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Managing Maternal Sepsis: Early Warning Criteria to ECMO

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Abstract: Maternal sepsis is now a leading cause of direct maternal death during pregnancy. This review addresses the latest advances in the identification and management of critically ill parturients. Specifically, this review will focus on the vulnerability of pregnant women to sepsis, the utility of early warning criteria in the identification of the septic parturient, emphasize the immediate antibiotic management of suspected sepsis, and elaborate upon the latest understanding in the ventilatory management of parturients with sepsis.
Key words: maternal sepsis, early warning criteria, SIRS, ECMO in pregnancy, septic shock, obstetric levels of care

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Managing Maternal Sepsis: Early Warning Criteria to Extracorporeal Membrane Oxygenation (ECMO)

Approximately 75,000 pregnant women die each year because of sepsis.[1] Though a great majority of these deaths occur in low-income countries in sub-Saharan Africa and South Asia, the incidence of maternal sepsis continues to increase throughout the world. For instance, in the United States and the United Kingdom, maternal sepsis is now considered the leading cause of direct maternal death during the peripartum period. In the United Kingdom, maternal mortality from sepsis has increased in the last 15 years to an incidence rate of 1.13 per 100,000 cases, nearly doubling in incidence from 0.65 per 100,000 cases 15 years ago. The incidence of severe sepsis is ~21 per 100,000 deliveries, with a case

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TABLE 1. Classification of Factors That Increase Susceptibility to or Severity of Sepsis in Pregnant Women

Increased Susceptibility	Increased Severity
Immunosuppressed state	Rapid myocardial dysfunction
Asymptomatic bacteremia	Predisposition to pulmonary edema and ARDS
Predisposition to pyelonephritis	Poor metabolic compensation for acidemia
Changes in vaginal pH and flora	Increased oxygen consumption
Increased interventions	

ARDS indicates acute respiratory distress syndrome.

fatality rate of 7% to 8%.[2] Severe sepsis with organ involvement has a 20% to 40% mortality rate, which increases to 60% in the presence of septic shock. Therefore, there is a critical need to understand why women are vulnerable to sepsis during pregnancy, recognize the risk factors, and identify the onset of critical illness early so that appropriate escalation of care could be facilitated.

Pregnant Women Are Vulnerable to Sepsis

Unlike hematological changes of pregnancy that confer evolutionary advantages during childbirth, changes in other organ systems either increase the susceptibility or enhance the severity of sepsis during pregnancy (Table 1).[3] First, are changes in the immune system which makes pregnant women vulnerable to infection. Pioneering work by the Nobel Laureate Sir Peter Medawar established that pregnancy is characterized by relative immunosuppression to enable the mother to tolerate paternal alloantigens expressed in fetal tissues. However, the extent and exact nature of modification of the maternal immune system during pregnancy and its contribution to susceptibility to infection still remains largely unknown. In general, there is both an increase and a reduction in the maternal immune response during pregnancy. Some of the enhanced immunologic responses include an increase in monocytes and granulocytes, which has been shown to be protective against bacterial infections. However, there is also suppression of natural killer cells and cytokines which are believed to protect the fetus from an maternal fetal immune response. Studies in pregnant mice have shown an altered cytokine profile which increases susceptibility to *Escherichia coli* lipopolysaccharide (LPS). Enhanced tumor necrosis factor-α and a decrease in interleukin-10-specific immune responses to LPS has been shown in the third trimester of pregnancy in mice. More importantly, these animal studies showed that pregnancy increases LPS-induced mortality, which has direct implications for the septic parturient.[4]

In addition to an altered immune response, normal physiological changes of pregnancy in the cardiovascular, respiratory, and metabolic systems causes pregnant women to decompensate quickly with the onset of sepsis. Altered Frank-Starling curve due to increased blood volume, increased susceptibility to acute respiratory distress syndrome (ARDS), and renal excretion of bicarbonate that reduces buffer base, all serve to limit maternal response to sepsis. Third, increased invasive interventions (cervical examination, urinary bladder catheterization, forceps application, and invasive electronic fetal monitoring), predisposition to pyelonephritis due to ureteral compression by a gravid uterus, and a higher predilection for asymptomatic bacteremia make the pregnant woman

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TABLE 2. Risk Factors for Sepsis During Pregnancy

