	≥70 mm Hg	<70	Dopamine <5 μg/kg per minute or any dose of dobutamine	Dopamine 5.1–15 μg/kg per minute or epinephrine ≤0.1 μg/kg per minute or norepinephrine ≤0.1 μg/kg per minute	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system: Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
Renal	Serum creatinine <1.2 mg/dL (110 μmol/L)	Serum creatinine 1.2–1.9 mg/dL (110–170 μmol/L)	Serum creatinine 2.0–3.4 mg/dL (171–299 μmol/L)	Serum creatinine 3.5–4.9 mg/dL (300–440 μmol/L) or urine output <500 mL/d	Serum creatinine >5.0 mg/dL (440 μmol/L) or urine output < 200 mL/d

F_IO_2, fraction of inspired oxygen; *MAP*, mean arterial pressure; *PaO_2*, partial pressure of oxygen.

Reproduced, with permission, from Vincent et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707-10.

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look carefully for organ dysfunction, start or escalate therapy, increase the acuity of monitoring, and consider transfer to an intensive care unit (ICU).[11]

The qSOFA score does not define sepsis; rather, it is a rapid method of identifying those patients at high risk of developing severe complications who require more aggressive therapy. Importantly, fever is neither necessary nor sufficient to determine whether sepsis is present. While the best early warning system has not been clearly defined, an important principle is that the implementation of an early warning system may decrease maternal risk.[12] **We recommend that sepsis and septic shock be considered medical emergencies and that treatment and resuscitation begin immediately (GRADE 1B). We recommend that providers consider the diagnosis of sepsis in pregnant patients with otherwise unexplained end-organ damage in the presence of an infectious process, regardless of the presence of fever (GRADE 1B).**

How do the clinical features of sepsis differ in pregnancy?

Normal human pregnancy is a state of expanded plasma volume, increased cardiac output, and peripheral vasodilation. None of the existing definitions of sepsis account for the physiologic alterations of normal pregnancy. When nonpregnant norms are used, either overdiagnosis or underdiagnosis of sepsis may occur.

Of the SOFA criteria, those most affected by pregnancy are creatinine and MAP. The SOFA score assigns a point value above zero once serum creatinine reaches 1.2 mg/dL, but this level is well above the upper limit of normal in normal pregnancy. In addition, the SOFA considers a MAP >70 abnormal, while in midpregnancy this level may be normal.

An obstetric-modified qSOFA has been proposed by the Society of Obstetric Medicine Australia and New Zealand (SOMANZ) and includes systolic blood pressure ≤ 90 mm Hg, respiratory rate >25 per minute, and altered mental status. The SOMANZ guidelines also include modifications to laboratory components when applying the SOFA score to pregnancy, including a point value above zero for a creatinine of >90 μmol/L (1.02 mg/dL).[13]

An analysis of normal maternal physiologic parameters[14] compared with the 1992 sepsis criteria[15] showed that sepsis cutoffs for respiratory rate, heart rate, partial pressure of carbon dioxide and white blood cell count overlapped with the normal range for pregnancy, labor, and/or the early puerperium. This overlap between normal and abnormal ranges during pregnancy may lead to false-positive diagnoses, although in contrast, the obstetric care provider may underreact to signs of sepsis, being accustomed to a degree of tachycardia or leukocytosis in normal pregnancy.

Most important in optimizing outcomes is the early recognition of organ dysfunction in the septic patient. To that end, in addition to the SOMANZ guidelines, there have been other attempts to devise a pregnancy-specific scoring system for sepsis. Evaluation of the Sepsis in Obstetrics Score, a combination of maternal temperature, blood pressure, heart rate, respiratory rate, peripheral oxygen saturation, white blood cell count, and lactic acid level as predictors of ICU admission for sepsis and modified to account for normal physiologic changes of pregnancy reported a positive predictive value of only 16.7% for ICU admission.[16] A prospective validation study of the Sepsis in Obstetrics Score found that a score of 6 or greater had a sensitivity of 64%, specificity of 88%, positive predictive value of 15%, and negative predictive value of 98.6%.[17]

What is the pathophysiology of sepsis?

