MATERNAL

Maternal sepsis

María Fernanda Escobar, MD, MSc; María Paula Echavarría, MD; María Andrea Zambrano, MD; Isabella Ramos, MD; Juan Pedro Kusanovic, MD

Maternal sepsis is "a life-threatening condition defined as an organ dysfunction caused by an infection during pregnancy, delivery, puerperium, or after an abortion," with the potential to save millions of lives if a proper approximation is made. Undetected or poorly managed maternal infections can lead to sepsis, death, or disability for the mother, and an increased likelihood of early neonatal infection and other adverse outcomes. Physiological, immunologic, and mechanical changes that occur in pregnancy make pregnant women more susceptible to infections than nonpregnant women and may obscure signs and symptoms of infection and sepsis, resulting in a delay in the recognition and treatment of sepsis. Prioritization of the creation and validation of tools that allow the development of clear and standardized diagnostic criteria of maternal sepsis and septic shock, according to the changes inherent to pregnancy, correspond to highly effective strategies to reduce the impact of these conditions on maternal health worldwide. After an adequate diagnostic approach, the next goal is achieving stabilization, trying to stop the progression from sepsis to septic shock, and improving tissue perfusion to limit cell dysfunction. Management protocol implementation during the first hour of treatment will be the most important determinant for the reduction of maternal mortality associated with sepsis and septic shock.

Key words: maternal mortality, maternal sepsis, sepsis, sequential organ failure assessment

Introduction

In 2017, the World Health Assembly (WHA), the World Health Organization (WHO)'s decision-making body, adopted a resolution on improving the prevention, diagnosis, and management of sepsis. The WHA resolution recognized sepsis as a major threat to patient safety and global health, with the potential to save millions of lives if a proper approximation is made.[1] Indeed, the systematic analysis conducted in 2014 including 416 databases from 115 countries reported a total of 60,799 maternal deaths; of those, sepsis was the cause of death in 10.7% of the cases.[2] The reduction of maternal deaths is a priority for achieving the Sustainable Development Goals and implementing the United Nations Global Strategy for Women's, Children's, and Adolescents' Health, and it is critical for the strategies toward ending preventable maternal mortality[2]; despite being the third cause of maternal death, maternal sepsis receives less attention than other pathologies.

From the High Complexity Obstetric Unit, Department of Obstetrics and Gynecology, Fundación Valle del Lili, Cali, Colombia (Drs Escobar and Echavarría); Centro de Investigaciones Clínicas, Fundación Valle del Lili, Cali, Colombia (Dr Zambrano); Faculty of Health Sciences, Universidad Icesi, Cali, Colombia (Drs Zambrano and Ramos); Center for Research and Innovation in Maternal-Fetal Medicine (CIMAF), Department of Obstetrics and Gynecology, Hospital Sótero del Río, Santiago, Chile (Dr Kusanovic); and the Division of Obstetrics and Gynecology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile (Dr Kusanovic).

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Corresponding author: María Fernanda Escobar, MD, MSc. maria.escobar.vi@fvl.org.co

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Undetected or poorly managed maternal infections can lead to sepsis, death, or disability for the mother, and an increased likelihood of early neonatal infection and other adverse outcomes.[3] Approximately 8% to 12% of admissions of obstetric patients to intensive care units (ICUs) are because of sepsis.[4] Compared with other pregnancy complications, the case fatality rate of maternal sepsis is very high.[4,5] Sepsis with acute organ dysfunction had a mortality rate between 20% and 40% in high-income countries in the early 2000s, but more recent data indicate an overall rate between 8% and 14% in women with septic shock. The United Kingdom reported that 19.5% of pregnant women with confirmed sepsis evolved to septic shock and, of those, 1.4% evolved to death.[5] The reasons to explain this high mortality and morbidity in maternal sepsis are related to delays in the identification of cases and nonstandardized management. Indeed, for pregnant women, there is no agreement with the definitions of sepsis and septic shock from the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) in 2016.[2]

The effective prevention, early identification, and adequate management of maternal infection and sepsis can contribute to reducing the burden of infection as an underlying and contributing cause of morbidity and mortality. The objective of this review is to evaluate the evidence related to the definition, pathophysiology, diagnosis criteria, early warning systems, and management key points of sepsis during pregnancy. Specific fetal impact factors are beyond the scope of this review.

Definition of maternal sepsis

The incidence of sepsis in pregnancy is difficult to determine because the diagnosis is not always made owing to a lack of medical suspicion and standardization in the diagnostic criteria. Since 1992, several strategies have been

TABLE 1
Definition of systemic inflammatory response syndrome and sepsis by American College of Chest Physicians and Society of Critical Care Medicine

SIRS	Two or more of the following criteria: • Temperature >38°C or <36°C • Heart rate of >90 beats per min • Respiratory rate of >20 breaths per min or $PaCO_2$ of <32 mmHg • Abnormal white blood cell count (>12,000/μL or <4,000/μL or >10% bands)
Sepsis	Documented infection with 2 or more SIRS criteria
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension
Septic shock	Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities

$PaCO_2$, partial pressure of carbon dioxide; *SIRS*, systemic inflammatory response syndrome.

