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Maternal Sepsis: Recognition, Treatment, and Escalation of Care

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Abstract

Purpose of Review The purpose of this article is to provide a brief review of maternal sepsis and the supporting literature for recognition and management.

Recent Findings Recent findings suggest that there is significant room for improvement in identifying patients at risk, expeditiously providing appropriate intervention, and developing action plans to best care for these patients and prevent morbidity and mortality.

Summary Improved education and understanding of the unique presentation of sepsis during pregnancy may help to improve detection, timely treatment, and expedite appropriate transfer to higher levels of care.

Keywords Sepsis · Maternal mortality · Maternal death · Septic shock · Postpartum period · Delayed diagnosis

Introduction

Maternal sepsis is currently the third leading cause of maternal mortality in the USA, accounting for 13% of all maternal deaths with a cause-specific maternal mortality ratio of 2.2 deaths per 100,000 live births [1]. Maternal sepsis is currently defined by the World Health Organization as a life-threatening condition with organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or in the postpartum period [2•]. Septic shock is a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with an increased risk of mortality than with sepsis [3].

Prior maternal sepsis estimates vary widely due to differing definitions and case ascertainment. The current definition of sepsis is more aligned with the prior definition of severe sepsis [4]. The reported incidence of sepsis based on the prior definition of severe sepsis is between 1 in 2000 to 10,000 deliveries [5, 6•, 7•, 8•]. There have not been any recent studies providing sepsis incidence data since the adoption of the new definitions for sepsis and septic shock in 2016 [3]. The incidence may be underreported because most studies rely on billing data using delivery hospitalization coding and do not capture all antepartum and postpartum cases [5, 6•, 8•]. The rates of maternal deaths from hemorrhage, hypertensive disorders of pregnancy, and anesthesia complications have decreased over time; however, the mortality rate of sepsis has not declined and remains around 11–13% over the last three decades despite the publication of Surviving Sepsis Guidelines starting in 2004 [1, 9].

The most common reported etiologies of maternal sepsis include chorioamnionitis, endometritis, genitourinary infection, pneumonia, and pyelonephritis. [7•, 8•, 10••] The most common reported pathogens in maternal sepsis include *Escherichia coli*, streptococcus, staphylococcus, and other gram negative bacteria [7•, 8•, 10••].

Mortality associated with maternal sepsis is potentially preventable. Findings from maternal mortality studies in North Carolina, Michigan, and Confidential Enquiries into Maternal Deaths and Morbidity in the UK and Ireland determined that modifications and/or improvements in care could have resulted in a better outcome [11••, 12, 13]. The Michigan case series of maternal deaths from sepsis specifically identified delays in recognition, treatment, and escalation of care contributed to the deaths from sepsis [11••]. This review will provide education to aid in recognition, treatment, and escalation of care in maternal sepsis.

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Recognition

Risk Factors

Sepsis is a diverse condition with multiple etiologies making it challenging to establish a definitive list of risk factors. However, there are some conditions that have been associated with a higher incidence of maternal sepsis in population studies (Table 1). The common associations across multiple studies were Medicaid insurance/public insurance, African American race, induction of labor, cesarean delivery, preterm delivery, multiple gestation, retained products of conception, stillbirth, operative vaginal delivery, postpartum hemorrhage, chronic liver disease, chronic renal disease, congestive heart failure, obesity, and anemia [5, 6•, 7•, 8•, 10••, 14]). Although cesarean delivery is often cited as a risk factor for sepsis, many of the database studies using administrative data are unable to determine if sepsis occurred before or after cesarean delivery or whether it was causally related. It is not uncommon for parturients with sepsis to require cesarean delivery to improve clinical status. In a retrospective study of pregnant women admitted to the ICU with sepsis/septic shock, 71% required emergent cesarean delivery mostly due to worsening respiratory status [15]. These studies highlight the numerous potential risk factors for sepsis, but make it difficult to determine a patient's actual risk because most patients will have one or more risk factors and will not develop sepsis. Conversely, it is important to note that sepsis often occurs in absence of risk factors and authors recommended that surveillance systems should be developed to help aid in disease detection [8•].

