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Recognition and Management of Maternal Sepsis in Low and Middle-Income Countries: What do we know and where are the Gaps?

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Abstract

Recognition and management of maternal sepsis continues to be a major cause of maternal mortality in low and middle-income countries (LMICs). A review of the literature on maternal sepsis was conducted using these electronic databases; Pubmed, Medline and Global Health. Shortcomings exist in the recognition, initial resuscitation and post-resuscitation monitoring and treatment of maternal sepsis. This is further complicated by a lack of trained healthcare professionals, adequate equipment and technologies, as well as intravenous fluids and antibiotics. International consensus on the identification and management of maternal sepsis in low-resource settings are lacking. The key to maternal sepsis management is timely recognition, aggressive resuscitation, antimicrobial therapy, source control, and continued monitoring and assessment. This review discusses ways of adapting research findings to maternal sepsis management where it is most needed in low and middle-income countries, which includes resuscitation via peripheral routes and reliance on clinical diagnosis. There is a need for low cost, technology advances to aid detection of sepsis and robust management pathways adapted to low-resource environments.

Abbreviations: HIC: High Income Country; LMIC: Low Middle Income Country; JAMA: Journal of The American Medical Association; WHO: Word Health Organisation; RCOG: Royal College of Obstetricians and Gynaecologists; SOFA: Sequential Organ Failure Assessment; EGDT: Early Goal Directed therapy; SSC: Surviving Sepsis Campaign.

Introduction

Globally, 62,000 maternal deaths a year can be attributed to maternal sepsis, making it a significant cause of preventable maternal mortality [1]. This is a particular problem in lower and middle-income countries (LMICs), accounting for 13.7% of maternal deaths in southern Asia and 10.3% in Sub-Saharan Africa [2]. This is in contrast to 4.7% in high-income countries (HICs) [2], where absolute numbers are magnitudes less between the years 2012-2014, 0.4 per 100,000 maternal deaths were due to sepsis in the United Kingdom [3]. Maternal sepsis, despite being among the three leading causes of maternal mortality [2], suffers from a lack of research and consensus regarding international guidelines on its recognition and management, particularly compared to other leading causes such as post partum haemorrhage and hypertensive disorders. To our knowledge there are no randomised controlled trials on the management of sepsis in pregnant and postpartum women, particularly on haemodynamic resuscitation, but also on antimicrobial therapy and source control. Yet it is well known that timely recognition is the most crucial step in severe sepsis management [4]. Therefore reliable, easy-to-use tools to facilitate diagnosis and timely management in LMICs are vital. This review is a critical analysis of recent developments in this field and their application to LMICs.

Methods

A review of the literature on maternal sepsis was conducted in 29th August to 23rd September 2016 using these electronic databases; Pubmed, Medline and Global Health. Search terms included 'maternal sepsis', 'puerperal sepsis', 'maternal mortality', 'low and middle-income countries', and 'low-resource setting'.

Results

The burden of maternal sepsis is greater in LMICs for several reasons. The widely known three delays model [5], which describes factors influencing maternal mortality, has been adapted for severe sepsis to identify delays in treatment after patients arrive at a health facility in resource-limited settings [6]. Delays in recognition, initial resuscitation and post-resuscitation monitoring, stem from shortages in drugs, equipment as well as trained health staff, who are often overworked and underpaid, and working in overcrowded and unhygienic health facilities. Whilst improvements in health systems are necessary in the long term, the development of specific guidelines for maternal sepsis management should be adapted in the interim for such resource-limited settings to overcome the third delay and prevent maternal deaths.

Pregnant and peripartum women are particularly vulnerable to infection due to physiological and immunological changes. Physiological barriers to infection are disrupted during labour when the cervix dilates, and at caesarean section through the abdominal wound, and women are at a higher risk of exposure to pathogens at the surgical site and in the endometrium [7]. This is confounded in a low-resource setting, where malnutrition, anaemia and HIV are more common and predispose women to sepsis [8]. Delivery in unhygienic conditions with untrained birth attendants, as well as delays in seeking and reaching healthcare is further factors. The single biggest risk factor is caesarean section, rates of which are increasing in some LMICs [9]. Other risk factors for the development of puerperal infections include multiple vaginal examinations in labour, prolonged rupture of membranes and obstructed labour [8] all of which are more common in understaffed low-resourced health facilities.