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proposed to make its diagnosis universal and optimize response time to attempt minimizing the damage and complications associated with this deregulated response.[2]

Definition of sepsis in nonpregnant individuals

In 1991, the American College of Chest Physicians and the Society of Critical Care Medicine (SCCM) established definitions for the spectrum of sepsis.[6] The terms systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome began to be used in clinical practice (Table 1). Since then, these definitions have evolved through the years according to the way this pathology was understood and approached (Table 2).[7]

The latest update of these concepts was presented in 2016 as Sepsis-3, which was characterized by an excessive focus around the concept of inflammation without having a continuum model from sepsis to shock and with an inadequate sensitivity and specificity reported for SIRS diagnostic criteria.[2,8] Having taken into account the limitations in the previous definitions, a taskforce with expertise in sepsis pathophysiology, clinical trials, and epidemiology was convened by SCCM and the European Society of Intensive Care Medicine. They concluded that sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection. For clinical operationalization, organ dysfunction is represented by an increase in the sequential organ failure assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock was defined as a subset of sepsis in which particularly profound circulatory and cellular or metabolic abnormalities were related to substantially increased mortality.[8] Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of ≥65 mmHg and serum lactate concentration >2 mmol/L (>18 mg/dL) in the absence of hypovolemia.[8]

Definition of sepsis in pregnancy

To diagnose maternal sepsis, a limitation has been established for a heterogeneous use of definitions and a diversity of recognition criteria in pregnant women.[9] This is why the WHO convened a consultation with experts in the field to analyze, formulate, and propose an update for the definition of maternal sepsis to be applied worldwide. With the information obtained from the bibliographic review, the new definition of maternal sepsis reflects the concepts included in the definition of the consensus Sepsis-3 in adults. The proposed new definition of maternal sepsis is "a life-threatening condition defined as an organ dysfunction caused by an infection during pregnancy, delivery, puerperium, or after an abortion."[10] This definition is useful for documenting confirmed cases of sepsis and allowing comparisons of the frequency of sepsis in different settings.

Pathophysiology of maternal sepsis

Physiological, immunologic, and mechanical changes that occur in pregnancy make pregnant women more susceptible to infections than nonpregnant women,[3] particularly during the postpartum period. Furthermore, from the beginning of gestation to the postpartum period, physiological adaptations to pregnancy and maternal efforts during labor may obscure signs and symptoms of infection and sepsis. This may result in a delay in the recognition and treatment of sepsis.

Changes in the cardiovascular system during pregnancy are profound and begin as early as the eighth week of pregnancy. Throughout gestation, the intravascular volume gradually increases by approximately 30% to 50% because of the effect of the renin-angiotensin-aldosterone system. In response, the maternal heart rate (HR) rises, reaching values of 10 to 20 beats per minute faster than the normal rate for an adult. By Frank-Starling law, the cardiac output (CO) can increase by up to 50%. This is achieved predominantly because of a greater stroke volume and, to a lesser extent, a rise in HR. An increase in stroke volume is possible owing to the early growth in ventricular wall muscle mass and end-diastolic volume (but not end-diastolic pressure) observed during pregnancy. The heart is physiologically dilated, and the myocardial contractility is enlarged. The peripheral vasodilatation is mediated by endothelium-dependent factors including nitric oxide synthesis and upregulated by estradiol and vasodilatory prostaglandins. Peripheral vasodilation leads to a 25% to 30% fall in systemic vascular resistance, causing a decrease in blood pressure (BP) between 12 and 26 weeks, increasing again around 36 weeks.[11]

TABLE 2
Definition of sepsis, 1991–2016

	Sepsis I-1991	Sepsis II-2001	Sepsis III-2016
Sepsis	Documented infection with 2 or more SIRS criteria	Unchanged	Life-threatening organ dysfunction caused by a dysregulated host response to infection
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension	Unchanged	Abandoned
Septic shock	Sepsis with hypotension, despite adequate fluid resuscitation	Unchanged	Sepsis accompanied by profound circulatory and cellular or metabolic abnormalities related to substantially increased mortality

SIRS, systemic inflammatory response syndrome.

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The adequacy of tissue oxygenation depends on the rate of oxygen delivered (DO_2) to the tissues and the rate of oxygen consumed (or oxygen uptake [VO_2]) by the tissues. Oxygen delivery is the volume of DO_2 per minute to the systemic vascular bed and is the product of CO and arterial oxygen concentration (including CaO_2). VO_2 is the amount of oxygen that diffuses from capillaries to the mitochondria. Tissue oxygenation is adequate when tissues receive sufficient oxygen to meet their metabolic needs. When the tissues do not receive enough oxygen, a cellular injury could potentially occur. VO_2 remains independent of DO_2 over a wide range of values, because oxygen extraction, which is the ratio of VO_2 over DO_2, can readily adapt to the changes in DO_2 until DO_2 falls below a critically low threshold. An abrupt increase in blood lactate concentrations then occurs, indicating the development of anaerobic metabolism.

Sepsis and septic shock are characterized by peripheral vasodilation associated with excessive release of proinflammatory mediators resulting in a decrease in systemic vascular resistance, effective intravascular volume, and tissue hypoperfusion. In the presence of inflammatory markers, oxygen extraction capabilities are reduced. In these conditions, VO_2 can become dependent on DO_2. In addition, sepsis causes a generalized response that is overexpressed by the host in case of infection. In the recognition of bacterial products, such as endotoxins and exotoxins, the immune system activates a cascade of proinflammatory mediators (eg, cytokines by macrophages), recruitment of inflammatory cells, and complement activation.[12–15] These events lead to widespread cellular injury with ischemia, mitochondrial dysfunction, apoptosis, immunosuppression, organ dysfunction, and death.