Table 1 Risk factors for maternal sepsis

Citation in two or more studies	Single study
Demographics	
Medicaid insurance	Less than high school education
African American race	
Obstetric Factors	
Induction of labor	Cerclage
Cesarean delivery	3rd or 4th degree tears
Preterm delivery	Episiotomy
Multiple gestation	
Retained products of conception	
Operative vaginal delivery	
Stillbirth	
Postpartum hemorrhage	
Comorbidities	
Chronic liver disease	Tobacco use
Obesity	Human immunodeficiency virus
Anemia	Systemic lupus erythematosus
Chronic renal failure	Recent febrile illness or antibiotics in 2 weeks prior to presentation
Congestive heart failure	

Screening Tools

Screening tools to identify patients at risk for developing sepsis can aid in early recognition and management. It has been recommended that qSOFA should be used for screening outside of the intensive care unit (ICU) [3]. The qSOFA score is a bedside assessment that can be repeated frequently that includes the following criteria: respiratory rate > 22 breaths per minute, systolic blood pressure < 100 mmHg, and altered mental status (Table 2) [3]. A recent systematic review criticizes the qSOFA criteria because although they are specific, they lack the sensitivity required to adequately identify all patients with sepsis [16]. The qSOFA score has also not been validated in pregnant women. In a prospective study of pregnant women with a known infection, qSOFA had a sensitivity of 36% and a specificity of 89% for sepsis. More importantly, none of the patients with maternal sepsis demonstrated mental status changes [17•]. A recent multicenter case-control study of maternal sepsis identified a sensitivity of 50% for qSOFA and a specificity of 95%. In addition, only 37.8% of patients had mental status changes [10••]. In pregnant women, it appears that even in the setting of sepsis, mental status changes do not commonly occur. Given the low sensitivity found in these two studies with very few patients exhibiting mental status changes, future research should be done prior to using qSOFA as a screening tool for sepsis in pregnant women.

Table 2 Screening tools for maternal sepsis

SIRS criteria
Temperature > 38 °C or < 36 °C
Respiratory rate > 20 breaths per minute or $PaCO_2$ < 32 mmHg
Pulse > 90 beats per minute
White blood cell count > 12,000 cells/mm^3 or < 4,000 cells/mm^3, or bands > 10%
qSOFA
Respiratory rate > 22 breaths per minute
SBP < 100 mmHg
Altered mental status
MEW criteria
SBP < 90* or > 160 mmHg
DBP < 100 mmHg
HR < 50 or > 120*
RR < 10 or > 30*
Oxygen saturation on room air at sea level < 95%*
Oliguria <35 mL/h or > or = 2 h*
Maternal agitation, confusion, or unresponsiveness*
Patient with pre-eclampsia reporting a non-remitting headache or shortness of breath

* Parameters consistent with the physiology of sepsis

The SIRS criteria are defined as two or more abnormal physiologic parameters of temperature > 38 °C or < 36 °C, respiratory rate > 20 breaths per minute or PaCO2 < 32 mmHg, pulse > 90 beats per minute, and white blood cell (WBC) count > 12,000 cells/mm^3 or < 4,000 cells/mm^3, or bands > 10%. The prior definition of sepsis required meeting criteria for SIRS in the setting of infection (Table 2) [4]. Due to physiologic changes of pregnancy, many healthy pregnant women will meet SIRS criteria without having an infection. A meta-analysis of over 8000 patients and 87 studies reporting heart rate, white blood cell count, temperature, respiratory rate, and $PaCO_2$ defined the expected range of values separated by first through third trimester, labor, and postpartum in healthy pregnant women and found that with the exception of temperature, SIRS criteria fall within the normal range [18]. A case-control study evaluating maternal sepsis screening tools found that SIRS criteria had a sensitivity of 93%, but a specificity of 63%. Although SIRS may identify more patients with sepsis than qSOFA, 37% of those identified did not have sepsis, leading to potential alarm fatigue if used as the screening criteria for sepsis [10••]. In contrast, qSOFA score may have better specificity for the actual diagnosis of sepsis [16].