Sepsis results from a dysregulated host response to infection resulting in organ damage, and virtually any organ system can be affected (Table 2). The excessive inflammatory response that occurs with sepsis includes extravasation of albumin and fluid, with resultant intravascular hypovolemia. Cytokine release leads to decreased systemic vascular resistance and increased cardiac output, although up to 60% of patients with sepsis have an ejection fraction below 45% (systolic dysfunction).

Septic cardiomyopathy may also manifest with diastolic dysfunction because of cardiac edema and diminished compliance. The noncompliant left ventricle will cause decreased diastolic filling and less stroke volume, increasing the risk of pulmonary edema with excessive fluid resuscitation. Tissue ischemia (and dysfunction) results not only from hypotension but also secondary to microvasculature occlusion from microthrombi because of disseminated intravascular coagulation.

What are the most common infectious etiologies of sepsis in pregnancy?

The source of infection in puerperal sepsis can be either pelvic or nonpelvic. The most common causes are presented in Table 3. Antepartum cases of sepsis are most

TABLE 2
Organ damage caused by sepsis

Organ system	Clinical features
Central nervous system	Altered mental status
Cardiovascular system	Hypotension from vasodilation and third spacing; myocardial dysfunction
Pulmonary system	ARDS
Gastrointestinal system	Paralytic ileus
Hepatic system	Hepatic failure or abnormal transaminases
Urinary system	Oliguria or acute kidney injury
Hematologic system	Thrombocytopenia or disseminated intravascular coagulopathy
Endocrine system	Adrenal dysfunction and increased insulin resistance

ARDS, acute respiratory distress syndrome.

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TABLE 3
Common sources of infection in sepsis

Variables	Antepartum	Postpartum
Obstetric	Septic abortion	Endometritis
	Chorioamnionitis	Wound infection
Nonobstetric	Urinary tract infection	Urinary tract infection
	Pneumonia	Pneumonia
	Appendicitis	Gastrointestinal

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commonly nonpelvic in origin, while intrapartum and postpartum cases are more likely to have a pelvic source.[18,19] In 30% of cases, no source is identified.

Microbiology is not specifically addressed in most reports of maternal sepsis. In the UK Obstetric Surveillance System, clinical laboratory testing was able to identify the causative microorganism in only 64% of maternal sepsis cases, and the clinician could identify the source in only 74%. In 16%, neither the inciting organism nor the source of sepsis was identified.[20] These figures are consistent with the overall experience of sepsis in a general adult population, in which blood cultures are negative in two thirds of patients, and cultures from all sites are negative in one third.[21]

The most frequently isolated organisms in maternal sepsis are *Escherichia coli* and group A and group B Streptococcus,[9,20] although staphylococci, Gram-negative and anaerobic bacteria, and many other organisms have been reported.[18,22] Mixed infections are also possible; in 15% of maternal sepsis deaths in which organisms could be identified, the infection was polymicrobial.[23] This finding lends support to the recommendation to start empiric broad-spectrum antimicrobial therapy until a pathogen is identified. **We recommend that empiric broad-spectrum antibiotics be administered as soon as possible, ideally within 1 hour, in any pregnant woman in whom sepsis is suspected (GRADE 1B).** Antibiotic coverage should be narrowed and focused once culture results are available.

Molecular techniques have improved the ability to identify inciting organisms not detected by culture-based methods. Peptide nucleic acid fluorescent in situ hybridization stains, matrix-assisted laser desorption-ionization/time-of-flight mass spectroscopy, and polymerase chain reaction–based systems are commercially available and can provide pathogen identification from blood samples before cultures become positive.[24] Polymerase chain reaction testing results are positive in approximately 11% of patients with a clinical suspicion of bacteremia but negative blood cultures.[25]

What is the initial management of sepsis?

