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## **Maternal Sepsis: Opportunity for Improvement**

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### **Short title**

Puerperal Sepsis

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## **Introduction**

Maternal sepsis is an important cause of maternal morbidity and mortality worldwide. Maternal sepsis can be a severe complication of pregnancy, which, if untreated, can rapidly progress along to shock and eventually death. Maternal sepsis is also associated with an increased risk of newborn death, with maternal fever intra partum increasing the odds of neonatal mortality approximately ten times.<sup>1</sup> A recent World Health Organization (WHO) systematic analysis of global, regional, and sub-regional estimates of the causes of maternal death found that sepsis accounted for 10.7% (5.9-18.6) of all maternal deaths.<sup>2</sup> Estimates varied between high-income countries (4.7%, 2.4-11.1) and low-income countries (10.7%, 5.9-18.6).<sup>2</sup>

The 2009-2012 MBBRACE United Kingdom (UK) Confidential Enquiry found that almost a quarter of the women who died had sepsis.<sup>3</sup> Think Sepsis, a key message from the report, advocates for key actions for diagnosis and management of sepsis at an early stage.<sup>3</sup> These include: timely recognition, fast administration of intravenous antibiotics and quick involvement of experts.<sup>3</sup> While there has been a decrease in the number of deaths due to genital tract sepsis (classified as 'direct'), sepsis due to other causes (classified as 'indirect') remains amongst the leading causes of maternal death in the UK.<sup>4</sup>

Despite the high burden of maternal morbidity and mortality from maternal sepsis, definitions remain unclear and there is conflicting data on associated factors and outcomes. As recently as February 2016, medical sepsis was re-defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.<sup>5</sup> As a consequence, maternal sepsis definitions are also

being re-examined. We discuss the newly launched WHO guidelines on peripartum infections and two recently published papers from the UK and US that attempt to examine these key issues.

### **Severe sepsis in women with group B Streptococcus in pregnancy: an exploratory UK national case–control study<sup>6</sup>**

As there have been no comprehensive studies documenting the incidence and epidemiological characteristics of maternal group B Streptococcus (GBS) sepsis in the UK, this study sought to assess the burden of disease and explore the associated maternal and newborn outcomes. It is a secondary analysis of all cases of severe GBS sepsis taken from a national data set of women with severe maternal sepsis from all causes identified over 1 year at all 214 consultant-led maternity units using the UK Obstetric Surveillance System (UKOSS).

Women were identified using clinical criteria for severe sepsis and laboratory confirmation of GBS. Clinical criteria was based on the Systemic Inflammatory Response Syndrome (SIRS) criteria with two modifications for pregnancy: heart rate >100 bpm (non-pregnant) and white blood cell count >17 000 (non-pregnant). There were a total of 30 cases; 7 confirmed by positive blood cultures and 23 presumed cases (defined as severe sepsis occurring in the context of positive GBS cultures from a non-sterile site, such as urine or vaginal swab cultures, where there was no other causal organism for the sepsis clearly identified and where the clinical staff caring for the women considered this to be the most likely cause of her sepsis). Of the 30 cases, 15 women were diagnosed antenatally and 15 women were diagnosed postnatally.

The overall incidence of severe GBS was 3.75 per 100,000. This was considerably lower than population surveillance studies from USA and Canada where the incidence were 12 and 41 per

100 000 respectively; however, these studies included all women with laboratory evidence of GBS infection, rather than the stricter clinical definition of severe sepsis applied here. The study could not cross check case identification with national laboratory data, which may have presented additional cases; however, crosschecking with national data showed that there were no deaths from maternal GBS. The study also acknowledges that the presumed cases could be false positives as another unidentified pathogen may have caused the infection, so the incidence may actually be over-estimated.

Antenatal severe GBS sepsis was associated with increased odds of delivery by Caesarean section compared to controls without sepsis [OR], with maternal compromise due to sepsis being the most common reason for Caesarean section. There was no maternal mortality but 23% had another maternal morbidity. There were higher odds of requiring ICU stay, longer hospital stay (median 6 days, range 2-39 days) and re-admission. Although, there were no stillbirths or neonatal deaths, there was an increased likelihood of preterm birth. The risk of infants developing sepsis (21%) was also significantly higher in severe maternal GBS cases.<sup>6</sup> However, this was lower than other studies, which could be due to a lack of correlation between severity of maternal and infant sepsis.

As numbers of cases were small the study had limited power to analyze differences between cases and controls in terms of risk factors and associations with pregnancy and newborn outcomes. However, the study highlights the importance of measuring *clinically significant* GBS and raises important questions about GBS in pregnancy. With the low incidence of severe GBS found in this study, consideration should be given to exploring the best approach for intrapartum antibiotic prophylaxis: treating all women with GBS (as in North America) versus a risk factor based approach for intrapartum antibiotic prophylaxis to women with GBS (as in the United

Kingdom). Future cost-effectiveness analyses could contribute further to this debate as well as being important to consider in vaccine development.

### **Maternal Deaths Due to Sepsis in the State of Michigan, 1999-2006<sup>7</sup>**

Little is known about pregnant and postpartum women who died of maternal sepsis in the United States and this case series sought to review maternal deaths due to sepsis in the state of Michigan by focusing on events leading to diagnosis, and identifying areas for improvement.

