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REVIEW

Maternal sepsis - challenges in diagnosis and management: A mini-summary of the literature

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Sepsis is still one of the leading causes of maternal mortality and morbidity, being the third most common cause of maternal death, after hemorrhage and hypertensive disorders. Maternal sepsis may appear due to obstetric causes such as: chorioamnionitis, endometritis, abortion-related uterine infections, and wound infections. For non-obstetric causes of maternal sepsis, the most common are urinary tract infections and respiratory tract infections. This mini summary presents the challenges in early diagnosis and prompt management, caused by pregnancy physiological changes. Physiological alterations during pregnancy, like an increase in white cell count, heart rate, and respiratory rate, associated with a decrease in blood pressure are also known signs of infection, making the diagnosis of sepsis during pregnancy more difficult. The three pillars of sepsis treatment are early antibiotics, vital organ support and fluid therapy, the last one being controversial. A more restrictive approach for fluid resuscitation could be more suitable for pregnant women, considering the risk of fluid overload and pulmonary edema. Criteria for early recognition and appropriate management customized for maternal sepsis are mandatory.

Keywords: maternal sepsis, pregnancy, early diagnosis, maternal death

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Introduction

Worldwide sepsis remains one of the leading causes of maternal mortality and morbidity; despite the decrease in global maternal mortality [1], most of these cases are reported in low- and middle-income countries [2].

The burden of maternal deaths caused by sepsis is higher in low-income countries (10.7%), than in high-income countries (4.7%) [3]. However, it seems that the rate of maternal mortality and morbidity caused by infections is increasing in high-income countries [4].

The Third Consensus Conference highlighted the need for a revised definition of sepsis and new criteria for diagnosing sepsis, redefining sepsis as a: "life-threatening organ dysfunction caused by a dysregulated host response to infection" and developing a new set of criteria based on clinical identification of signs for the suspected infection [5], but normal physiological changes during pregnancy might significantly alter diagnosis criteria and the treatment response in case of maternal sepsis [6].

Recognizing the lack of focus and research in the area, in 2016 WHO created a consensus definition, based on international expert consultation and a systematic review: "Maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or post-partum period" [7]. This was the first step in reducing maternal mortality and morbidity due to sepsis by improving prevention, creating a pregnancy customized set of criteria for early identification and prompt management of maternal and neonatal sepsis. The last global evaluation regarding maternal sepsis during the Global Maternal Sepsis Study shows a ratio of severe maternal outcome related to infection/1000 live births of 15.1 (12.0–18.2) in low-income countries and 15.0 (11.8–18.3) in upper-middle income countries [8].

Causes and risk factors

Maternal sepsis may appear due to obstetric causes such as: chorioamnionitis, endometritis, abortion-related uterine infections, and wound infections. For non-obstetric causes of maternal sepsis, the most common are urinary tract infections and respiratory tract infections [9]. According to WHO Global Maternal Sepsis Study, conducted in 52 countries, the most common sources of infection causing severe maternal outcomes were endometritis, skin/soft tissue infection, and abortion-related uterine infection [8].

Risk factors associated with maternal sepsis are divided into two categories: obstetric-related risk factors: cervical cerclage; multiple gestations; stillbirth; prolonged rupture of membranes; instrumental birth; cesarean section; postpartum hemorrhage; retained products of conception and pre-existing maternal conditions such as: obesity; anemia; chronic hypertension; diabetes mellitus; immunosuppression [4, 10-12].