Organ dysfunction in a previously healthy woman should raise suspicion for sepsis. If the history or physical examination supports sepsis as a possible diagnosis, cultures (blood, sputum, urine, and others as clinically indicated) and serum lactate levels should be obtained and antibiotics initiated within 1 hour of diagnosis.[26]

Empiric antibiotic choices will be driven by the presumed source, likely microorganisms, and local patterns of antibiotic resistance but should be broad spectrum. Initial coverage should include anaerobic and aerobic Gram-positive and Gram-negative bacteria. Hospitals may have specific recommendations in place or guidance may be sought from a consultant in infectious disease and/or from specialty society guidelines. Recommendations are expected to change as antibiotic resistance spreads. Table 4 summarizes some options for empiric antibiotic coverage for common infections in pregnant women.

When sepsis is suspected or certain, after antibiotics are initiated and cultures obtained, a search should begin for a focus of infection amenable to source control. Imaging is often required. If a specific focus is identified, appropriate steps should be undertaken, such as curettage for retained products of conception or drainage of an abscess.

The intervention with the least potential for physiologic derangement should be used (eg, percutaneous drainage is preferable to more extensive surgery).[26] The exception to this rule is necrotizing soft tissue infections, in which extensive debridement is required. **We recommend obtaining cultures (blood, urine, respiratory, and others as indicated) and serum lactate levels in pregnant or postpartum women in whom sepsis is suspected or identified. Early source control should be completed as soon as possible (GRADE 1C).**

What is the role of fluid therapy in the management of sepsis?

Fluid resuscitation should be part of the initial intervention if hypotension or hypoperfusion is present. Fever, venodilation, and capillary leakage all lead to inadequate preload in the patient with sepsis. The Surviving Sepsis Campaign recommends an initial bolus of 30 mL/kg of crystalloid,[26] but this recommendation may be overly aggressive in pregnancy, in which colloid oncotic pressure is lower and the risk of pulmonary edema is higher. Only about 50% of hypotensive septic patients are fluid responders. In those who are not, aggressive fluid administration may produce third spacing, leading to left ventricular diastolic dysfunction from ventricular wall edema, as well as pulmonary edema, cerebral edema, bowel edema with increased intra-abdominal pressure, and higher mortality.[27]

In most pregnant women, initial administration of 1–2 L of crystalloids is reasonable. Static measures of preload (eg, central venous pressure or pulmonary artery occlusion pressure) are poor predictors of fluid responsiveness and should not be used to guide fluid therapy.[28] Patients who are fluid responsive should be identified prior to further fluid administration (especially after the initial 1–2 L, or 30 mL/kg, have been administered). The latter may be accomplished by using either pulse-pressure variation or passive leg raising.

TABLE 4
Proposed broad-spectrum empiric antibiotic coverage in sepsis complicating pregnancy

Source infection	Recommended antibiotics
Community-acquired pneumonia	Cefotaxime, ceftriaxone, ertapenem, or ampicillin plus azithromycin, clarithromycin, or erythromycin[a]
Hospital-acquired pneumonia	Low-risk patients may be treated with piperacillin-tazobactam, meropenem, imipenem, or cefepime.
	Patients at high risk of mortality may need double coverage for Pseudomonas (beta lactam plus an aminoglycoside or a quinolone) and MRSA coverage with vancomycin or linezolid.[b]
Chorioamnionitis	Ampicillin plus gentamicin.[c] Add anaerobic coverage with clindamycin or metronidazole if cesarean delivery required.
Endomyometritis	Ampicillin, gentamicin, and metronidazole (or clindamycin)
	Alternatively may use cefotaxime or ceftriaxone plus metronidazole[d]
Urinary tract infections	Gentamicin with ampicillin
	Alternatively, may use monotherapy with a carbapenem or piperacillin-tazobactam[e]
Abdominal infections	Ceftriaxone, cefotaxime, ceftazidime, or cefepime plus metronidazole[f]
	Complicated cases may require monotherapy with a carbapenem or piperacillin-tazobactam.
Skin and soft tissues (necrotizing)	Vancomycin plus piperacillin-tazobactam[g]
	If Streptococcus Group A or *Clostridium perfringens* are present, use penicillin G plus clindamycin.