Antenatal	Puerperal
Obesity, anemia, immunosuppression, diabetes, history of pelvic infection, history of Group B streptococcal infection, invasive procedures such as amniocentesis and cervical cerclage, prolonged rupture of membranes, group A streptococcal infection in close contacts	Induction of labor, instrumented or cesarean delivery, preeclampsia, postpartum hemorrhage, mastitis

more vulnerable to sepsis. Finally, is the fact that the changes in physiological variables during pregnancy can mask early recognition of sepsis. In fact, in the confidential enquires report published from the United Kingdom, almost 70% of maternal deaths due to sepsis was due to suboptimal care primarily because of a delay in diagnosis.

Risk Factors for Sepsis in Pregnancy

Risk factors for sepsis can be broadly categorized into antenatal and puerperal factors (Table 2). The overall risk associated with *a priori* demographic and clinical factors is significantly cumulative; compared to women without sepsis, for every additional risk factor, risk of uncomplicated sepsis increases by 25% [odds ratio (OR) = 1.25; 95% confidence interval (CI), 1.17-1.32), and the risk of progression to severe sepsis/septic shock increases by 57% (OR = 1.57; 95% CI, 1.41-1.74), respectively.[5] Most commonly recovered organisms include *E. coli* and *Staphylococcus aureus*, but the most virulent infection is caused by Group A Streptococcus.

Early Recognition of Pregnancy-related Sepsis

One of the widely recognized factors that contribute to increased mortality and morbidity from maternal sepsis is a delay in the recognition of critical illness. The 2007 *Saving Mother's Lives* report from the Confidential Enquiries into Maternal and Child Health in the United Kingdom strongly advocated adoption of an early warning system to identify critically ill parturients.[6] Though numerous such screening tools exist,[7] they are primarily designed for nonpregnant patients, and do not consider the physiological changes of pregnancy. To address this concern, the National Partnership for Maternal Safety in the United States proposes the use of Maternal Early Warning Criteria which is similar to the Modified Early Obstetric Warning System in the United Kingdom.[8] The goal of this proposal is to identify the sick parturient for prompt escalation of care, but the criteria are not specific for maternal sepsis.

Early recognition of sepsis is often difficult because of the significant overlap between normal maternal physiological parameters and early signs of systemic inflammatory response syndrome. Important work from Bauer et al using physiological data points from 87 studies involving pregnant women, established that a temperature $>38.1^{\circ}C$, respiratory rate >25/min, heart rate >107/min, mean $PaCO_2 > 32$ mm Hg, and a WBC $>$ 18,000 were highly likely to be abnormal during pregnancy.[9] These findings are consistent with the Modified Early Obstetric Warning Score and the Maternal Early Warning criteria, though these criteria are not specific for sepsis. Because of this overlap with normal physiology, most screening tools have a disproportionately high number of false alarms and a poor positive predictive value (PPV). For example, Modified Early Warning Score and systemic

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inflammatory response syndrome criteria had a PPV of only 0.05% and 1%, respectively, in predicting disease progression and intensive care unit (ICU) admission in 913 parturients with chorioamnionitis.[10] The Sepsis in Obstetrics Score with a PPV of 16.7% compares favorably,[11] but remains to be validated in different practice settings. Sepsis-specific scores such as qSOFA (quick Sequential Organ Failure Assessment) have not been specifically validated in the obstetric population. Collectively, there is a critical need to optimize and calibrate early warning systems during pregnancy.

Management of Sepsis in Pregnancy

Management of sepsis during pregnancy is no different than management of nonpregnant patients, with some caveats. The key treatment principle is initiation of broad-spectrum antibiotic therapy within 1 hour after suspicion of severe sepsis (the Golden Hour). The choice of antibiotics is guided by the most likely pathogen and the severity of disease (Table 3). Several antibiotics have been classified by the US Food and Drug Administration by their safety profile in pregnancy. Health care providers caring for the septic parturient should be familiar with commonly prescribed antibiotics in pregnancy and their associated safety margin (Table 4). Blood cultures should be drawn prior to initiation of antibiotic therapy, and if facilities exist, serum lactate should be measured as early as possible. Serum lactate is an important and valuable biomarker to identify patients with suspected sepsis; a 1 mmoL/L increase in serum lactate was associated with a 2.34 increased odds of admission to the ICU in women with suspected sepsis either during pregnancy or the postpartum period.[12] Consistent with the new criteria for sepsis,[13] a lactate >2 mmoL/L should trigger escalation of care and a critical care consult. If serum lactate is >4 mmoL/L despite adequate fluid resuscitation (solution 20 mL/kg of crystalloid solution) and vasopressor therapy, it is recommended that a central venous line be placed to achieve a central venous pressure of ≥ 8 mm Hg (and a central venous oxygen saturation of $\geq 70\%$). Given the vagaries of obstetric practice and the limitations in managing critically ill patients on a labor

