INVITED ARTICLE

Sepsis in the Parturient

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Abstract

Sepsis is a leading cause of maternal morbidity with a high case fatality rate and leads to significant perinatal loss. Early identification and appropriate time management can significantly improve maternal and perinatal outcomes. The physiological changes of pregnancy and puerperium make pregnant women more susceptible to sepsis and also pose a challenge for early diagnosis because of overlap of clinical features and laboratory values. The validation of scoring/warning systems for sepsis in parturient needs further research. Infections during puerperium are commonly polymicrobial in nature and warrant broad-spectrum antibiotics. Maternal resuscitation in antepartum period has to be tailored to ensure fetal well-being and adequate placental perfusion. For the management of sepsis in pregnancy, the guidelines from surviving sepsis campaign (SSC) for general adult population are extrapolated with modifications related to physiological alterations in pregnancy and puerperium. Timing of delivery is based on the obstetric indications unless the source of sepsis is intrauterine.

Keywords: Pregnancy complications, Pregnancy, Sepsis.

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Introduction

Sepsis is a leading cause of maternal morbidity and mortality worldwide and is an ever-evolving challenge. Infections contribute to 25–40% of all maternal deaths if all infection sites are included while 10–11% of maternal deaths are directly caused by pregnancy-related sepsis. Additionally, sepsis leads to 10–15% of intensive care unit (ICU) admissions and has a high case fatality rate when compared to other pregnancy-related complications.[1] Maternal sepsis leads to significant perinatal loss in the form of abortion, preterm birth, stillbirths, and neonatal sepsis. The Centers for Disease Control and Prevention (CDC) reports that for every maternal mortality secondary to sepsis, around 50 women suffer from maternal near miss.

It has been proven that early identification and appropriate time management can significantly reduce the mortality and morbidity secondary to sepsis. Hence, it is imperative for every obstetrician, physician, and anesthetist to be appraised with literature on causes, identification, and management of sepsis in a parturient.

Definition of Sepsis and Septic Shock

Over the last two decades, with a better understanding of pathophysiology of sepsis, the definitions of sepsis and septic shock have evolved. Presently, the definitions are based on the third international consensus definitions for sepsis and septic shock, referred to as Sepsis-3.[2] Sepsis is recognized as a "life-threatening organ dysfunction caused by a dysregulated host response to infection." Organ dysfunction is clinically defined using various predictive scoring systems based on clinical parameters, laboratory values, or therapeutic interventions. As per Sepsis-3, septic shock is defined as a subset of sepsis with profound circulatory and metabolic abnormalities that are clinically recognized by the requirement of vasopressor to maintain mean arterial pressure (MAP) of ≥65 mm Hg and/or serum lactate of >2 mmol/L (18 mg/dL) without hypovolemia.[2]

These guidelines have not made any specific recommendations for pregnancy. To create consensus on sepsis in pregnancy, the World Health Organization (WHO) in 2017 stated that maternal sepsis is "a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, postabortion, or postpartum period."[3] This definition has been endorsed by the International Federation of Gynecology and Obstetrics (FIGO) and Surviving Sepsis Campaign (SSC 2016) and is presently followed worldwide. It has been emphasized that the criteria of systemic inflammatory response syndrome (SIRS) are not appropriate for diagnosing maternal sepsis and must not be used. The definition of septic shock in pregnancy is extrapolated as from nonpregnant adults.

Effect of Pregnancy on Sepsis

Pregnancy, by itself, has a significant effect on sepsis in the following ways:

- The physiological, immunological, and mechanical changes of pregnancy put pregnant women at an increased risk of developing infections.
- The peripartum period is associated with a high rate of surgical interventions. As the placental bed is highly vascular and closely related to maternal circulation, these interventions can quickly lead to bacteremia and sepsis.

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- There is considerable overlap between normal changes of pregnancy and clinical manifestations of sepsis which may lead to delayed detection of sepsis. These mainly include vasodilatation, tachycardia, and tachypnea.