MRSA, methicillin-resistant *Staphylococcus aureus.*

Sources:

[a] Mandell LA, Wunderink RG, Anzueto A, Bartlet JG, et al. Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the management of community-acquired pneumonia in adults. Clinical Infect Dis 2007; 44: S27-72; [b] American Thoracic Society and Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005; 171: 388-416; [c] Higgins RD, Saade G, Polin RA, Grobman WA, et al, for the Chorioamnionitis Workshop Participants. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. Obstet Gynecol 2016; 127: 426-36; [d] Chebbo A, Tan S, Kassis C, Tamura L, Carlson RW. Maternal sepsis and septic shock. Crit Care Clin 2016; 32: 119-35; [e] International clinical practice guidelines for treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of American and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011; 52(5):e103-e120; [f] Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of American. Clin Infect Dis 2010; 50: 133-64; [g] Stevens DL, Bisno AL, Chambers HF, Dellinger EP, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Disease Society of American. Clin Infect Dis 2014; 1-43.

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Determination of pulse-pressure variation is accomplished by analyzing the waveform of an arterial line, which should not be affected by pregnancy. However, it is reliable only in sedated individuals receiving positive-pressure, controlled mechanical ventilation and who are in sinus rhythm.[29] If the pulse pressure varies by more than 13% with the respiratory cycle, the patient is considered to be volume responsive.

In patients who are breathing spontaneously or not in sinus rhythm, a rapid and reversible test of fluid responsiveness can be performed with passive leg raising to 30–45º, which causes an autotransfusion of close to 300 mL of blood from the legs into the chest. After 2–3 minutes of passive leg raising, fluid responders will have an increase in cardiac output (utilizing noninvasive cardiac output monitors), while those who do not improve are probably better treated with vasopressors.[30]

Passive leg raising may not be useful during the third trimester because of uterine compression of the inferior vena cava and should not be used to guide therapy.[31] In such cases, an increase in cardiac output may be identified by administering a small bolus of fluid (250–500 mL); if the cardiac output increases after such an intervention, further fluid administration is likely indicated. In a mechanically ventilated patient with an arterial line, pulse-pressure variation may be used as an alternative way to assess fluid responsiveness.

Point-of-care ultrasound has also been used to identify fluid responsiveness by measuring the diameter of the inferior vena cava with respiration (inferior vena cava diameter <1.5 cm with significant variation in caliber with the respiratory cycle predicts fluid responsiveness, while a diameter >2–2.5 cm with minimal variability with the respiratory cycle suggests that the patient is already fully fluid loaded). This technique is most commonly used in patients receiving mechanical ventilation and has not been validated in pregnancy. **We recommend early administration of 1–2 L of crystalloid solutions in sepsis complicated by hypotension or suspected organ hypoperfusion (GRADE 1C).** After initial fluid resuscitation, further fluid therapy should be guided by dynamic measures of preload.

When are vasopressors and inotropes indicated in sepsis?

In hypotensive patients who are not fluid responsive or who are not candidates for further fluid resuscitation (eg, women who are in pulmonary edema), vasopressors should be utilized to increase blood pressure. The purpose of vasopressors is to constrict the pathologically dilated systemic circulation and maintain adequate perfusion. Current guidelines recommend norepinephrine as the first-line agent with a target MAP 65 mm Hg or greater, although the latter threshold has not been studied in pregnant women.[26] Determining the target MAP in a septic pregnant patient must be individualized, with consideration of overall organ

perfusion. Early goal-directed therapy is no longer recommended in the management of sepsis.[32-34]

Norepinephrine has been studied in human pregnancy and is often used to maintain blood pressure with regional anesthesia at the time of cesarean delivery.[35] Acknowledging the lack of high-quality evidence in the setting of pregnancy-associated septic shock, norepinephrine nevertheless appears to be safe for the fetus, especially at low doses.