TABLE 3. Choice of Antibiotics During the Golden Hour

Critically Ill	Less Severe Disease
Invasive GAS/*Escherichia coli* β-lactam + gram-negative coverage + clindamycin ± flagyl If MRSA, teicoplanin or vancomycin	Broad-spectrum β-lactam

GAS indicates group A streptococcus; MRSA, methicillin-resistant staphylococcus aureus.

TABLE 4. Antibiotics and Their Safety Classification Profile in Relation to Pregnancy, According to the Food and Drug Administration

Pregnancy Category	Antibiotics
Category B- Labeled "safe" for maternal use in pregnant patients, showing no evidence of risk in humans	Amphotericin B, cephalosporins, daptomycin, fosfomycin, metronidazole, penicillins, merepenem
Category C- Must be given with judicious estimation of the potential risk to benefit ratio	Vancomycin, trimethroprim, floroquinolones, imipenem-cilastisin, sulfonamides
Category D- The following antibiotics show evidence of potential harm in pregnancy	Tigecyclin, tetracyclines, aminoglycosides

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and delivery floor, effective and aggressive management of sepsis is best achieved by involving intensivists and infectious disease specialists as early as possible.

Special Considerations

EARLY ICU INTERVENTION

The American College of Obstetricians and Gynecologists recommends "high-intensity ICU physician staffing" as a superior model in comparison to models where an intensivist consultation is optional. This underscores the importance of early critical care involvement, as a delay in diagnosis and involvement of intensivist care teams has been recognized as suboptimal care that directly contributes to maternal death. An emphasis toward multidisciplinary care, with coordination among multiple subspecialties, is advocated as an optimal model for care. In fact, experts have advocated for the reclassification of high-risk maternal care, often referred to as "obstetric critical care" to "maternal critical care."[14] The latter term is not confined to a specific specialty, as "critical care" accurately reflects the level of care provided. Given the acuity and increasing incidence of maternal sepsis, these broad terms may help encourage providers to seek early intensive care therapy. In addition, levels of maternal care as recently defined by the American College of Obstetricians and Gynecologists and the Society of Maternal and Fetal Medicine advocate for appropriate ICU resources for high-risk parturients, further prompting physicians to seek early ICU-driven multidisciplinary care. Factors that are associated with progression from sepsis to death during pregnancy include lack of timely antibiotic treatment (adjusted OR = 22.7, 95% CI, 3.64-141.6), maternal comorbidities such as anemia and immunosuppression (adjusted OR = 2.53, 95% CI, 1.23-5.23), and multiparity (adjusted OR = 3.57, 95% CI, 1.62-7.89).[15] It must be remembered that the ICU scoring systems to assess severity such as APACHE II (Acute Physiology and Chronic Health Evaluation II) and SAPS II (Simplified Acute Physiology Score II) are not designed for use in obstetric patients and hence it is difficult to assess illness severity or predict outcomes.[16] Normal physiological variables in obstetric patients are often scored as abnormal, and tests that are important in the assessment of preeclamptic patients (platelet count, liver function tests) do not influence the scores. In general, with the currently existing scoring systems, the predicted mortality rate is more often higher than the observed mortality rate.