The Maternal Early Warning Criteria (MEWC) is a set of parameters developed by the National Partnership for Maternal Safety to identify patients with impending maternal morbidity (Table 2) [19••]. Although this was not developed specifically to identify sepsis, the parameters were adapted to account for the physiologic changes of pregnancy. The goal of the MEWC is that once a patient meets one of the triggers, a provider is contacted in order to assess the patient and escalate care if needed. In the case-control study evaluating maternal sepsis screening tools, MEWC demonstrated a sensitivity of 82% and specificity of 87% in patients with maternal sepsis [10••]. A state of Michigan case series of maternal deaths due to sepsis reported that 75% of the patients who died met the MEWC with presenting vital signs [11••]. In several cases, just one criteria was abnormal rather than derangements across multiple parameters. Importantly, the study noted that only a small fraction of the women who died from sepsis presented with a fever [11••]. One of the major points of this study is that abnormalities may be subtle but that failure to recognize sepsis in pregnancy is common and can be fatal. If the care teams had been alerted to these abnormal vital signs, there may have been an opportunity to recognize and diagnose maternal sepsis, escalate care, and promptly initiate treatment. Although there is no way to test if the outcome would have been different for these cases, it is intuitive that it would be helpful to receive an alert of abnormal parameters to identify women at risk on the labor and delivery ward.

Treatment

Antibiotics

The treatment of sepsis is time sensitive and calls for early administration of antibiotics. The Surviving Sepsis Campaign recommends administration of IV antibiotics as soon as possible and within 1 h for both sepsis and septic shock [20••]. In a case series of maternal deaths in the state of Michigan, only 13% of pregnant patients who died from maternal sepsis received appropriate initial antibiotic coverage and even after ICU or infectious disease specialist consultation, only 67% of patients received antibiotics appropriate for the clinical situation [11••]. These findings suggests that there is significant room for improvement for providing timely and correct antibiotic therapy in this group and that it is imperative for improved survival outcomes. In a retrospective case-control study of maternal sepsis, patients who received antibiotics more than 1 h after diagnosis had double the mortality compared to those who received antibiotics within 1 h [10••].

Antibiotic coverage for maternal sepsis should be aimed at covering the most common bacteria: *Escherichia coli*, staphylococcus, streptococcus, and other gram negative bacteria [7•, 8•, 10••]. Cultures should be obtained promptly to identify the pathogen and tailor therapy but only if obtaining cultures does not delay antibiotic therapy [20••, 21]. Mortality is increased by 7.6% each hour delay in appropriate antibiotic administration in the general population [22]. Obstetric patients should receive prompt empiric combination therapy with broad-spectrum antibiotics. In a maternal sepsis review by Barton and Sibai, it was recommended to prescribe a regimen of vancomycin and piperacillin/tazobactam or a regimen of penicillin, gentamycin, and clindamycin as soon as possible within 1 h [21]. Given the number of group A streptococcal infections in this population (7–9%), it is important to consider combination therapy (i.e., two antibiotics of different classes/mechanisms aimed at the most likely pathogen) such as adding clindamycin to already existing gram positive coverage [7•, 10••]. Studies show mortality benefit with the combination of clindamycin and penicillin in streptococcal toxic shock infections as well as evidence that clindamycin may decrease toxin production [20••, 23]. In maternal septic shock, clindamycin use should be strongly considered.

Early antibiotic therapy with broad-spectrum antibiotics in critical on labor and delivery and requires a collaborative effort with other practitioners. Efforts to facilitate timely antibiotic therapy include increasing accessibility of broad-spectrum antibiotics by placing them in automated medication dispensing systems, providing adequate intravenous (IV) access, and engaging in closed-loop communication regarding ordering and administration of antibiotics [10••].