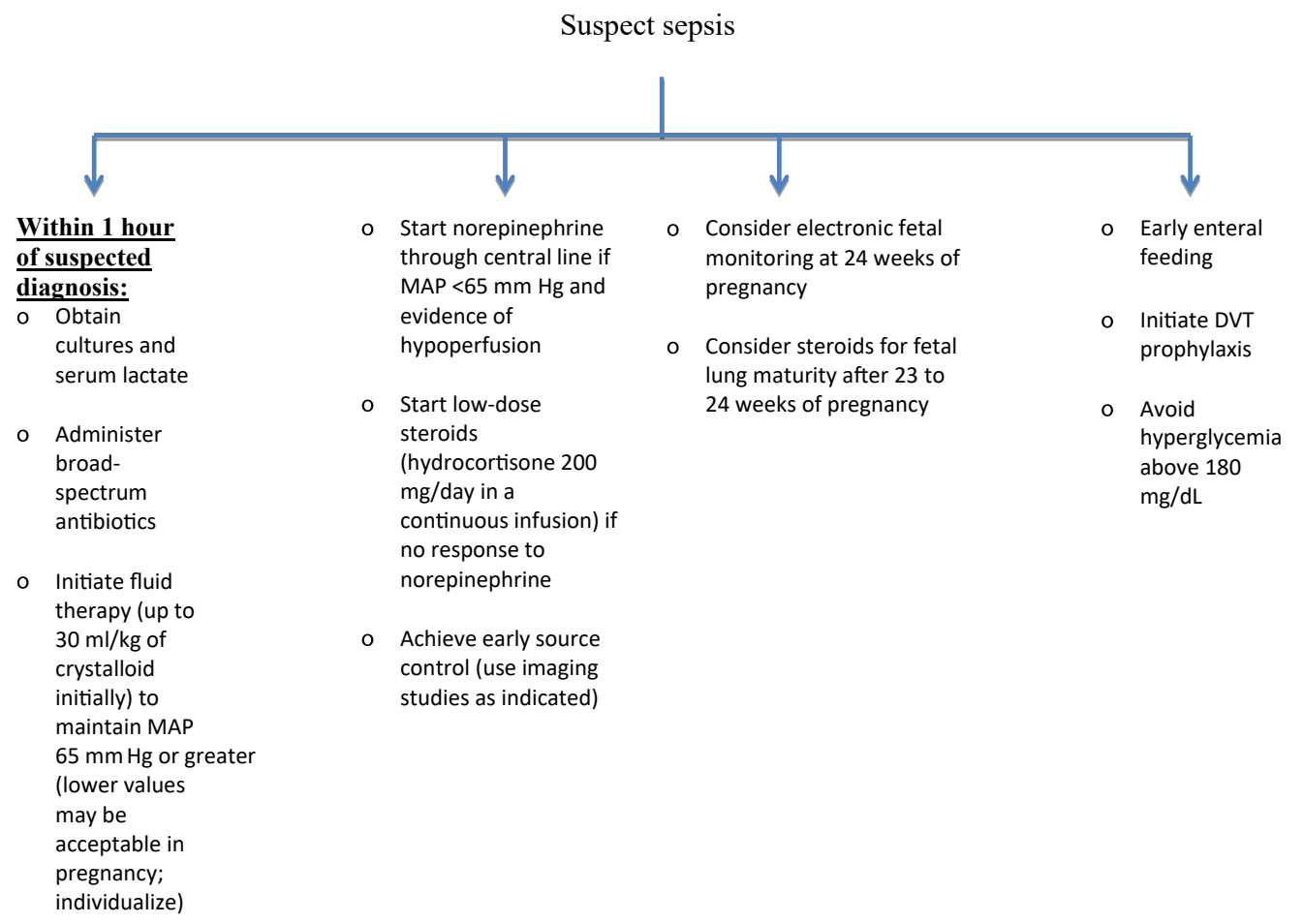
Providers should not hesitate to administer norepinephrine to a septic pregnant woman when indicated (eg, with hypotension refractory to fluid therapy). The evidence regarding the use of other vasopressors (eg, vasopressin) is more limited, and a theoretical interaction of vasopressin with oxytocin receptors has been hypothesized.[36] **We recommend the use of norepinephrine as the first-line vasopressor during pregnancy and the postpartum period in sepsis with persistent hypotension and/or hypoperfusion despite fluid resuscitation (GRADE 1C).**

