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Maternal sepsis is an evolving challenge

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Abstract

Despite major advances in the last century, particularly in high resource settings, maternal sepsis remains a common and potentially preventable cause of direct maternal death globally. A barrier to further progress has been the lack of consensus on the definition of maternal sepsis. Publications from two recent multidisciplinary consensus conferences, one on sepsis in the non-pregnant adult and the other on sepsis in the pregnant woman, concluded that the criteria for diagnosing sepsis should be clinically-based, applicable at the bedside, and should not be laboratory-based. Informed by reviews of the evidence, in 2017 WHO published a new definition of maternal sepsis based on the presence of suspected or confirmed infection. It also announced a Global Maternal and Neonatal Sepsis Initiative to identify the diagnostic criteria for the early identification, epidemiology, and disease classification of maternal sepsis. Standardizing the criteria for maternal sepsis optimizes clinical audit and research. It may facilitate the evaluation of the role of different clinical parameters and biomarkers in the diagnosis, earlier recognition and management of maternal infection and sepsis. Further work is required to develop an international consensus on the criteria for diagnosing maternal sepsis and any associated organ dysfunction.

KEYWORDS

Early neonatal sepsis; Maternal infection; Maternal infection complications; Maternal morbidity; Maternal mortality; Maternal sepsis; Maternal sepsis criteria; Obstetric early warning scores

1 | NEW GUIDELINES ON SEPSIS

In both low-income and high-income countries, sepsis is a common cause of death and consumes considerable healthcare resources. Maternal infection, particularly if left untreated or treated inappropriately, may lead to sepsis which is strongly associated with critical illness and an increased risk of premature death.[1]

In the past there was little consensus internationally about the definition of sepsis and, furthermore, the quality of clinical data was generally poor which hindered audit and research, particularly research on the early recognition and optimum management of sepsis. Over the last 30 years, two major factors have driven the need for better definitions.[2] First, there have been major technical advances in providing organ support in critical care units, particularly in well-resourced settings. Second, there is an increased awareness that the human and financial costs of critical illnesses due to sepsis are potentially preventable.

Following a Consensus Conference, in 1992 several North American and European intensive care societies published recommendations on the definition of sepsis and its management.[1–4] The Conference introduced the concept of the Systemic Inflammatory Response Syndrome (SIRS) based on the patient having more than one abnormal recording of the following parameters: temperature, heart rate, respiratory rate or $PaCO_2$, and white cell count. Sepsis was defined as SIRS plus infection. A second Consensus Conference by the societies a decade later revisited the definitions of sepsis and related conditions.[3] After discussion

it was agreed that, while unsatisfactory, the concepts of sepsis, severe sepsis, and septic shock should remain unchanged. It was also agreed that, while SIRS remained a useful concept, the diagnostic criteria for SIRS were overly sensitive and non-specific. The use of biomarkers to diagnose sepsis was considered premature. Revised international guidelines for the management of severe sepsis and septic shock were subsequently published in 2004, 2008, and 2012.[1–4]

In 2015–2016, a Third Consensus Conference of specialists representing 30 international organizations recommended a revised definition of sepsis.[4] The Conference decided unanimously that the use of SIRS criteria was unhelpful and should be abandoned. Studies had shown that SIRS is nearly ubiquitous in hospital patients and occurs in many benign conditions which are unrelated to infection.[2] Abnormal SIRS parameters are too non-specific to be helpful in diagnosing sepsis. Sepsis is now defined as "life-threatening organ dysfunction caused by a dysregulated host response to infection".[4]

The Conference recognized that sepsis was a syndrome without a validated standard diagnostic test, and this had been problematic in measuring incidence and mortality rates.[4] The syndrome is also determined by pathogen factors and by host factors which may evolve over time in an individual patient depending on the clinical management.

One scoring system for assessing the severity of organ dysfunction in the setting of an intensive care unit is the Sepsis Organ Failure Assessment (SOFA) scoring system based on oxygenation, platelet count, bilirubin level, mean arterial blood pressure, Glasgow Coma Score, and renal assessment (creatinine and urinary output).[4] An acute increase of >1 SOFA points could be used as a proxy for organ dysfunction.

Outside the intensive care unit setting, it was suggested that a quick SOFA (qSOFA) could be used to assess organ dysfunction.[4] This is based on two abnormalities out of three parameters that could be assessed at the bedside, namely, altered mentation, a systolic blood pressure less than 101 mm Hg, or a respiratory rate greater than 21/min. The qSOFA can be calculated quickly without the need for laboratory tests, particularly in resource-poor settings. However, SOFA or qSOFA scores have not been widely used outside a critical care setting and other scoring systems exist.