Microorganisms

The predominant pathogens in maternal sepsis are *Escherichia coli, Streptococcus agalactiae, Staphylococcus* spp., and other gram-negative bacteria [4, 10, 13-22]. There are numerous studies that identified *Streptococcus pyogenes* as the most causative bacteria when evaluating microorganisms implicated in maternal death related to sepsis, a significant percentage of these deaths occurring within 24 hours of admission [23-26]. Harris K. et al have shown in their systematic review regarding the outcome of puerperal

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group A streptococcal infections that the majority of these infections affect postpartum women, after vaginal birth at term. In almost a third of those cases sepsis occurred, with a burden of death of 2% [27]. There are cases described of anaerobic bacterial strains implicated in puerperal sepsis, such as *Actinomyces neuii* and *Clostridioides difficile* [28-30]. With the critically rising antibiotic resistance, low- and middle-income countries have the highest burden of infection with carbapenem-/polymyxin–resistant *Klebsiella pneumoniae*, *E. coli*, and *Acinetobacter baumannii,* resulting in a higher maternal and neonatal morbidity and mortality [31]. There are cases of maternal sepsis described, caused by *Candida* spp., the most common risk factors being preterm premature rupture of membranes, pregnancy with a retained intrauterine contraceptive device, and pregnancy resulting after in vitro fertilization [31-34].

Diagnosis

Pregnant women are excluded from most of the studies regarding sepsis due to the physiological changes that appear during pregnancy or due to fear of harm to the baby, when it comes to clinical trials [35]. Physiological alterations during pregnancy, like an increase in white cell count, heart rate, and respiratory rate, associated with a decrease in blood pressure are also known signs of infection, making the diagnosis of sepsis during pregnancy more difficult, changes illustrated in Table 1 [36-38]. Creating a new set of specific diagnostic criteria for maternal sepsis was mandatory for early recognition [39].

Screening tools were evaluated in order to create an algorithm for maternal early warning signs, nowadays scores like Systemic inflammatory response syndrome (SIRS), Quick sequential organ failure assessment (qSOFA), or obstetrically modified quick sequential organ failure assessment (omqSOFA) are used in early identification of maternal sepsis [6, 40, 41]. The modified version for maternal sepsis was proposed by Foller and Gibbs, taking into consideration physiological changes that appear during pregnancy and can alter the diagnosis of sepsis like systolic blood pressure, abnormal mentation, and respiratory rate [41]. Nowadays, there is no ideal diagnostic algorithm for maternal sepsis, qSOFA being recommended as a screening tool outside of the intensive care unit (ICU) [6].

Sequential (sepsis-related) organ failure assessment score (SOFA) is used for the diagnosis of sepsis, with the help of parameters to identify cardiovascular, renal, liver, respiratory, coagulation, or central nervous system dysfunction. A score of ≥2 indicates a suspicion of infection; a higher risk of mortality is associated with a high score [42].

Sepsis biomarkers such as procalcitonin, C-reactive protein and lactate are used in clinical diagnosis of infection. Even though lactate levels in pregnant women are belived to be consistent with the general population, during labour and puerperium these levels are expected to be elevated, but rarely above 4 mmol/l. This makes lactate monitoring an important key in evaluating severity of infection and outcome prediction in pregnant women alongside procalcitonin, that is a highely specific marker in evaluating bacterial infection [43, 44]. Culture remains the appropriate investigation for sepsis, but according to guidelines timely administration of antibiotics it's mandatory before receiving culture results in case of suspected sepsis [45, 46].

Antibiotics

Prophylaxis

Numerous guidelines and reviews emphasize the importance of obstetric prophylactic interventions like skin preparation and vaginal cleansing before caesarean section. The benefit of prophylactic antibiotics in circumstances such as caesarean section (ampicillin, first-generation cephalosporin, or second generation cephalosporin), premature or prolonged rupture of membranes, manual removal of the placenta, third- or fourth-degree perineal tears (a single dose of second-generation cephalosporin), and incomplete abortion is well known and documented [47-53]. The WOMAN trial, a secondary analysis, conducted to evaluate the risk of maternal sepsis for women undergoing treatments for postpartum hemorrhage that are invasive showed the benefit of prophylactic antibiotics [12]. Knight et al. found, after conducting the ADONE trial, the benefit of one dose of prophylactic antibiotic such as intravenous amoxicillin and clavulanic acid after operative vaginal birth [54].