Scoring/Warning Systems for Sepsis in Parturient

Many scoring systems have been suggested in the literature, both for nonpregnant adult population and specific obstetric population. The organ failure-based scores are generally considered superior to obstetric-specific scoring systems. Worldwide Sequential Organ-Failure Assessment Score (SOFA score) (recommended by Sepsis-3) has been found to facilitate the identification of septic patients in an ICU setting who are at increased risk of death and it may be used without modifications in obstetric population.[2] With no preexisting acute or chronic organ dysfunction before the onset of infection, the baseline SOFA score is assumed to be 0 and a score of ≥2 has an overall in-hospital mortality of 10% in a patient with presumed infection. Even in the obstetric population, SOFA score has been shown to have a sensitivity of 87%, specificity of 90%, and the area under the receiver operating characteristic (AUROC) 0.95.[4]

Outside ICU, a quicker and simpler bedside assessment tool (quick SOFA or qSOFA) is used.[2] The presence of at least two of three points is suggestive of sepsis outside of ICU.

The physiological changes of pregnancy are not accounted for in the parameters of SOFA and qSOFA and hence some guidelines suggest modifications in these scoring systems when applying in the obstetric population. Obstetrically modified SOFA (omSOFA) and obstetrically modified qSOFA (omqSOFA) have been suggested by the Society of Obstetric Medicine Australia and New Zealand (SOMANZ) in 2017; however, further studies are needed for the validation of these scores (Tables 1 and 2).[5]

Similarly, the warning systems which aid rapid identification of critically ill patients in general population have not been proven to be useful in parturient. Many attempts have been made to develop an obstetric-specific early warning system like sepsis in obstetric score, modified early obstetric warning system (MEOWS), maternity early warning criteria (MERC), and maternity early warning trigger (MERT) tool. However, there is no clear evidence to choose any specific system as proven mortality benefit is lacking and studies have shown high sensitivity but low specificity. Some authors have suggested that the normal values of vital signs change with stages of pregnancy and hence the development of such systems for obstetric population is expected to remain a challenge. Royal College of Obstetrics and Gynecology (RCOG) presently recommends the use of MEOWS chart.[6]

Risk Factors and Causes of Sepsis in Parturient

The risk factors predisposing a parturient to sepsis include obstetric and nonobstetric factors.

- Medical/nonobstetric risk factors include advanced age, nulliparity, black race, comorbid conditions (like chronic renal disease, chronic liver disease, and diabetes), anemia, and history of group B streptococcal infection.
- Obstetric risk factors include the use of assisted reproductive technology (ART), prenatal invasive procedures, prolonged labor/rupture of membranes, operative delivery, and retained products of conception.

Screening and treatment for asymptomatic bacteriuria and sexually transmitted diseases during pregnancy and the routine prophylactic use of antibiotics prior to operative deliveries have markedly reduced the incidence of sepsis in pregnancy worldwide. The causes of sepsis in a parturient can be broadly classified as follows:

- Infections specific to pregnancy: chorioamnionitis, endometritis, surgical site infections, etc.
- Infections exacerbated by pregnancy: urinary tract infection, Hepatitis E, malaria, etc.
- Incidental infections during pregnancy: lower respiratory tract infections, tuberculosis, sexually transmitted diseases, etc.

In spite of thorough evaluation, the source of infection is not identified in 25–30% of the cases of maternal sepsis. It is important to note that most of the infections during antenatal period are

Table 1: Obstetrically modified SOFA score (omSOFA)

	Score		
System parameter	*0*	*1*	*2*
Respiration PaO_2/FiO_2	≥400	300–<400	<300
Coagulation platelets, $\times 10^3$/L	≥150	100–150	<100
Liver bilirubin (µmol/L)	≤20	20–32	>32
Cardiovascular MAP (mm Hg)	MAP ≥70	MAP <70	Vasopressors required
Central nervous system	Alert	Rousable by voice	Rousable by pain
Renal creatinine (µmol/L)	≤90	90–120	>120

Table 2: Obstetrically modified qSOFA score (omqSOFA)

	Score	
Parameter	*0*	*1*
Systolic blood pressure	≥90 mm Hg	<90 mm Hg
Respiratory rate	<25 breaths/minute	25 breaths/minute or more
Altered mentation	Alert	Not alert

extra-uterine in origin while most of the infections in postabortal/postpartum period are of genital origin. The most common postpartum infection is endometritis. Other foci of infection in the puerperium include mastitis, urinary tract, pneumonia, skin and soft tissue infection, gastroenteritis, pharyngitis, and rarely bacterial meningitis.