STRATEGIES FOR MECHANICAL VENTILATION

Though the need for mechanical ventilation in pregnancy is rare, anatomic and physiological changes of pregnancy mandate modifications to standard ventilatory approaches. Hyperventilation should be avoided as it adversely affects uterine blood flow. Permissive hypercapnia, that accompanies ventilatory strategies to minimize iatrogenic pulmonary injury, has not been evaluated in pregnancy. Because chest wall compliance is reduced, higher inflation pressures may be required to achieve adequate tidal volumes. Unlike maternal hypoxia, the effects of maternal hyperoxia on the fetus are unclear; nevertheless, optimization of maternal oxygenation and acid-base status can be considered as appropriate surrogate end points to ensure fetal well-being. Ventilation in the prone position is unfeasible in this population, and hence simple measures such as left uterine displacement and/or left lateral decubitus position must be considered to improve ventilation-perfusion mismatch. Whether expedited delivery improves outcomes in

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pregnancy-related sepsis is unknown. In a series of such patients requiring mechanical ventilation for sepsis, Lapinksy et al[17] demonstrated that oxygenation index (FiO_2/PaO_2) and lung compliance improved within 2 to 5 hours after delivery of the fetus, but this was not accompanied by a significant improvement in the PaO_2/FiO_2 ratio.

ARDS in pregnancy should not be underestimated, as both antepartum and postpartum mortality rates in the pregnant population is ~23% and 50%, respectively.[18] Although the treatment of ARDS in obstetric patients remains largely the same as that in the general population, with low tidal volume ventilation representing a core strategy, key differences in obstetric physiology warrant slight adjustments to standard ventilatory approaches. These differences include: maintaining a SaO_2 of 95%, instead of 88% as compared to the general population for fetal oxygenation and well-being, limiting maternal hypercapnia to $PaCO_2 < 45$ mm Hg as a gradient of 10 mm Hg is required for fetal clearance of $PaCO_2$.[18] Given the rapid increase in minute ventilation during pregnancy, the standard ventilation of 6 mL/kg based on ideal body weight may potentially underestimate ventilatory demands in the parturient. If oxygenation goals are not met, respiratory rate can be increased before increasing the tidal volume. Most of our advances in ventilatory management of pregnant patients comes from managing the H1N1 influenza pandemic in pregnant women.[19]

USE OF ECMO IN PREGNANCY

The utility of ECMO, a form of portable cardiopulmonary bypass, deserves recognition as an adjunct for women with cardiopulmonary and respiratory failure, such as in ARDS. In general, 2 forms of ECMO exist, venoarterial ECMO, used in cardiorespiratory failure, and venovenous ECMO, used primarily for respiratory failure. After the H1N1 pandemic, ECMO has gained acceptance as a viable choice for managing cardiorespiratory failure during pregnancy. A recent review examining 31 published reports of ECMO use in pregnancy and in the postpartum period showed that the overall maternal and fetal survival rate was 80% and 70%, respectively.[20] More importantly, the rate of survival of pregnant patients is comparable to nonpregnant patients requiring ECMO support. The use of ECMO support in septic shock secondary to bacterial infection remains controversial, although previous reports have shown promising results in septic shock.

FETAL MONITORING IN THE ICU

Establishing the viability of the fetus (using antenatal records, ultrasonogram) is important in deciding the need for fetal surveillance. A previable fetus (< 23 to 24 wk depending on institutional practice) may not need fetal monitoring. As the fetal heart rate (FHR) is a direct reflection of the adequacy of uteroplacental perfusion, new-onset late decelerations and absence of baseline variability should prompt a thorough reevaluation of maternal cardiorespiratory status. In addition, care must be taken to exclude maternally administered sedative and analgesic drugs as the cause for altered FHR tracing. Because of the nuances of FHR monitoring, it may be prudent to have a labor and delivery nurse continually available at the bedside.

Conclusion

The incidence of maternal sepsis and related mortality is on the rise despite advances in medical care. Recognition of antenatal risk factors, early detection with early warning criteria and referral to the ICU, and prompt administration of broad-spectrum antibiotics are necessary. Early critical care intervention should not be underestimated, as experts now agree that multidisciplinary focused care, with

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an emphasis on high acuity intensivist staffing provides better outcomes. If fetal monitoring is continued in the ICU, a qualified labor and delivery nurse should be at the bedside to interpret changes in the FHR. Maternal sepsis is associated with an increased risk of perinatal mortality and preterm delivery. If mechanical ventilation is required, adjustments should be made to optimize pulmonary ventilation/perfusion mismatch. Expedited delivery shows promise in improving maternal respiratory parameters, but the need for such delivery has to be assessed as part of a multidisciplinary discussion. Finally, ECMO can be safely used for enhanced cardiorespiratory support during ARDS in pregnancy.

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