From 1999 to 2006, maternal deaths due to *all causes* of sepsis during pregnancy and up to 42 days postpartum were identified using the Maternal Mortality Surveillance records from the Michigan Department of Community Health Deaths occurring from another cause, but with sepsis as a contributing factor, were defined as “maternal sepsis contributing deaths”. Sepsis was defined as

During the study period, the rate of maternal death due to sepsis was 2.1 per 100,000 live births and the rate of maternal death due to sepsis and sepsis-contributing deaths was 2.9 per 100,000 live births. Of the 22 women who died due to sepsis, 13 presented to hospital with sepsis, 2 developed sepsis during hospitalization and 7 developed sepsis at home without admission to hospital for care. Two-thirds of the women died during the delivery period or post-partum but only 4 (18%) died from intrauterine infection; comparable to 19% of women in the UK.<sup>6</sup>

The study identifies three key delays that may have contributed to the deaths; delays in recognition of sepsis, administration of appropriate of antibiotics, and escalation of care.

Seventy-five percent of septic women demonstrated abnormalities in respiratory rate, heart rate,

oxygen saturation or blood pressure. Only 18% of women were febrile on presentation and 25% never developed a fever during hospitalization. Seventy-three percent of septic women presenting to hospital for care received initial antibiotics with inadequate coverage and 53% had a delay in escalation of care.<sup>7</sup> Clindamycin was underused in this population and was not used for any women with Group A Streptococcus.

The study period preceded the recommendation for Maternal Early Warning Criteria by the National Partnership for Maternal Safety.<sup>8</sup> It highlights the importance of utilizing these early warning trigger tools and acting upon them. The abnormalities in vital signs in the septic women would have triggered such a tool prompting evaluation by a physician or clinician and the initiation of diagnostic and therapeutic interventions. Interestingly, the first set of the Surviving Sepsis Campaign<sup>9</sup> was published during the study period but antibiotic selection was not improved following it.<sup>7</sup> The number of deaths at home in this study also raises questions about care-seeking in the community and the need for appropriate tools to improve detection in the community setting such as the efforts in the United Kingdom.<sup>10</sup>

### **WHO recommendations for prevention and treatment of maternal peripartum infections<sup>11</sup>**

The overall approach of these recommendations is to highlight and encourage effective practices that are underused and discourage practices that are either ineffective or potentially harmful.

While this guideline will be useful for health care professionals directly providing care to pregnant women, the primary audience is health professionals, managers and policy makers who are responsible for developing national and local health protocols and policies. The guideline is targeted to mainly low-income settings but is applicable to high-income countries as well.<sup>12</sup>

The guideline panel identified a set of principles of good clinical practice that are needed to optimise the effects of the interventions recommended in the guideline. For each recommendation or intervention, the guideline uses sub-headings such as benefits, harms and resource implications. Systematic reviews were used to inform the recommendations and there is transparency regarding the quality of evidence.

The guideline uses the term “maternal peripartum infection” which was adopted to consider bacterial infections of the genital tract or its surrounding tissues occurring at any time between the onset of rupture of membranes or labour and the 42nd day post partum. This adapts the older WHO definition of “puerperal sepsis”<sup>13</sup> to include delivery-related wounds, and though the term “peripartum” tries to clarify the time-period of interest. However, although the definitions are clear, the terminology can still be easily misunderstood.

The main focus of the guideline is on the indications for antibiotic use and the panel acknowledges that generally the level of evidence is low and there are variations in practice across settings. Caesarean section was recognized as the most important risk factor for maternal infection in the immediate postpartum period. As such, the document offers strategies to prevent post-caesarean infections and addresses the use of antibiotics before skin incision versus after cord clamping. This guideline also makes recommendations on prophylactic antibiotics for minor uncomplicated procedures and obstetric conditions at high risk for infections such as third or fourth degree perineal tears.



Despite the very low quality evidence to support comparative effectiveness of one antibiotic over another to treat maternal infections, the current guideline conditionally recommends specific classes of antibiotics for the management of chorioamnionitis (ampicillin and gentamicin) and postpartum endometritis (clindamycin and gentamicin), but the panel acknowledged that other simple, effective, and locally available antibiotics could be used as an alternative.<sup>12</sup>

What this leaves out is all the other women who become septic: the women antenatally, the women with intact membranes and the women who have non-bacterial sepsis. I think the paper should mention this, so that the authors are clear about targeting a specific group of women, in poorer countries perhaps the majority of women who die, but in richer countries many women with sepsis are not in these groups

## **Conclusion**

Sepsis is a significant cause of maternal and perinatal morbidity and mortality around the world including in high-income countries. These articles emphasize the need for better recognition, early diagnosis and appropriate treatment of maternal sepsis. They also advocate for the introduction and implementation of guidelines and early warning trigger tools.

Key research priorities include the need for large studies to explore approaches to GBS screening and treatment as well as the impact of these approaches on pregnancy and neonatal outcomes. Confidential enquiries, maternal death audits and population-based cohorts can be used to evaluate the impact of national level sepsis campaigns and strategies as well as trigger tools.

Finally, implementation of the WHO guidelines should be monitored at health facility, regional, and country levels, using clearly defined indicators that are associated with locally agreed targets.

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