As opposed to nonpregnant adults with sepsis where the leading organisms are gram-positive bacteria and only 5% of the cases are polymicrobial, infections during puerperium are commonly polymicrobial in nature. Aerobes include groups A and B streptococci, *Staphylococcus*, *Klebsiella*, *Proteus*, *Enterobacter*, *Enterococcus*, and *Escherichia coli*. Anaerobes include *Peptostreptococcus*, *Peptococcus*, *Bacteroides*, *Fusobacterium*, *Prevotella*, and *Clostridium*.[7] Clostridium species is a rare, but potentially lethal, cause of endometritis. In the last decade, there has been an increase in severe infections caused by β-hemolytic Group A streptococci. Fungal systemic infections in pregnancy are rare. No causative organism is identified in spite of all efforts in around one-third of the cases of maternal sepsis.

Bedside Physical Examination in Sepsis

The patient could present with nonspecific symptoms such as lethargy and reduced appetite. Clinical signs should be looked for to get a clue to the focus of infection. High spiking fever with rigors suggests abscess or infected hematoma. Abdominal/pelvic pain and tenderness unrelieved by usual analgesics, foul-smelling vaginal discharge, and delay in uterine involution suggest genital tract sepsis. Breast engorgement/redness suggests mastitis. Redness or discharge at the surgical site suggests wound infection. Productive cough or urinary symptoms point to the lung or urinary tract as the focus of infection, respectively. Bedside physical examination can assist in timely diagnosis of septic shock in resource-limited countries where the access to laboratory parameters and professional experts is limited.

In hemodynamically stable patients with sepsis, microcirculatory alterations can cause abnormal regional brain perfusion and lead to brain dysfunction. An altered mental status is a distinguishing feature of septic shock. Therefore, regular physical neurological assessment should be done. Capillary refill time (CRT) more than 5 seconds following initial hemodynamic optimization can help differentiate between stable patients and those at higher odds for worsening organ failure. Mottling of skin typically seen around knees and elbows reflects abnormal skin microperfusion. Variation in skin temperature is associated with peripheral vasodilatation with extremities cool to touch in the initial phase.[8]

Laboratory Parameters

The most common biomarkers for sepsis used in clinical practice include total leukocyte count (TLC), C-reactive protein (CRP), procalcitonin (PCT), and lactate. An elevated TLC is indicative of sepsis (15,000–30,000 cells/μL), but this can also be a normal finding in postpartum women due to the physiologic leukocytosis of pregnancy and the effects of labor. Mean TLC in laboring patients ranges from 10,000 to 16,000 cells/μL and may be as high as 29,000 cells/μL. Therefore, in the postpartum period, a rising neutrophil count and a left shift (bandemia) are considered as markers of sepsis.[9] TLC and CRP are nonspecific for inflammation versus infection, but PCT appears to be more specific for bacterial infection. A venous lactate of >2 mmol/L warrants critical care input. A high lactate (>4 mmol/L) along with hemodynamic instability is an indication to measure central venous pressure (CVP) and central venous oxygen saturation [$ScvO_2$] with a goal of keeping CVP ≥8 mm Hg and $ScvO_2$ ≥70% and urine output of at least 0.5 mL/kg/hour.[2]

Management of Sepsis in a Parturient

The goals of the treatment of sepsis are to improve tissue perfusion, limit cell dysfunction, and stop progression to septic shock. The basic principles of stabilization with airway-breathing-circulation (ABC) sequence must be followed. Management consists of two key approaches: resuscitation and source control.

General Principles and Initial Resuscitation

Sepsis and septic shock must be considered as medical emergencies where resuscitation must begin immediately. As there are no specific evidence-based recommendations regarding the management of sepsis in pregnancy, the guidelines from SSC for general adult population are extrapolated.[10] In contrast to 2012 recommendations of 3- and 6-hour bundles, the present recommendations include the "1-hour bundle" or the set of intervention packages which must be applied together within one hour to resuscitate a patient with proven/suspected sepsis/septic shock.[11] These interventions include:

- Measure serum lactate. Remeasure if initial lactate >2 mmol/L
- Obtain blood cultures and cultures from the suspected focus of infection before administration of antibiotics. These may include throat swabs, midstream urine, high vaginal swab, placental swabs, sputum, cerebrospinal fluid, epidural site swab, Cesarean section or episiotomy site wound swabs, and expressed breast milk.
- Administer broad-spectrum antibiotics.
- Rapid administration of crystalloid in case of hypotension/lactate >4 mmol/L.
- Start vasopressor to maintain MAP ≥65 mm Hg if the patient is hypotensive after fluid resuscitation.