Diagnosis criteria

The Surviving Sepsis Campaign (SSC) criteria (Table 3) can be applied to the general population in the identification of serious cases, but they were not established for pregnant patients.[2]

In 2016, the task force of Sepsis-3 recognized that sepsis is a syndrome without, at present, a validated criterion standard diagnostic test. This group determined that there was an important need for features that can be identified and measured in individual patients and should identify all the elements of sepsis (infection, host response, and organ dysfunction). The term severe sepsis disappeared in the third consensus, and septic shock is now identified by the requirement of vasopressors to maintain a mean BP ≥65 mmHg or the presence of serum lactate >2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with a mortality rate greater than 40%.[16–19] The use of 2 or more SIRS diagnostic criteria to identify sepsis was unanimously considered unhelpful by the task force.[8]

The severity of organ dysfunction has been assessed with various scoring systems that quantify abnormalities according to clinical findings, laboratory data, or therapeutic interventions. The most common score used is SOFA (originally the sepsis-related organ failure assessment) (Table 4), which is not intended to be used as a tool for patient management but as a means to clinically characterize a septic patient.[6,7,12–14] The task force of Sepsis-3 recommended using a change in the baseline of the total SOFA score of ≥2 points to represent organ dysfunction. The baseline SOFA score should be assumed to be 0 unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. Patients with a SOFA score of ≥2 had an overall mortality risk of approximately 10% in a general hospital population with a presumed infection.[8]

Moreover, a clinical model developed with multivariable logistic regression termed quick SOFA (qSOFA) identified that 2 of any of the 3 clinical variables—Glasgow Coma Scale score <15, systolic BP ≤100 mmHg, and respiratory rate ≥22/minute—offered a predictive validity (area under the receiver operating characteristic curve, 0.81; 95% confidence interval [CI], 0.80–0.82) similar to that of the full SOFA score outside the ICU. The qSOFA provides simple bedside criteria to identify adult patients with suspected infection who are likely to have poor outcomes. Although the qSOFA is less robust than a SOFA score ≥2 in the ICU, it does not require laboratory tests and can be assessed quickly and repeatedly. The task force of Sepsis-3 suggested that the qSOFA criteria should be used to prompt clinicians to further

TABLE 3
Diagnostic criteria for sepsis and severe sepsis—Surviving Sepsis Campaign 2012

Infection, documented or suspected, and some of the following:

General variables	■ Fever >38.3°C ■ Hypothermia (core temperature <36°C) ■ Heart rate >90 beats per min or more than 2 SD above the normal value for age ■ Tachypnea ■ Altered mental status ■ Significant edema or positive fluid balance (>20 mL/kg over 24 h) ■ Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables	■ Leukocytosis (WBC count >12,000 IL^{-1}) ■ Leukopenia (WBC count <4,000 IL^{-1}) ■ Normal WBC count with greater than 10% immature forms ■ Plasma C-reactive protein more than 2 SD above the normal value and/or plasma procalcitonin more than 2 SD above the normal value
Hemodynamic variables	■ Arterial hypotension (SBP <90 mmHg, MAP <70 mmHg, or an SBP decrease <40 mmHg in adults or fewer than 2 SD below normal for age)
Organ dysfunction variables	■ Arterial hypoxemia (PaO_2/FiO_2 <300) ■ Acute oliguria (urine output <0.5 mL kg^{-1} h^{-1} for at least 2 h despite adequate fluid resuscitation) ■ Creatinine increase >0.5 mg/dL or 44.2 lmol/L ■ Coagulation abnormalities (INR >1.5 or aPTT >60 s) ■ Ileus (absent bowel sounds) ■ Thrombocytopenia (platelet count <100,000 IL^{-1}) ■ Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 lmol/L)
Tissue perfusion variables	■ Hyperlactatemia (>1 mmol/L) ■ Decreased capillary refill or mottling

Sepsis-induced hypotension

- Lactate above upper limits laboratory normal
- Urine output <0.5 mL kg^{-1} h^{-1} for more than 2 h despite adequate fluid resuscitation
- Acute lung injury with PaO_2/FiO_2 <250 in the absence of pneumonia as infection source
- Acute lung injury with PaO_2/FiO_2 <200 in the presence of pneumonia as infection source
- Creatinine >2.0 mg/dL (176.8 lmol/L)
- Bilirubin >2 mg/dL (34.2 lmol/L)
- Platelet count <100,000 IL
- Coagulopathy (INR>1.5)

aPTT, activated partial thromboplastin time; *FiO2*, fraction of inspired oxygen; *INR*, international normalized ratio; *MAP*, mean arterial pressure; *PaO_2*, partial pressure of oxygen; *SBP*, systolic blood pressure; *SD*, standard deviation; *WBC*, white blood cell count.

Adapted from Dellinger et al.[2]

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investigate for organ dysfunction, to initiate or escalate therapy as appropriate, and to consider increasing the frequency of monitoring or refer to critical care if such actions have not been undertaken already.[8]