Treatment

The "golden hour of sepsis" highlights the correlation between early initiation of antibiotic treatment and the out-

Table 1. Pregnancy physiological changes versus changes in sepsis

System	Pregnancy	Sepsis
Renal	Increased renal flow Increased glomerular filtration rate	Vasoconstriction Ischemia with renal reperfusion injury
Cardiovascular	Increase in heart rate Increased blood volume Aorto-caval compression Decrease in blood pressure	Vasodilatation Reduced vascular resistance Tachycardia
Respiratory	Decrease in pulmonary vascular resistance Increased minute ventilation Compensated respiratory alkalosis Decrease in residual volume	Increased pulmonary microvascular pressure Acute lung injury
Coagulation	Higher levels of factors I, II, VII, VIII, IX, XII Reduced protein S Elevated plasminogen activator inhibitors I and II	Procoagulant effects Higher thrombin production Reduced activated protein C

come of patients with signs of infection; with each hour of delay in antibiotic treatment the chance of sepsis survival is reduced by 7.6% [55]. Timely and correct use of antibiotics is mandatory to reduce the burden of maternal deaths caused by sepsis. It is recommended that empiric broad-spectrum antibiotics be administered as soon as possible, combined with fluid resuscitation, and correction of hypoxia [56-60]. Combined antibiotic therapy is preferred, but antibiotic stewardship is recommended for reducing the risk of multidrug resistance [56]. Thromboembolism prophylaxis is crucial, with both pregnancy and sepsis being risk factors for venous thromboembolic disease [61, 62]. There are controversies regarding fluid therapy, and it was shown that aggressive therapy can be harmful, the FEAST trial demonstrated that the administration of fluids in bolus can be detrimental for children with sepsis [63]. Previous studies have shown that for pregnant women a more restrictive fluid therapy could be even more appropriate, given the decrease in capillary oncotic pressure and reduction in levels of serum albumin [64]. It is considered that an aggressive fluid resuscitation can be fatal among pregnant patients, with a high risk of pulmonary oedema, as shown in the report from 2006 and 2008 published by The Centre for Maternal and Child Enquiries and in newer publications [65-67]. A more restrictive approach such as the intravenous administration of 1 up to 2 L crystalloid solutions is more appropriate for pregnant women, compared to at least 30 mL/kg of fluids administrated in the first 3 hours for non-pregnant patients with with suspected sepsis or septic shock [67, 68].

Fetal considerations

When evaluating sepsis in pregnant women, the decision to deliver the fetus depends on numerous factors regarding gestational age, the fetal status, the severity and patient's condition, and the source of infection. The aim is to treat the infection and to be able to prolong the pregnancy when it comes to prematurity if it's possible and the source of infection is not uterine [46]. Early-onset sepsis appears in neonates in the first 72 hours after birth, maternal transmission being incriminated in these cases. Studies show that the most frequent bacteria isolated are *Acinetobacter* spp., *K. pneumoniae* and *E. coli,* presenting carbapenem resistance of 32.6% for *K. pneumoniae* and 71.4% for *Acinetobacter* spp. [69, 70]. With an incidence of 22 per 1000 live births and a mortality of 11-19%, neonatal sepsis still does not have a consensus definition accepted internationally, making early diagnosis and prompt treatment even more difficult [71, 72].

Conclusions

Nowadays, sepsis is still a leading cause of both direct and indirect maternal deaths. To reduce the burden of maternal sepsis, it is mandatory to establish criteria for early diagnosis and prompt management of sepsis among pregnant, postpartum, or post-abortion women. This algorithm needs to be based on principles applied for non-pregnant patients, but taking into consideration the pregnancy physiological changes that can alter the criteria for diagnosis or the response to treatment.

Author's contribution

MAB (Conceptualization, Data curation, Investigation, Methodology, Writing – original draft)
AIC (Data curation, Investigation, Writing – review & editing)
SV (Conceptualization, Methodology, Writing – review & editing)

Conflict of interest

None to declare.

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