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The causes of puerperal infections include endometritis, wound infection, mastitis, urinary tract infection, and retained products of pregnancy from incomplete miscarriage and unsafe abortions. The latter is a growing problem in LMICs where access to family planning services is low [10]. Severe puerperal sepsis is commonly caused by beta-haemolytic streptococci group [11]. Without swift treatment, complications are common such as septicaemia, endotoxic shock, peritonitis and abscess formation, leading to surgery and future sub fertility.

Recognition

Timely recognition is the most crucial step in severe sepsis management; delayed treatment correlates directly with increased mortality [4]. A shortage in healthcare workers [12, 13], especially those trained in sepsis recognition, in addition to a lack of sepsis triage protocols in LMICs, delays appropriate management [14]. Physiological changes in pregnancy may mimic or mask early presentation of sepsis; both sepsis and pregnancy result in hyper dynamic circulation with tachycardia and hypotension [15]. This makes early recognition of sepsis in pregnant women more difficult, which is vital as fetal compromise is a direct result of maternal decompensation. Additionally, pregnancy causes respiratory alkalosis with mild compensatory metabolic acidosis, giving pregnant women less reserve to compensate for metabolic acidosis from sepsis [16]. For these reasons, caution must be taken when interpreting laboratory results and monitoring septic pregnant women.

The Word Health Organisation (WHO)developed guidelines for the diagnosis of puerperal sepsis (when two or more of the following are present pelvic pain; fever ≥38.5^{o}C; abnormal vaginal discharge abnormal smell of discharge; delay in the rate of reduction of size of uterus) [17]. As the diagnosis is clinical and can be checked quickly at the bedside, these guidelines are well adapted to the low-resource setting. The assessment of the patient's level of 'sickness' which includes low level of consciousness, high fever and rapid pulse is also useful. Whilst the assessment of septic shock is recommended, the WHO guideline does not offer any clinical criteria. These guidelines have not been updated since they were developed in 1992 by a technical working group of experts.

In contrast, sepsis guidelines developed for use in high-income settings, for example the Royal College of Obstetricians and Gynaecologists (RCOG) guideline for sepsis in pregnancy and pueperium [18, 19], lists a wide array of clinical criteria. Whilst it includes general signs and symptoms such as temperature, pulse and respiratory rate, it also includes inflammatory and tissue perfusion variables (white blood cell count and lactate) that are frequently not available in low-resource settings. Thus translation of these guidelines into clinical practice in different contexts is not practical.

In 2016 the Journal of The American Medical Association (JAMA) produced new guidelines on sepsis recognition, stating that organ dysfunction can be represented by a Sequential Organ Failure Assessment (SOFA) score of ≥2 [20, 21]. SOFA includes measurements of partial pressure of oxygen, platelets, bilirubin and creatinine [22]. JAMA defined identification of septic shock as persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥65mmHg and serum lactate >2mmol/L despite adequate volume resuscitation [20, 21]. Invasive arterial blood pressure monitoring is resource-intensive and impractical, and again laboratory measures are frequently unavailable in this setting.

LMICs must rely on basic equipment such as axillary thermometers, sphygmomanometers and pulse oximeters to diagnose sepsis. Even this equipment is often unavailable, poorly functioning or misused. Most recently simple scores have been created which take this into consideration. The Quick SOFA (qSOFA) criteria was developed, which encompasses altered mental state, systolic blood pressure ≤100mmHg, and respiratory rate ≥22 [20]. The presence of two of the three clinical variables offered a predictive validity similar to SOFA (P=0.55). The taskforce behind JAMA recommends the use of qSOFA to prompt healthcare professionals to further investigate for organ dysfunction, commence treatment and consider referral to critical care when available. These criteria could all be assessed in LMICs, yet caution should be exerted in applying these cut-offs, chosen for non-pregnant adults, to the pregnant population. Research is needed to ascertain whether qSOFA and peripheral perfusion assessment can also be used for maternal sepsis recognition.

The recently developed clinical toolkit for maternal sepsis by the UK Sepsis Trust provides a more accessible tool for diagnosis and management of sepsis in pregnancy and postpartum [23]. It comprises of a flow chart of signs of maternal sepsis, which incorporates cut-offs for heart rate, respiratory rate, blood pressure, oxygen saturations and urine output. Lactate is included but not essential in diagnosing maternal sepsis and initiating the Sepsis Six Pathway, which includes the administration of oxygen, intravenous antibiotics and fluids, measuring urine output, taking blood cultures and checking serial lactates. As the emphasis is on clinical diagnosis and prompt commencement of therapy, and the parameters are specific to the pregnant population, the toolkits could be easily adapted to the low-resource setting.