Regarding the applicability of these scales in the obstetric population, a retrospective observational descriptive study conducted in a fourth-level clinic in Colombia compared SIRS diagnostic criteria and SOFA among 688 pregnant women who met the inclusion criteria for maternal sepsis (defined as 2 SIRS criteria plus infection). Patients with systemic compromise were admitted to the high complexity obstetric unit (HCOU), whereas those with multiorgan dysfunction were admitted to the ICU. At admission, the 4 diagnostic criteria for sepsis according to SIRS were positive in 431 patients (63%), 279 (65%) in the HCOU group and 152 (35%) in the ICU group. The SOFA test at admission was positive in 69 of 179 patients with complete data (39%). The concordance, measured using the κ statistic, between SIRS and SOFA was low (0.016). According to this study, the SIRS sepsis criteria have greater sensitivity than SOFA for the diagnosis of sepsis in pregnant women, which could aid the identification of patients requiring admission to the HCOU or ICU for early initiation of clinical management strategies.[20] This is very important given the high mortality rate associated with sepsis in the obstetric population. The use of the SOFA scale to diagnose maternal sepsis requires additional analysis with a clinical and public health approach, especially among low-income and middle-income countries where the availability of laboratory tests can be limited. In this study, only 39% of the cohort with the required data for calculation had a SOFA score $\geq$2. This scale is more specific and indicated a more

TABLE 4
Sequential organ failure assessment score

System	Score 0	1	2	3	4
Respiration					
PaO_2/FiO_2 mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular					
MAP	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dosage)[a]	Dopamine 5.1–15[a] or epinephrine ≤0.1[a] or norepinephrine ≤0.1[a]	Dopamine >15[a] or epinephrine >0.1[a] or norepinephrine >0.1[a]
Central nervous system					
Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/d				<500	<200

FiO_2, fraction of inspired oxygen; *MAP*, mean arterial pressure; *PaO_2*, partial pressure of oxygen; *SOFA*, sequential organ failure assessment.

[a] Catecholamine doses are given as g/kg/min for at least 1 hour.

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accurate correlation with the severity of the case than SIRS among patients with severe clinical dysfunction, especially those admitted to the ICU. In other words, a SOFA score ≥2 in an obstetrical patient definitely identifies a severely ill patient with a higher probability of extreme maternal morbidity and death. From a clinical perspective, this population was composed of patients who were truly ill and for whom investing clinical resources is mandatory for improving their survival. However, owing to the diagnostic difficulties previously mentioned and the importance of early management of pregnant women with sepsis, delaying the start of treatment for obstetric patients with positive SOFA could have detrimental results.[20] The identification of patients with sepsis under noncritical conditions through clinical systems with clear reproducibility in low- and middle-income countries may be the key to reducing mortality because of maternal sepsis.

Similarly, in the review of maternal sepsis published by the Society for Maternal-Fetal Medicine, it was emphasized that none of the definitions of sepsis consider the physiological changes that occur during pregnancy.[21] These changes can complicate the early identification of sepsis in pregnant women. In a systematic review conducted by Bauer et al,[22] the authors tried to define the normal ranges for pregnancy and puerperium of each of the SIRS criteria in 8834 healthy pregnant patients. The study showed that all current SIRS criteria are present in healthy pregnant women during the second and third trimesters of pregnancy, and during labor and puerperium, except for high temperature, suggesting that patients with a temperature >38°C persistent for >1 hour require complementary studies.[23] Therefore, SIRS criteria are not so applicable to pregnant women and its normal ranges need to be clarified in the obstetric population through further research, because it is possible that current SIRS criteria lead to over- or underestimating the diagnosis of an infection in pregnancy.

In 2017, the Society of Obstetric Medicine of Australia and New Zealand

TABLE 5
Obstetrically modified sequential organ failure assessment score

System parameter	Score 0	1	2
PaO_2/FiO_2 mmHg (kPa)	≥400	300 to <400	<300
Platelets, $\times 10^6$/L	≥150	100–150	<100
Bilirubin, mg/L	<20	20–32	>32
MAP	MAP ≥70 mmHg	MAP <70 mmHg	Vasopressors required
Central nervous system	Alert	Rousable by voice	Rousable by pain
Creatinine (μmol/L)	<90	90–120	>120

FiO_2, fraction of inspired oxygen; *MAP*, mean arterial pressure; *PaO_2*, partial pressure of oxygen; *SOFA*, sequential organ failure assessment.

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established the guidelines for the investigation and management of sepsis in pregnancy, and they recommended modifications in the diagnostic criteria according to the changes inherent to pregnancy.[24] For the qSOFA criteria, they proposed an obstetrically modified qSOFA, and maternal sepsis should be considered where 2 or more of the following are present: systolic BP ≤90 mmHg, respiratory rate ≥25/minute, or altered mental status. Based on the concept that the SOFA score has not undergone appropriate prospective validation in pregnant and postpartum women, this guideline recommends several modifications when applying the SOFA score to pregnancy (obstetrically modified SOFA) (Table 5). Future studies are needed for the validation of this interesting and pertinent proposal.

To help healthcare professionals, several tools have been designed including clinical, laboratory, and treatment indicators (early warning systems) to identify septic pregnant women at risk for complications.[10] These tools employ different variables for the recognition of abnormal vital signs, including HR, BP, respiratory rate, oxygen saturation, and temperature, allowing for timely identification of clinical deterioration, thresholds to foresee the need for specialized attention, or predicting mortality.[25] However, these tools do not work well to predict the risk of maternal sepsis or to identify women who may need early treatment or intensive care because of an infection.[25,26] The lack of information regarding the validation and normalization of data from pregnant or postpartum women limits the possibility of using these tools, particularly in low-resource settings. Therefore, applicable criteria are urgently needed to identify possible severe cases of maternal infection (presumed maternal sepsis) with sufficient anticipation in the clinical evolution to allow timely treatment and to optimize perinatal outcomes.

To determine the criteria needed to identify women with possible serious maternal infections (presumed maternal sepsis) and confirmed cases of maternal sepsis, the Global Maternal Sepsis Study (GLOSS) was undertaken to establish and validate diagnostic criteria for possible severe cases of maternal infection and to evaluate the frequency of recommended essential practices for the prevention, early identification, and management of maternal sepsis.[3] The results of GLOSS will be published this year.