The following points must be remembered while treating a case of sepsis/septic shock:

- Each hour delay in the administration of antibiotics leads to 6–7% decrease in survival. Hence, antibiotics must never be delayed in case obtaining cultures is logistically not feasible.[12]
- Basal lactate level is an objective measurement of tissue perfusion and correlates directly with mortality.
- Early goal-directed therapy (EGDT) has proven to be of no benefit in the management of sepsis in obstetric patients and, hence, must not be followed.

Resuscitation Principles Specific to Pregnancy

- Maternal resuscitation in antepartum period should focus on fetal well-being also, ensuring left decubitus position and relieving aortocaval compression for adequate fetal blood flow. The aim of the management is to maintain oxygenation and perfusion of vital organs and placenta while identifying and treating infection. Oxygen should be administered to achieve a saturation ≥94%.
- An initial volume of 30 mL/kg of crystalloid is recommended if either hypotension or lactic acid >4.0 mmol/L is present. However, pregnant patients, especially in the third trimester,

have a greatly increased fluid volume, have decreased oncotic pressure, may have preeclampsia, or may receive uterotonic drugs that lead to fluid retention. They are at risk of developing pulmonary edema. RCOG suggests the initial bolus to be 20 mL/kg instead of 30 mL/kg.[13] If resuscitation requires a large volume of crystalloids, balanced salt solutions or albumin should be considered. Use of hydroxyethyl starches and gelatin are not recommended for intravascular volume replacement. Dynamic measures of fluid responsiveness should be employed such as passive leg raising, point-of-care ultrasound to check inferior vena cava (IVC) diameter, pulse pressure variation, or stroke volume variance for guiding fluid therapy.[14]

Source Control and Suggested Antibiotics

Empirical broad-spectrum antibiotics must be started at the earliest. The choice of antibiotics should be based on the presumed source, likely causative organism, and local pattern of antibiotic sensitivity/resistance. This should be accompanied by a thorough search for the focus of infection followed by early source control. Imaging studies like chest X-ray, ultrasound scan, or computed tomography scan can help to identify the source of infection. Once the focus of infection is identified, it has to be dealt with by procedures like uterine evacuation or drainage of a breast, wound, or pelvic abscess. Institutes should have a local antibiotic policy in accordance with common causative organisms and antimicrobial sensitivity patterns. Table 3 broadly mentions likely organisms and recommended antibiotics in some common infections leading to maternal sepsis.

ICU Care of Critically Ill Septic Parturient

Indication of Transfer to Intensive Care

Transfer to critical care is indicated if the patient is hemodynamically unstable, needs vasopressor support or mechanical ventilation. A joint collaborative team comprising critical care team, obstetrician, and obstetric anesthetist should be involved for further management.

Vasopressors

A poor response to fluid administration indicates treatment using vasopressors. Reversible myocardial depression has been associated with sepsis, and inotropes can be considered when cardiac output has been compromised. There are no specific guidelines for vasopressors in pregnancy for the management of septic shock. A goal to keep MAP at or above 65 mm Hg should be followed. The first-line treatment as in nonpregnant population is noradrenaline because of its efficacy. Dopamine can cause arrhythmias and should be used only in women with a low risk of tachyarrhythmias and bradycardia. Low-dose dopamine is not recommended for renal protection. Vasopressin and adrenaline are indicated as second-line management. In the rare setting of septic myocarditis, dobutamine may be chosen as the preferred inotrope.[15,16]

Role of Corticosteroids

The indication of corticosteroids in septic patients is the subject of controversy in the literature.[15,16]