In nonpregnant patients in whom hemodynamic stability cannot be achieved with the use of vasopressors, the use of hydrocortisone is recommended because of the possibility of sepsis- induced adrenal failure.[26] Dobutamine, which is an inotrope (increases cardiac output), rather than a vasopressor, is recommended in the setting of myocardial dysfunction or continued hypoperfusion despite fluid and vasopressor therapy.[26] A target MAP of 65 mm Hg is generally recommended in nonpregnant individuals. However, lower blood pressures may be acceptable during pregnancy, provided no signs of hypoperfusion are present (such as altered mental status, oliguria, elevated serum lactate, cold extremities, or evidence of fetal compromise).

When is delivery indicated in pregnant women with sepsis?

The presence of sepsis alone is not an immediate indication for delivery (except in cases of chorioamnionitis). The decision to deliver the fetus should be individualized and will

FIGURE
Initial treatment of sepsis during pregnancy



DVT, deep-vein thrombosis; *MAP*, mean arterial pressure.

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depend on gestational age as well as maternal and fetal conditions. In most cases, resuscitation that improves maternal hemodynamics will result in improved uteroplacental perfusion and therefore improved fetal condition. Delivery should be reserved for the usual obstetric indications after stabilization of the woman; there is no evidence that delivery improves maternal outcomes.

The primary objective should be hemodynamic supportive therapy for maternal benefit and antimicrobial treatment with appropriate source control of the infection. If the uterus is found to be the source of the infection, delivery is indicated. Involvement of neonatology, anesthesiology, and critical care consultants is fundamental. Corticosteroids for fetal lung maturity are not contraindicated and may be used in sepsis if indicated (regardless of use of hydrocortisone for refractory septic shock). Key interventions in the treatment of sepsis are depicted in the Figure. **We recommend against immediate delivery for the sole indication of sepsis and that delivery should be dictated by obstetric indications (Grade 1B).**

What are the maternal and perinatal outcomes associated with sepsis?

The mortality rate of sepsis in pregnant women is difficult to quantify. The few existing studies have reported rates from 1% to 4.6%.[37,38] The fatality rate is lower when H1N1 influenza, which has a high case fatality rate, is excluded. In the general population, actual case fatality rates of sepsis have decreased over time: the highest estimate was a case fatality rate of 35% in 2004, which fell to 25% in 2009, while the lowest estimate was 18% in 2004, declining to 14% in 2009.[39] It appears that the mortality rate caused by sepsis is lower in pregnancy. However, both the incidence and mortality of sepsis are dependent on age, which makes it difficult to find an appropriate comparison group for reproductive-age women.

An analysis from New Zealand and Australia of all adults with severe sepsis admitted to an ICU between 2000 and 2012 included a breakdown of young adults (age ≤44 years; mean age 31.6 years). For this group, average in-hospital mortality was 12%, and in the absence of comorbidities was 8%. Similar to US figures, mortality in this age group of Australians and New Zealanders with severe sepsis decreased significantly over time, from 22% in 2000 to 7% in 2012.[40]

It is important to note that survival to hospital discharge does not guarantee a normal outcome or quality of life; in the United States, only 20% of sepsis survivors were discharged to home, while 35% were discharged to a skilled nursing facility and 12% to some type of home care.[4] Without data specific to pregnancy, it is unknown what proportion of pregnant or postpartum sepsis survivors also require assisted recovery.