Early warning systems

The rapid identification and early guided therapy of critically ill patients have reported better outcomes in terms of mortality if they are initiated by the emergency department.[25,26] In the general population, the use of early warning systems has been established for the detection of the degree of illness during the first 24 hours of hospital admission, which favors a rapid redirection of patients to the respective services and ensures early interventions, trying to rapidly define whether or not they require admission to the ICU.[26]

The aim of these scoring systems, specifically designed for groups of obstetrical patients receiving nonICU care, is to reduce maternal morbidity and mortality. Although some of these newly developed maternal warning systems are specific for particular maternal conditions (sepsis, eclampsia, and venous thromboembolism), others are more comprehensive.[27–34] Most of these maternal early warning scores have been developed retrospectively and need to be implemented prospectively.[22,26,28] Table 6 summarizes a comparison of some of these emergency classification scales.[28,35] The evaluation of the predictive power of modified obstetric early warning scoring systems (MOEWS) for the development of severe sepsis in women with chorioamnionitis was evaluated in a retrospective cohort study using prospectively collected clinical observations at a single tertiary unit. During the study period, 15,027 births were recorded and 913 cases of chorioamnionitis were confirmed (6.1%). Of this group, severe sepsis was observed in 5 women (0.5%; 95% CI, 0.2%–1.3%), including 1 maternal death. Interestingly, 364 cases with complete clinical data were included in the analysis using 6 MOEWS with different thresholds and clinical triggers. The sensitivities to predict severe deterioration ranged from 40% to 100% and the specificities varied from 4% to 97%. The positive predictive values were low

TABLE 6
Comparison of emergency classification scales applied in the obstetric population

	SOS	MEOWS	MEWS	REMS
Full name	Sepsis in Obstetrics Score	Modified Early Obstetric Warning System	Modified Early Warning System	Rapid Emergency Medicine Score
Specific for obstetrical population	Yes	Yes	No	No
Evaluated Parameters	Temperature (°C)	Temperature (°C)	Temperature (°C)	Age
	SBP	SBP	SBP	HR
	HR	DBP	HR	RR
	RR	HR	HR	MAP
	SpO_2 (%)	RR	RR	Glasgow Coma Scale
	White blood cell count	State of consciousness	State of consciousness	SpO_2 (%)
	% Immature neutrophils	% of oxygen required to maintain $SatO_2$ >95%		
	Lactic acid (mmol/L)			
Sensitivity, %	88.9	89	100	77.8
Specificity, %	99.2	79	77.6	90.3
PPV, %	16.7	39	4.6	11.1
NPV, %	99.9	98	100	99.7

DBP, diastolic blood pressure; *HR*, heart rate; *MAP*, mean arterial pressure; *NPV*, negative predictive value; *PPV*, positive predictive value; *RR*, respiratory rate; *$SatO_2$*, oxygen saturation; *SBP*, systolic blood pressure; *SpO_2*, peripheral oxygen saturation.

Adapted from Albright et al.[28]

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(ranging from <2%−15%).[26] In 2017, a study was published to prospectively validate the Sepsis in Obstetrics Score to identify risk for ICU admissions because of sepsis in pregnancy. They found that a score of ≥6 had a sensitivity of 64%, a specificity of 88%, a positive predictive value of 15%, and a negative predictive value of 99% to identify patients that will be admitted to ICU because of maternal sepsis.[34]

Another criterion that has been studied in cases of sepsis is the shock index (SI). This is the calculation of a ratio between HR and systolic BP, generating a value that provides rapid diagnosis and response to hypovolemic, cardiogenic, distributive, and obstructive shock events. Values between 0.5 and 0.7 normally represent patients without risk for shock in the general population. An elevated SI (>0.9) is associated with higher mortality secondary to hemorrhagic and septic shock.[36−38] However, because of the physiological hyperdynamic state of pregnancy, it could be common to have a higher SI than the established normal value.

Recently, normal SI values during pregnancy have been established. The range of the cutoff values of SI as gestation progresses is from 0.756 (±0.127) in pregnant women with ≤12 weeks of gestation, 0.795 (±0.132) from 13 to 20 weeks, 0.825 (±0.149) from 21 to 27 weeks, 0.831 (±0.144) from 28 to 32 weeks, 0.821 (±0.140) from 33 to 36 weeks, and 0.790 (±0.139) >37 weeks.[39]

SI was already studied as a form of rapid action to shock and septic shock in areas such as pediatrics and intensive medicine, obtaining promising results in the composition of a tool for rapid response and as a predictor of severity.[40,41] However, to date, it is still unclear whether SI can be an adequate tool for predicting the severity of sepsis in pregnant women[42] and whether it is possible that it can be a marker of severity for pregnant women that arrive at emergency units with sepsis. The search for diagnostic methods to trigger faster and more efficient responses in potentially severe cases of maternal sepsis is necessary because of the high morbidity and mortality related to the disease, which is most of the time treatable and curable.

Maternal sepsis treatment

The goal of maternal sepsis treatment is to start stabilization, try to stop the progression from sepsis to septic shock, and improve tissue perfusion to limit cell dysfunction. Therefore, at the beginning of the treatment, all patients with maternal sepsis must receive resuscitation standards for critical patients ensuring the ABCD sequence. There must be continuous monitoring of oxygenation to achieve oxygen saturation between 92% and 94% and establish

TABLE 7
First hour bundle—initial resuscitation for sepsis and septic shock

Bundle element
1. Measure lactate concentration. Remeasure if initial lactate is >2 mmol/L.
2. Obtain blood cultures before administration of antibiotics.
3. Administer broad-spectrum antibiotics.
4. Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L.
5. Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain mean arterial pressure ≥65mm Hg.