Studies have shown the effectiveness of assessing peripheral perfusion in identifying critically ill patients with organ dysfunction and elevated lactate levels [24]. Typical signs of reduced cutaneous microcirculation include cold and clammy extremities and prolonged capillary refill time [25]. Such criteria could replace the role of lactate measurement in the diagnosis and monitoring of organ perfusion in maternal sepsis when resources are unavailable.

Whilst toolkits to prompt diagnosis based on the clinical signs are beneficial, advances in technology may also help to accurately detect vital signs and alert the healthcare provider to action. Shock index (systolic blood pressure/pulse) has been identified as an accurate predictor of adverse outcome in women with postpartum haemorrhage in LMICs [26]. It has been incorporated, along with blood pressure and pulse into a new non-invasive vital signs monitor, the CRADLE VSA. This device was developed to fulfil the requirements by WHO for use in low-resource settings [27], with results shown on a traffic light alert system, a low power requirement and low cost [28, 29]. Future research will determine whether this device is beneficial for detecting shock as a result of sepsis [30].

Management

One of the main principles of sepsis management is early resuscitation with intravenous fluids and vasoactive drugs. Rivers et al was the first to show that early goal-directed therapy (EGDT) which involves early haemodynamic resuscitation - can significantly reduce severe sepsis mortality [31]. In an attempt to standardise treatment globally, critical care and infectious disease experts incorporated Rivers' protocol into management guidelines under the Surviving

Sepsis Campaign (SSC) in 2002 [32]. Health facilities globally have applied these guidelines, resulting in numerous reports of improved survival [33]. The RCOG adapted the SSC resuscitation 'bundle' into their guidelines in 2012, which includes obtaining blood cultures prior to broad-spectrum antibiotic administration within one hour of recognition, measuring serum lactate and administering intravenous fluids [19].

The use of SSC guidelines in the development of RCOG guidelines may be problematic for several reasons. Firstly, the Rivers et al study was conducted in a single urban centre (in a HIC) in non-pregnant septic adults and thus the management might not be appropriate in the pregnant population, given the physiological and immunological differences. For example, the use of filling pressures to predict the response to fluid administration could lead to fluid overload and mortality, particularly in pregnancy where the peripheral vascular resistance is low and intravascular volume is already high. Secondly, whilst subsequent non-randomised studies showed reduction in mortality after the implementation of EGDT [34-37], several multicentre randomised trials in HICs which followed illustrated that EGDT does not reduce mortality from sepsis [38-40]. There were also concerns that EGDT could increase the likelihood of admission to intensive care, possibly due to large volumes of fluid administration resulting in pulmonary oedema.

In the WHO guideline on puerperal sepsis, management of septic women at the village, healthcare centre and referral levels are discussed [17]. While the WHO states the volume of intravenous fluids that should be given (1L saline stat and 3L every 24hours), it does not discuss which evidence this is based on, nor how to assess for response. In a pregnant population, the threshold of going into fluid overload reduces; therefore aggressive intravenous fluid administration becomes more life-threatening. This may be of even greater concern in LMICs where tight fluid control and measurement of peripheral oxygen saturation (let alone central venous oxygen) may not be possible [19]. It may be beneficial for future guidelines to advice on clinical features such as mean arterial pressure, peripheral perfusion, urine output, and pulmonary and peripheral oedema for assessment of fluid status within management pathways.