Preterm delivery is common after critical maternal illness, including sepsis, even when the source is not uterine. This is consistent with the pathophysiology of sepsis, in which inflammatory mediators are released systemically.[41-43] In a series from Ireland reporting on pregnant and postpartum women with bacteremia, the rate of preterm birth was 16.8%, nearly 3 times the rate in the control groups at the same institutions.[19] This rate included women diagnosed with bacteremia antepartum, intrapartum, and postpartum. Examining only those women with antepartum bacteremia, 69% either miscarried or delivered preterm. The outcome was worse for women with antepartum bacteremia of uterine origin; all delivered within 24 hours of onset.

Among women with a nonpelvic source of bacteremia in the antepartum period, 12% miscarried, 33% delivered soon after onset, and the remainder delivered between 1 week and 7 months after onset. Bacteremia during pregnancy was associated with a 29% risk of preterm delivery in a French study, with an overall fetal mortality rate of 10%; when maternal bacteremia occurred during the second

Summary of Recommendations

Number	Recommendation	GRADE
1	We recommend that sepsis and septic shock be considered medical emergencies and that treatment and resuscitation for sepsis begin immediately.	1B Strong recommendation, moderate-quality evidence
2	We recommend that providers consider the diagnosis of sepsis in pregnant patients with otherwise unexplained end-organ damage in the presence of an infectious process, regardless of the presence of fever.	1B Strong recommendation, moderate-quality evidence
3	We recommend that empiric broad-spectrum antibiotics be administered as soon as possible, ideally within 1 hour, in any pregnant woman in whom sepsis is suspected.	1B Strong recommendation, moderate-quality evidence
4	We recommend obtaining cultures (blood, urine, respiratory, and others as indicated) and serum lactate levels in pregnant or postpartum women in whom sepsis is suspected or identified. Early source control should be completed as soon as possible.	1C Strong recommendation, low-quality evidence
5	We recommend early administration of 1—2 L of crystalloid solutions in sepsis complicated by hypotension or organ hypoperfusion.	1C Strong recommendation, low-quality evidence
6	We recommend the use of norepinephrine as the first-line vasopressor during pregnancy and the postpartum period in sepsis with persistent hypotension and/or hypoperfusion despite fluid resuscitation.	1C Strong recommendation, low-quality evidence
7	We recommend against immediate delivery for the sole indication of sepsis and that delivery should be dictated by obstetric indications.	1B Strong recommendation, moderate-quality evidence

trimester, the fetal death rate was 40%.[44] In a small study focused specifically on *E. coli* bacteremia during pregnancy, the same researchers determined that the rate of fetal death was 27% overall, despite adequate antibiotic therapy.[45]

How can deaths from sepsis be prevented?

Among the studies of sepsis-related maternal mortality, some clear patterns emerge. Among women who died from sepsis, a majority had a delay in care and a delay in escalation of care. Most were afebrile, possibly delaying the recognition of the presence of sepsis. Even after diagnosis, 73% of women were started on antibiotics that provided inadequate coverage.[23] With publication of the Surviving Sepsis guidelines, the early involvement of consultants with expertise in infectious disease may expedite treatment of sepsis and help improve outcomes.

Conclusions

Sepsis continues to be a major cause of morbidity and mortality worldwide. Treatment during pregnancy should follow the same basic principles as in the nonpregnant population, including early recognition, fluid therapy, timely broad-spectrum antibiotics, and source control. Vasopressors, such as norepinephrine, should be used when indicated during pregnancy. In most cases, delivery should be guided by obstetric indications. Sepsis in pregnancy is associated with an increased risk for preterm delivery, prolonged recovery, stillbirth, and maternal death.

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