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advanced devices to secure the airway if necessary. Once the venous accesses are secured (at least 1 with angiocath number 16 or 18), laboratory tests must be taken to clarify sepsis diagnosis and severity of the condition according to multiorgan dysfunction.[2,3]

In the absence of evidence-based management recommendations regarding sepsis and septic shock during pregnancy, the best option likely is to follow the guidelines of general population management and apply the SSC guide.[43] In 2018, the recommendation for the implementation of an intervention's package during the first hour of management was published and called Hour-1 Bundle (Table 7).[44] This recommendation must be seen as an opportunity to update care quality by reducing the intervention time, which is essential in the management of patients with sepsis and septic shock. The following interventions are recommended during this period:

- Measure maternal blood lactate concentration.
- Obtain blood cultures before administering antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30 mL/kg crystalloid in case of hypotension or maternal blood lactate concentration ≥4 mmol/L.
- Apply vasopressors in case of hypotension during or after fluid resuscitation to maintain MAP ≥65 mmHg.

Although these interventions are key, the most important is to control the focus, trying to make a quick identification and drainage, if necessary (eg, abscesses or uterine evacuation in cases of endometritis).[8,45,46]

Lactate

Basal lactate concentrations in maternal blood are useful to identify patients at high risk for mortality because of infection. Lactate concentrations <2 mmol/L are correlated to 15% mortality, between 2 and 4 mmol/L to 25%, and >4 mmol/L to 40%.[47] In addition, the SSC suggests performing resuscitation to normalize lactate concentrations in patients with elevated lactate as a marker for tissue hypoperfusion (weak recommendation and low-quality evidence). Lactate is a more objective measure for tissue perfusion evaluation than physical examination and diuresis. At least 5 randomized clinical trials (647 patients) and 2 metaanalyses have evaluated the lactate-guided resuscitation of patients with septic shock, finding an important reduction in mortality when compared with resuscitation without lactate monitoring (relative risk, 0.67; 95% CI, 0.53−0.84; low-quality evidence).[48−54]

In 2019, the Andromeda-Shock randomized clinical trial was published, a clinical controlled trial performed in 28 ICUs in 5 countries with 424 patients in septic shock, in which the effectiveness of early resuscitation guided by peripheral perfusion evaluation (capillary refill time [CRT]) was compared with lactate-guided resuscitation.[55] This study did not find a significant mortality reduction in patients with septic shock whose resuscitation strategy was guided by peripheral perfusion (P=.006), but there was a clear tendency toward mortality reduction at 28 days in this group of patients. Nevertheless, based on this study, the use of CRT as a cost-effective strategy is reborn, especially in low- and medium-income countries, to guide precise resuscitation in patients with septic shock. The use of CRT in pregnant women needs to be validated.

Blood cultures

Sterilization of cultures can occur within minutes to hours after the first dose of the appropriate antibiotic.[56,57] Therefore, it is recommended to include blood cultures and cultures of the suspected focus of infection, including wounds, drains, and catheters in patients with suspected sepsis or septic shock (expert recommendation).[9] These routine microbiological cultures should include at least 2 sets of blood cultures (for aerobic and anaerobic bacteria)[58] and can be extracted at the same time. The plan to obtain cultures before the antibiotic treatment starts must be balanced with the mortality risk that the delay of antibiotic treatment in critically ill patients may produce.[59,60]

Broad-spectrum antibiotics

Among patients with sepsis and septic shock, survival decreases 7% per every hour of delay in antibiotic administration.[60] Reducing the time from admission to the administration of antibiotics is a measure of quality improvement in several institutions,[61] and some international societies such as the Infectious Diseases Society of America favor the elimination of specific time frames for antibiotic administration, proposing that their administration should be performed once sepsis or septic shock is suspected.[62]

The lack of implementation of proper empirical treatment in sepsis and septic shock is associated with a considerable increase in morbidity and mortality.[45,63−65] Consequently, the initial selection of antibiotic treatment must be broad enough to cover all possible microorganisms. This selection will depend on many factors, including the patient's medical history (eg, recent use of antibiotics and previous organisms), comorbidities (eg, pregestational

TABLE 8
Most common obstetrical and nonobstetrical infectious conditions

Obstetric conditions	Most frequent pathogens
Chorioamnionitis	*Ureaplasma urealyticum* and *Mycoplasma hominis*, *Gardnerella vaginalis*, Bacteriodes; group B streptococcus
Endometritis	Polymicrobial Peptostreptococcus, Bacteriodes, *Clostridium* spp, group B streptococcus, enterococcus, *Escherichia coli*, *Streptococcus pyogenes*, *Staphylococcus aureus*
Septic abortion	*Escherichia coli*, *Enterobacter aerogenes*, *Proteus vulgaris*, hemolytic streptococcus, Staphylococcus, and some anaerobic organisms (eg, *Clostridium perfringens*)
Puerperal mastitis	*Staphylococcus aureus*, MRSA
Nonobstetrical conditions	Most frequent pathogens
Wound infection	Group A b-hemolytic streptococcus, *Staphylococcus aureus*
Urinary tract infection	*Escherichia coli Klebsiella*, *Enterobacter* spp, Proteus
Respiratory infection	*Streptococcus pneumonia*, *Heamophilus influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumonia*, *Legionella pneumophilia*, Influenza A and B
Gastrointestinal infection	*Escherichia coli*, Enterococcus, Klebsiella, Enterobacter

MRSA, methicillin-resistant *Staphylococcus aureus*.