Evidence is clear for the early administration of intravenous antimicrobials in patients with sepsis [41, 42] RCOG recommends the administration of high dose intravenous broad-spectrum antibiotics against Gram-negative bacteria and endotoxins from Gram-positive bacteria within one hour of suspicion of severe sepsis in pregnancy, such as a combination of intravenous piperacillin/tazobactam (4.5g 8-hourly) or a carbapenem (such as imipenem 0.5g 6-hourly, meropenem 0.5-1g 8-hourly orertapenem 1g once daily) plus clindamycin (0.6–2.7 g daily in 2–4 divided doses; increased if necessary up to 4.8 g daily) [18]. The WHO recommends a combination of ampicillin (0.5g 4–6 hourly), gentamicin (5-7mg/kg once daily) and metronidazole (0.5g 8-hourly) [43]. However, the selection of appropriate antimicrobials is particularly difficult in LMICs [44]; bacterial, parasitic, viral and fungal causes must be considered, particularly in HIV endemic regions [44]. A recent systematic review illustrated that HIV-infected pregnant and postpartum women had three times the risk of puerperal sepsis compared with non-HIV infected women. This risk increased to six-fold if the woman delivered by caesarean section [45]. Anti-retroviral therapy in pregnancy as well as prophylactic antibiotics during labour can substantially reduce this risk. Malaria is associated with anaemia, low-birth weight infants, stillbirth and maternal death. The WHO recommends intermittent preventative treatment during pregnancy in areas with stable malaria transmission with sulfadoxine-pyrimethamine (1.5g and 75mg at least twice during pregnancy) and insecticide treated bed nets [46]. Malaria in pregnancy is treated with quinine (20mg/kg loading dose then 10mg/kg 8-hourly) and clindamycin (450mg 8-hourly) in the first trimester, and artemisinin combination therapy such as artemetherand lumefantrine (80mg + 480mg twice daily for 3 days) in the second and third trimesters [47]. Viral infections such as herpes simplex virus may be treated with famciclovir (500mg twice daily), valacyclovir (1g twice daily), or acyclovir (400mg five times a day). Fungal infections may include cryptococcosisand pneumocystis jiroveci pneumonia, which are treated with amphotericin B (250 micrograms/kg daily gradually increased to 1mg/kg daily) and trimethoprim/sulfamethoxazole (120 mg/kg daily, avoid in 1st trimester) respectively [48]. Empirical use of antimicrobials should be guided by clinical presentation, local infectious disease patterns, pathogen spectrum, antimicrobial resistance, as well as availability [25]. Microbiological diagnosis of the causative organism is key to targeting specific antimicrobial therapy and minimising resistance [44]. Appropriate samples include blood, midstream urine and high vaginal swab [1, 44] for gram staining, culture and antibiotic susceptibility. When cultures are unavailable [25], collection of samples for microscopic analysis may still be useful.

Septic patients should be supported until their organs recover sufficiently to function independently. Continuing signs of organ dysfunction and persistent infection for more than 48-72 hours after commencing initial therapy suggests treatment failure [25], which commonly includes inadequate antimicrobial therapy and antimicrobial resistance [25]. Clinicians should be aware of this and seek alternative antimicrobial therapies. In addition, source control is key in maternal sepsis and includes the evacuation of retained products of conception, laparotomy (with hysterectomy if necessary) or an abortion following spontaneous miscarriage and intrauterine sepsis [1]. Infections from foreign devices are common in intensive care units in LMICs [49]. Frequent checks for signs of infection are necessary, which if suspected should be removed immediately.

The association between intrauterine devices (IUDs) and pelvic inflammatory disease is well known particularly in the first three weeks after insertion [50]. Whilst IUDs are one of the most effective forms of contraception, pregnancy can occur rarely. This carries numerous risks to both mother and child including spontaneous miscarriage, septic abortion, stillbirth, preterm birth and chorioamnionitis [51]. The WHO recommends that intrauterine devices should be removed in the first 12 weeks of pregnancy if the IUD strings are visible or can be retrieved safely from the cervical canal [52]. Whilst the removal of IUDs reduces the risk of chorioamnionitis, the risk is still higher than in non-IUD users. The probable mechanism is a reactive inflammation caused by the presence of a foreign body, which may result in a secondary infection [53]. Treatment is the same as discussed above, with particular attention on intravenous broad spectrum antibiotics and source control.

Conclusion

Growing research from developed and developing regions has suggested ways of overcoming shortcomings in healthcare systems in low-resource settings through the use of simple and low-cost technologies and methods. The evidence base on the recognition and management of sepsis in the pregnant and postpartum population needs expanding, particularly on haemodynamic resuscitation. Specific

protocols for maternal sepsis in low-resource settings need to be developed. Training of local healthcare professionals in the prevention, identification and management of maternal sepsis in LMICs is vital. Such efforts should reduce morbidity and mortality from maternal sepsis in the short term, whilst strengthening of healthcare systems should contribute further to improvements in maternal health in the long-term.

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