The Conference also recommended dropping the term "severe sepsis" and they redefined severe septic shock. They suggested that the new definitions be designated Sepsis-3. The latest consensus report from the Surviving Sepsis Campaign international guidelines is comprehensive and makes 89 recommendations for the early management and resuscitation of patients with sepsis or septic shock.[1] For the first time, pediatric guidelines will appear in a separate document. It is notable that the report, like all previous editions, does not make any recommendations specifically for pregnancy, but the guidelines are applicable for sepsis complicating infections in gynecology.[1]

2 | MATERNAL SEPSIS

Maternal sepsis was a common cause of death in the 18th and 19th centuries and resulted in half of reported maternal deaths in Europe.[5] Improved living conditions, the introduction of antibiotics, and advances in acute hospital care and medical specialization led to major reductions in critical illnesses and death associated with sepsis in the 20th century. Until recently, the main focus in preventing direct maternal deaths worldwide has been on improving the management of obstetric hemorrhage, pregnancy hypertension, and venous thromboembolism.[6]

At the start of the 21st century, however, maternal deaths due to sepsis in high-income countries were highlighted by individual tragedies and by national obstetric audits. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom for the years 2006–2008 found that, since previous reports, there has been a decline in the number of maternal deaths, predominantly as a result of a reduction in deaths from thromboembolism and, to a lesser extent, hemorrhage.[7] Despite this overall decline, there had been an increase in deaths due to genital tract sepsis, particularly from community acquired group A streptococcal disease.[7] Sepsis had emerged as the most common cause of direct maternal death in the UK.[7]

WHO estimated that the global prevalence of maternal sepsis is 4.4% among live births, with an incidence of 9–49 per 100 000 deliveries in high-income countries depending on the definition used and population studied.[8] There is a lack of data from low-income countries, but it is estimated that sepsis accounts for one in 10 maternal deaths globally. Furthermore, maternal sepsis is strongly associated with an increase in perinatal mortality and morbidity as a result of infection. These reports led to a renewed focus on maternal sepsis with the publication of national clinical guidelines, the development of obstetric early warning scores (EWS) to detect critical illness, the application of care bundles, and a growing awareness of the need to treat maternal infection early and appropriately.[7,9,10] Recognition of the need to reduce maternal mortality and morbidity in the USA resulted in the establishment of the National Partnership for Maternal Safety, which planned to develop Safety Bundles that focus on sepsis identification and treatment, as well as supplemental bundles on Maternal Early Warning Criteria.[6] The Partnership is collaborating with several national organizations including the American College of Obstetricians and Gynecologists.

One of the barriers hindering progress in the prevention and management of maternal sepsis has been the lack of consensus about definitions and the variety of terminology often used interchangeably. Thus, a systematic review of 78 citations and a multidisciplinary expert consultation were conducted in 2016, which led to the development of a consensus definition.[11] As a result, there is a new WHO definition of maternal sepsis: "a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, postabortion, or postpartum period".[11] This definition has been endorsed by a number of organizations including the Surviving Sepsis Campaign and the International Federation of Gynecology and Obstetrics (FIGO). As part of the consultation process, the majority of the experts were of the view that the definition of organ dysfunction should be adapted from the Sepsis-3 consensus for adults, and based on specific criteria for the obstetric population.[11] Experts preferred clinical markers over laboratory investigations, and preferred thresholds adapted to the obstetric population over those used for qSOFA.

In a previous systematic review and meta-analysis completed in June 2013 of 87 eligible studies, the normal range for each component

of the SIRS in healthy pregnant women was examined.[12] The review found that the normal range for physiological and laboratory measurements prepartum and postpartum overlapped substantially with SIRS criteria. In particular, the respiratory rate, $PaCO_2$, heart rate, and white cell count during a normal healthy pregnancy may meet the criteria for SIRS.[12] Thus, the SIRS criteria used to diagnose sepsis in the non-pregnant adult are not appropriate for use in diagnosing maternal sepsis. In particular, the review found a scarcity of data on the normal temperature during pregnancy, and there was difficulty establishing a normal white blood cell count during labor. The authors concluded that redefined criteria would be required to facilitate early diagnosis and to prevent adverse outcomes in women with maternal sepsis. It is also important to note that maternity EWS are designed to enable early identification of all critical illnesses and not just sepsis. Various parameters may differ in their sensitivity and specificity to identify abnormalities depending on the critical illness studied.

In Ireland, a Maternity Early Warning System (IMEWS) was successfully implemented in all hospitals in April 2014.[10] It was designated a system rather than a score to emphasize that it was intended to complement clinical judgment and not replace it. There was a concern that clinicians might focus solely on a score at the expense of the traditional history and examination. As part of the IMEWS, the SIRS criteria were adapted to allow for the physiological changes of pregnancy in respiratory rate, heart rate, temperature, and white cell count.[13]

In a retrospective evaluation of the customized criteria for the diagnosis of maternal sepsis compared with the standard non-pregnant SIRS criteria, women with proven bacteremia during 2009–2014 were reviewed.[13] Of the 93 women with bacteremia out of 52 032 deliveries, 61 (66%) had sepsis based on the standard criteria, in comparison with 52 (56%) based on the customized criteria (not significant). However, the standard criteria placed more emphasis on the finding of a leukocytosis, which could be physiological, while the customized criteria relied more on hyperthermia.