Escobar. Maternal sepsis. AJOG MFM. 2020.

diabetes and organ failure), immune defects (eg, HIV), clinical context (eg, infection acquired in the community or in the hospital), suspected infection location, presence of invasive devices, Gram stain data, and local prevalence and resistance patterns.[66–68]

The most common microorganisms that cause septic shock are Gram-positive and Gram-negative bacteria. Invasive candidiasis, toxic shock syndrome, and a series of rare pathogens should be considered in specific patients. Patients who acquire infections in the hospital are more likely to have sepsis owing to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*. In obstetrics, an increase incidence in group A streptococci infection cases since the 1980s has been reported, associated with high mortality especially in the postpartum period.[69,70] Table 8 summarizes the most common obstetric and nonobstetric infectious conditions and their respective etiological agents.[71,72]

However, because of the number of variables that need to be evaluated, it is not possible to provide a recommendation for a specific antibiotic scheme in patients with sepsis and septic shock. For most patients with sepsis but without septic shock, it is recommended to start empirical treatment with broad-spectrum antibiotics to cover most common microorganisms, such as Gram-positive and Gram-negative bacteria. If indicated, treatment should be initiated against fungi (eg, Candida) and rarely against viruses (eg, influenza). In cases of septic shock, the initial antibiotic treatment must be different. Frequently, a broad-spectrum carbapenem drug is used (eg, meropenem, imipenem, or doripenem) or a combination of extended-range penicillin and beta-lactam inhibitors (eg, piperacillin and tazobactam or ticarcillin and clavulanate). Third-generation cephalosporins can also be included, and the SSC suggests empirical polytherapy (weak recommendation and low-quality evidence).

It is recommended to adjust antibiotic treatment once the pathogen and antibiotic susceptibility are defined and proper clinical improvement is observed (expert recommendation). In situations where a pathogen is identified, a gradual reduction must be implemented to the most efficient antibiotic. However, in approximately one-third of patients with sepsis, the microorganism is not identified.[45,73] The reasons why there is no pathogen identification could include the following: (1) difficulty in obtaining samples (eg, need for an amniocentesis to obtain amniotic fluid); (2) low rate of bacterial identification with traditional culture techniques (molecular microbiological techniques, such as polymerase chain reaction, for microorganism identification in amniotic fluid are not available in most centers); and (3) cultures may have been obtained after the administration of antibiotics. If an infection is ruled out, antibiotic treatment must be timely interrupted to minimize the possibility of infection by an antibiotic-resistant pathogen or the possibility of having a drug-related adverse effect. Therefore, decisions regarding the continuation, reduction, or interruption of antibiotic treatment should be made on the basis of laboratory results and clinical response.

The optimal antibiotic dosage for patients with critical sepsis and septic shock (especially during pregnancy) has several considerations. Patients with sepsis or septic shock have a higher frequency of kidney and liver dysfunction. Perhaps what is most important regarding antibiotic dose administration is the increase of the volume of distribution of most antibiotics, in part because of the rapid expansion of extracellular volume because of aggressive rehydration. This causes an

unexpectedly high frequency of suboptimal pharmacologic concentrations of several antibiotics in patients with sepsis and septic shock.[46,74–77]

The duration of antibiotic treatment from 7 to 10 days is appropriate for severe infections associated with sepsis and septic shock (weak recommendation and low-quality evidence).[78–81] Longer treatments have been recommended in patients with slow clinical response, in whom it is impossible to drain the infection focus; bacteremia owing to *S aureus*; some viral or fungal infections; or immunologic deficiencies including neutropenia (weak recommendation and low-quality evidence).

Fluid treatment

The intravenous use of fluid for patient resuscitation is one of the key strategies of modern treatment, and its objective is to achieve rapid organ perfusion. The use of crystalloids as the preferred fluid for initial rehydration is recommended alongside the subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation and moderate-quality evidence). When patients require great quantities of crystalloids, the use of albumin may be allowed (weak recommendation and low-quality evidence).[82–88]

Fluid administration has been a strategy with the most contradictory evidence. Nevertheless, physicians attending obstetrical patients with sepsis need recommendations regarding the volume input when facing a medical emergency. SSC recommends initial rehydration with 30 mL/kg of crystalloids within the first 3 hours.[2] This fixed fluid volume allows the medical team to have the time for more specific information about the patient and, thus, to have a more precise measurement of her hemodynamic state.

Reevaluation of the patient must include a complete clinical examination and the assessment of physiological variables (HR, BP, blood oxygen saturation, respiratory rate, temperature, diuresis, and other variables) and the results of noninvasive or invasive hemodynamic monitoring, if available. SSC does not recommend the use of static measurements of left or right cardiac pressure and volumes (such as central venous pressure).[89–91] Dynamic measures have been proposed to assess whether a patient requires more liquids to improve fluid treatment and avoid fluid overloading by increasing systemic volume.[82]

To avoid fluid overload during resuscitation in pregnancy, one must take into account the intravenous infusions administered for maternal-specific conditions at the time, including magnesium sulfate and/or oxytocin, as part of the total volume to be replaced.[6,8,24]

Early use of vasoactives

MAP is the pressure that favors tissue perfusion. Although perfusion of critical organs, such as the brain or the kidneys, can be protected during systemic hypotension through regional perfusion self-regulation (below MAP threshold), perfusion turns out to be linearly dependent on BP. Therefore, SSC recommends a target MAP of 65 mmHg in patients with septic shock requiring treatment with vasopressors (strong recommendation and moderate-quality evidence). Resuscitation should also be performed to normalize lactate in patients with high lactate concentrations as a marker for tissue hypoperfusion (weak recommendation and low-quality evidence).