Resuscitation

Once a patient has been diagnosed with sepsis, the initial treatment and resuscitation should begin immediately with antibiotic therapy and fluids. Intravenous fluids should be administered for sepsis-induced hypoperfusion with at least 30 mL/kg of crystalloid solution within the first 3 h and subsequent administration of additional fluids as guided by hemodynamic assessment and monitoring [20••, 21]. Fluid responsiveness should be evaluated with dynamic indicators (e.g., pulse pressure variation, stroke volume variation, and/or IVC collapsibility) rather than static indicators (e.g., central venous pressure, pulmonary capillary wedge pressure) [24, 25]. A target mean arterial pressure (MAP) of 65 mmHg should be used and vasopressors may be required with norepinephrine as the first line recommended vasopressor of choice [20••]. Frequent assessment of physical exam and physiologic variables with non-invasive or invasive monitoring is necessary and clinicians should maintain a low index of suspicion for additional contributing factors to shock such as hemorrhage or cardiogenic etiologies [20••]. Providers should regularly assess volume status, cardiovascular performance, and vascular tone and manage abnormalities accordingly. It is suggested by the Surviving Sepsis Campaign Guidelines to guide resuscitation according to lactic acid levels [20••]. Lactic acid accumulates as a result of tissue hypoperfusion with a normal range of less than 2 mmol/L; the Surviving Sepsis Campaign recommends resuscitation to levels below 4 mmol/L [20••]. This value can be used in pregnant women with the exception that elevations in lactic acid may occur during normal labor. A meta-analysis of 1200 patients and 22 studies reported that in absence of labor, levels are expected to be within the normal range. However, the lactic acid levels can be within the intermediate range (2-4 mmol/L) during the first stage of labor, and above 4 mmol/L during second stage and time of delivery [26]. Lactic acid levels may be helpful to guide resuscitation during pregnancy except for the finite period of labor and peridelivery.

Escalation of Care

Delay in escalation of care was found in 53% of women who died of sepsis in a state of Michigan study of maternal sepsis deaths [11••]. The American College of Obstetricians and Gynecologists (ACOG) practice bulletin on Critical Care in Pregnancy recommended to consider ICU transfer using vital sign triggers from the taskforce for the American College of Critical Care Medicine [27]. The recommendation includes review of multiple objective parameters such as vital signs, laboratory values, imaging, electrocardiogram, and physical examination [27]. The vital sign parameters that are most relevant in the setting of maternal sepsis are heart rate > 150 beats/min, systolic blood pressure < 80 mmHg, and/or respiratory rate > 35 breaths/min [27]. In the setting of known infection, the Sepsis in Obstetric Score (SOS) is used to determine ICU admission in pregnant women based on measurements of temperature, systolic blood pressure, heart rate, respiratory rate, oxygen saturation, white blood cell count, percentage of immature neutrophils, and lactic acid [17•]. This score was prospectively validated to identify patients at risk and a score of six or greater had a negative predictive value of 98.6% for ICU admission [17•]. Providers may consider transferring a patient to the ICU with a score greater than six or worsening clinical status. There are now simple online calculators using this scoring system that use drop down values to calculate the score for increased accessibility [28].

Conclusions/Action Plans

Maternal sepsis remains a leading cause of maternal morbidity and mortality and presents a unique set of challenges including difficulty in recognition, delayed diagnosis, delayed antibiotic initiation, inadequate antibiotic coverage, and delay in escalation of the level of care. Education regarding the incidence, etiology, and risk factors for maternal sepsis is the first line for improvement in recognition. Protocols may help to increase detection with screening tools such as the MEWC and better identify patients to prompt early initiation of antibiotics. Early combination therapy with broad-spectrum antibiotics as well as infectious disease consultation is imperative to provide timely and appropriate antimicrobial coverage in patients with septic shock. In order to facilitate this initiative, it is important to ensure adequate IV access as well as the ability to provide antibiotics during off-hours with the help of the institution's pharmacy. Collaboration with nursing to ensure adequate education and knowledge of MEWC as well as the clinical pathways for treatment of sepsis may also facilitate appropriate sepsis management. Finally, further development and use of objective clinical criteria to identify patients with maternal sepsis is needed.

Compliance with Ethical Standards

Conflict of Interest Emily E. Naoum and Melissa E. Bauer declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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