3 | MATERNAL INFECTION

Terminology, together with variations in the classification of infection, had been a barrier hindering progress in optimizing the management and audit of maternal sepsis. Some reports base classification on organisms, such as group B streptococcus, and others on the organ or system infected, for example, the urinary tract. Some base classification on the timing of infection in relationship to delivery—pre-, peri- or postpartum—and the time limit for postpartum infection can vary from 10 to 42 days after delivery.[7]

The diagnosis of maternal infection may not be confirmed microbiologically and also the organism identified on microbiological culture of a high vaginal swab, for example, may not be the organism responsible for infection. Isolation of an organism on culture may be the result of contamination rather than infection, for example, on blood culture. Some classifications are based on operative procedures such as surgical site infection after cesarean delivery.

There are variations in the definition of infection. Chorioamnionitis, for example, may be a clinical diagnosis or a histological diagnosis, and may or may not be underpinned by a positive microbiological culture. These variations in the diagnosis of maternal infection make it difficult to compare rates in different settings, and to compare clinical outcomes either in practise or in a research setting. It hinders both the validation of obstetric EWS in identifying infection and the evaluation of the effectiveness of therapeutic interventions.

The classification suggested is shown in Table 1. Maternal infection may be classified into three categories: infections specific to pregnancy; infections exacerbated by pregnancy; and infections incidental to pregnancy. These are mutually exclusive categories which are aligned with the WHO classification used worldwide of maternal mortality into direct, indirect, and incidental deaths.

The infections specific to pregnancy include chorioamnionitis and endometritis which occur anatomically at the same site. As well as treating the chorioamnionitis, consideration may have to be given to delivering the baby which may be challenging, particularly around the age of fetal viability. As well as treating endometritis, consideration may have to be given to exploring the uterine cavity for retained placental products which risks traumatizing the soft uterine wall. The presentation of chorioamnionitis and endometritis may be florid or subtle. They are both strongly associated with a history of rupture of the membranes and/or cervical dilatation. As the placental bed is highly vascular and closely related to the maternal circulation, maternal bacteremia leading to sepsis can develop quickly. The site of infection may not be obvious and is not visible to the eye. Microbiological cultures of the uterine cavity are technically difficult to obtain without contamination by vaginal flora, and the appropriate choice of antibiotics may not be immediately obvious.

TABLE 1 Classification of maternal infection aligned with WHO classification of maternal death.[9,14]

1. Pregnancy-specific infections
Chorioamnionitis
Endometritis
Lactational mastitis
Site of perineal trauma
Surgical site, e.g. cesarean
2. Infections exacerbated by pregnancy, including
Urinary tract infection
Influenza
Listeriosis
Hepatitis E
Herpes simplex virus
Malaria
3. Incidental infections, including
Lower respiratory trace infection
Tuberculosis
Sexually transmitted diseases

Adapted from Irish Maternity Early Warning System.[10]

The other three infections specific to pregnancy, that is, breast, perineal, and surgical site infections (for example, cesarean delivery site), are more common. The source of infection is visible to the eye and more obvious by the presence of localized pain, erythema, or discharge. Microbiological culture and the choice of antibiotics is usually straightforward. These infections rarely lead to maternal bacteremia or sepsis unless they are left untreated. Infections specific to pregnancy are strongly associated with a breach in the physical integrity of the skin, or a breach in the physical barriers of a closed cervix and intact gestational sac. When such breaches occur, prevention with antibiotic prophylaxis or the early treatment of infection is key to avoiding the onset of maternal sepsis.

It is known that pregnancy does not suppress the maternal immune system as previously thought, but rather modulates immunity. As a result, maternal susceptibility to certain infections are increased, for example, influenza, listeriosis, hepatitis E virus, herpes simplex virus, and malaria.[14] The evidence for increased susceptibility in pregnancy is more limited for measles and varicella.

Finally, maternal infections may be incidental to pregnancy, for example, lower respiratory tract infections. There are additional challenges with emerging infections incidental to pregnancy, particularly as women travel abroad more often to exotic locations. Further work is also required, therefore, on the definition of individual maternal infections.[15] It is suggested that a new classification of maternal infection aligned with the WHO classification of maternal mortality will help determine the optimum parameters for the early recognition of sepsis complicating maternal infections.

4 | CONCLUSION

The recent WHO clinically-based definition of maternal sepsis is a welcome step forward. A standardized definition that can be applied at the bedside in all settings without recourse to laboratory investigations will improve epidemiological surveillance and evaluation of therapeutic interventions. There is still work to be done, however, in determining the optimum maternal parameters for the diagnostic criteria for both infection and sepsis which balances sensitivity with specificity. In evaluating new criteria, a distinction also needs to be drawn between diagnostic validation and prognostic validation. The early diagnosis and early commencement of treatment are both key in preventing the onset of maternal sepsis globally.[15]

AUTHOR CONTRIBUTION

The author is solely responsible for conceiving and writing the article.

CONFLICTS OF INTEREST

The author has no conflicts of interest.

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