In patients with sepsis, the duration of hypotension increases mortality. Therefore, the early use of vasopressors during the first hour of admission is recommended. The first choice is norepinephrine (strong recommendation and moderate-quality evidence), especially because it increases MAP because of its vasoconstrictor effect, with little change in HR and less increase in systolic volume than dopamine.[92] The use of dopamine should only be considered in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (weak recommendation and low-quality evidence). SSC suggests adding vasopressin (a dose of up to 0.3 U/minute) to norepinephrine to increase MAP up to the desired value (weak recommendation and moderate-quality evidence) or adding vasopressin to decrease norepinephrine dosage in cases of septic shock (weak recommendation and moderate-quality evidence). Nevertheless, there is less evidence for the use of vasopressin during pregnancy, and there is a hypothesis of possible interaction of vasopressin with oxytocin receptors.[93]

There is a great debate regarding the use of vasopressors in the management of pregnant patients because of the risk of acute placental insufficiency.[94] However, because the placenta is a low-resistance system, the sustained fall in maternal BP and perfusion fall is a determinant of perinatal outcome. The safety profile of norepinephrine against epinephrine has been studied during human pregnancy, especially for BP maintenance during regional anesthesia for cesarean sections.[94,95] Therefore, the timely use of norepinephrine is indicated and must not be delayed in the presence of septic shock. During pregnancy, fetal monitoring could be a precise marker of maternal and fetal response to vasopressors and the maintenance of perfusion.

Postinfection myocardial dysfunction occurs in a subset of patients with septic shock.[96] In this situation, dobutamine is the inotropic agent of choice for patients with measured or suspected low CO in the presence of satisfactory left ventricle filling pressure and an acceptable MAP (weak recommendation and low-quality evidence). There are no contraindications for its use during pregnancy. The use of steroids (eg, intravenous hydrocortisone) for septic shock is indicated in patients responding to fluid management and vasopressor treatment without achieving hemodynamic stability. In this case, SSC suggests the use of intravenous hydrocortisone in a dose of 200 mg per day (weak recommendation and low-quality evidence).[2]

Management after the first hour of treatment

After the first hour, complementary measures must be initiated. Among them, control of the source of infection is key for patient recovery. The principles

of infection control in sepsis and septic shock include the fast diagnosis of the specific infection location and determining whether that infection is susceptible to control measures such as abscess drainage, debridement of infected necrotic tissues, extraction of a possibly infected device, and the definitive control of a continuous source of microbial contamination.[97] A target of no more than 6 to 12 hours after diagnosis seems to be adequate in most cases.[98−104] Observational studies often find less survival beyond that point. Therefore, any kind of source control intervention during sepsis and septic shock should be implemented as soon as possible after diagnosis. Clinical experience suggests that, without proper source control, some very severe cases will not be stabilized or improve despite the fluid and antibiotic treatments. Thus, prolonged efforts for medical stabilization before source control in critically ill patients are often not justified, especially for those with septic shock.[99]

Pregnancy considerations

Pregnant women with sepsis have a high risk of perinatal complications such as abortion, preterm birth, and fetal death, even in patients whose source of infection is not intraamniotic.[105−108] Alteration in tests of fetal wellbeing during admission do not state immediate termination of the pregnancy before stabilization of the patient, unless you are facing imminent fetal death. Leading a patient to a state of greater stress, such as termination of pregnancy, in the context of an unbalanced septic condition markedly increases the probability of maternal death. Unless the underlying cause of sepsis is the obstetric focus (chorioamnionitis), the presence of sepsis itself is not an indication for pregnancy termination.[6,24] In a population cohort study developed in the United Kingdom with 646 pregnant patients with severe sepsis, cesarean sections were associated with a higher risk of admission to ICU than patients with vaginal delivery (relative risk, 6.2; 95% CI, 4.9−7.8).[108] Therefore, indications to consider delivery are strictly obstetrical, and immediate birth must be because of an emerging condition that defines it.

Specific treatment of obstetrical conditions must not be delayed by resuscitation in sepsis; conversely, it should be instituted at the same time.[8,21,24] Regarding the use of steroids for fetal lung maturation, tocolysis, and magnesium sulfate, the obstetrical management guidelines,[24,109,110] and the consensus of Sepsis-3 recommend that the indication of these interventions must be established according to gestational age and in the context of an imminent preterm birth.[3,6,15]

Conclusion

Maternal sepsis is a condition associated with high mortality, which is very difficult to diagnose because of the physiological changes that occur during pregnancy, delaying the initiation of key interventions for the reduction of mortality. One of the main challenges is to create and validate tools for evaluation and rapid response in obstetrical emergencies. The addition to clinical practice of clear and standardized diagnostic criteria of maternal sepsis and septic shock, in addition to early warning systems, can be highly effective strategies to reduce the effect of these conditions on maternal health worldwide. This strategy, alongside management protocol implementation during the first hour of treatment, will be the most important determinant for the reduction of maternal mortality associated with sepsis and septic shock. ■

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