Table 3: Recommended antibiotics in common maternal infections

Source	*Most likely organism*	*Recommended antibiotics*
Postpartum endometritis/septic abortion	Polymicrobial (genital tract aerobes + anaerobes)	Clindamycin 900 mg iv 8 hourly Plus gentamicin 5 mg/kg every 24 hours (or 1.5 mg/kg 8 hourly) Alternative: ceftriaxone/cefotaxime plus metronidazole RCOG: piperacillin-tazobactam or carbapenem plus clindamycin. If MRSA suspected: replace clindamycin with vancomycin or linezolid
Chorioamnionitis/intra-amniotic infection	Polymicrobial	Ampicillin 2 g 6 hourly plus Gentamicin 1.5 mg/kg 8 hourly Add clindamycin/metronidazole if cesarean delivery is needed. In case of penicillin allergy: replace ampicillin with vancomycin.
Community-acquired pneumonia	Bacterial: *Streptococcus pneumoniae, Klebsiella pneumonia*, *Haemophilus influenzae* Viral: Influenza	Cefotaxime, ceftriaxone, or ampicillin plus azithromycin. Antiviral: oseltamivir
Hospital-acquired pneumonia	*Pseudomonas*, *Streptococcus aureus* including MRSA, *S. pneumonia*, *K. pneumonia*, *H. influenza*	Piperacillin-tazobactam or a carbapenem
Group A streptococcal infection	*Streptococcus pyogenes*	Penicillin plus clindamycin
Urinary tract infections	*Escherichia coli*, *Klebsiella*, *Proteus*, gram-positive organisms	Ceftriaxone 1–2 g every 24 hours or ampicillin 1–2 g 6 hourly plus gentamicin 1.5 mg/kg 8 hourly Alternative: monotherapy with piperacillin-tazobactam or a carbapenem
Necrotizing fasciitis	Polymicrobial	Surgical debridement plus carbapenem/piperacillin-tazobactam plus agent against MRSA (vancomycin/linezolid)

Glycemic Control

Glycemic controls are important to avoid fetal complications. It is recommended that blood sugars are maintained at less than 180 mg/dL.[15,16]

Intravenous Immunoglobulins

It has been shown that immune regulation in sepsis is associated with improved outcomes. Literature has shown that intravenous immunoglobulin (IVIg) can be considered as an adjunct to antibiotics, particularly during severe invasive staphylococcal and streptococcal sepsis, even in obstetric settings. Mechanism of action is based on the premise that dysregulated cytokine release causes endothelial dysfunction that leads to hypotension, hemoconcentration, macromolecular extravasation, and oedema.[15,16]

Extracorporeal Membranous Oxygenation

Extracorporeal membranous oxygenation (ECMO) has been used for either cardiac or respiratory failure in a small number of patients in pregnancy and the puerperium, including as a consequence of severe sepsis and septic shock.[15,16]

Anesthetic Considerations in a Septic Parturient

Use of neuraxial block is not recommended as hypotensive patients do not tolerate the sympathetic block and intense vasodilation following spinal anesthesia. Also there may be associated coagulation abnormalities or thrombocytopenia due to sepsis. For general anesthesia drugs which preserve hemodynamic stability, ketamine and etomidate should be used. The oxytocin boluses should be given slowly over 5 minutes and the decision to extubate or directly transfer to ICU should be based on clinical condition of the patient. Analgesic regimen should avoid nephrotoxic drugs like nonsteroidal anti-inflammatory drugs.[17]

Timing of Delivery

Irrespective of the cause, sepsis in pregnancy is associated with an increased risk of abortion, preterm delivery (16–29%), and intrauterine fetal demise (10–40%). Overall maternal infections are associated with 10–25% of stillbirths in the developed world and up to 40–50% of stillbirths in the developing countries. Considering immediate delivery without stabilizing the maternal condition markedly worsens the maternal prognosis unless the underlying cause is intrauterine infection. Operative delivery has been associated with a sixfold increased risk of ICU admission as compared to vaginal delivery in a study of over 600 patients with sepsis in the UK.

The Society for Maternal–Fetal Medicine (SMFM) strongly recommends against immediate delivery for the only indication of sepsis and states that obstetric indications must dictate the timing of delivery.[18] RCOG also emphasizes that attempting delivery in an unstable septic patient increases mortality unless the source is intrauterine. They recommend that the decision on timing and mode of delivery must be made by a senior obstetrician and must be individualized based on the severity of illness, period of gestation, duration of labor, and neonatal facilities available. Corticosteroids for fetal lung maturity are not contraindicated in sepsis.

Conclusion

Sepsis in a parturient is associated with significant morbidity and mortality. Physiological changes in pregnancy and puerperium make early identification difficult. A favorable outcome requires early management, adequate monitoring, and multidisciplinary team approach. Validation of early warning signs and targets specific to pregnancy are areas of ongoing research. Future clinical trials in pregnancy and the puerperium may give further insight into the pathogenesis of sepsis in pregnancy and puerperium.

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