



Full length article

Development of a novel bedside index for the early identification of severe maternal infection



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ARTICLE INFO

Article history:

Received 2 November 2018
Received in revised form 23 January 2019
Accepted 25 January 2019

Keywords:

Obstetric early warning scores
Maternal critical illness
Sepsis

ABSTRACT

Objectives: International consensus reports have recently recommended that the Systemic Inflammatory Response Syndrome (SIRS) criteria for the diagnosis of sepsis should cease and that new bedside criteria need to be developed to improve prevention, early diagnosis and treatment.

The aim of this retrospective audit was to evaluate a suite of four bedside clinical criteria, called the Early Maternal Infection Prompts (EMIP), in helping to identify women with a suspected severe infection who were admitted to a High Dependency Unit (HDU) in a large tertiary referral stand-alone maternity hospital.

Study design: The four EMIP criteria were decided based on existing national obstetric guidelines and a review of the recent literature on maternal critical illnesses. Cases were identified from the HDU registry for the three years 2015–2017. Individual charts were retrieved, and the four EMIP parameters were measured at the time of the clinical assessment that led to the HDU admission. Clinical and sociodemographic details were computerised for analysis.

Results: Of 73 women admitted with suspected severe maternal infection, the handwritten records were available in 69. The mean age was 31.3 years, 71% were multiparous and 26.1% were obese. Three quarters of cases were antenatal admissions. Infection was confirmed microbiologically in 56 (81.1%) of cases. There were no maternal deaths. There was no case of organ dysfunction diagnosed but two women required vasopressors to maintain blood pressure. Recordings of the maternal vital signs were not always fully completed before admission. In 69.1% (n = 47) of cases the temperature was elevated ≥ 37.5 C, in 81.2% (n = 56) of cases the heart rate was increased ≥ 100 bpm, in 51.9% (n = 27) cases the respiratory rate was increased ≥ 20 bpm, and in 25.4% (n = 17) cases the systolic blood pressure was ≤ 100 mmHg. At least one of the four EMIP criteria was abnormal in 91.3% (n = 63) of cases of suspected severe infection.

Conclusions: The audit confirmed that this bedside index has potential in helping to identify maternal infection early before sepsis develops. Prospective studies are required to evaluate the index in different settings, for different infections and at the different stages of maternal infection.

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Introduction

In 1992, a Consensus Conference defined sepsis in the non-pregnant adult as a clinical syndrome due to an infection associated with Systemic Inflammatory Response Syndrome (SIRS) [1]. Subsequently, a Conference in 2001, expanded the SIRS criteria for the diagnosis of sepsis to include laboratory parameters. These criteria were also used to underpin the development of

the Sepsis Six Care bundle which was developed as part of the Surviving Sepsis Campaign [1].

In 2016, the Sepsis Definitions Task Force updated the definitions of sepsis and septic shock [2]. Following a systematic review and meta-analysis which informed a Delphi process, a major change was the abandonment of SIRS [3]. Sepsis is now defined as infection plus life-threatening organ dysfunction, which is characterised by an acute change >1 point in the Sequential Organ Failure Assessment (SOFA) score [4].

The SOFA, however, is not suitable outside a high-resource setting and a new bedside index, the quick-SOFA (qSOFA), was proposed to help identify patients with suspected infection who are at risk of a poor outcome outside Intensive Care. The qSOFA

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requires at least two abnormal of the following three variables: respiratory rate ≥ 22 breaths/minute, systolic blood pressure ≤ 100 mmHg and altered mental state [4].

Although sepsis is a common cause of maternal morbidity and mortality globally, there was a lack of agreement about its definition. Considering the heterogeneity of the population of women with infection from demographics to phenotype, robust diagnostic criteria are difficult to capture [2,3]. This led to a lack of clarity about incidence, prevention, and management. These uncertainties also hindered research on critical care in obstetrics. Maternal sepsis was excluded from publications arising from the three Consensus Conferences [1,3]. The physiological changes in pregnancy of the respiratory rate, heart rate and white cell count meant that SIRS criteria have to be customised for pregnancy, although the optimum cut-off measurements remain uncertain [5].

Following a literature review and expert consultation, the Global Maternal and Neonatal Sepsis Alliance, supported by the World Health Organization (WHO), developed a consensus which agreed that “maternal sepsis is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period” [6]. This definition reflected the thinking embedded in the 2016 Sepsis-3 Consensus [7]. The Alliance agreed that criteria, preferably bedside based, need to be developed for the early identification of severe maternal infections.

The purpose of this retrospective audit was to evaluate a novel index of four bedside clinical criteria that could prompt the early diagnosis of severe maternal infection and potentially prevent the onset of sepsis in both a low-resource and high-resource setting. The criteria were selected based on the existing national Irish Maternity Early Warning System (IMEWS) and the recent literature [8].

Study design

The Hospital is one of the largest maternity units in Europe and is a tertiary stand-alone hospital which accepts pregnant women from all sociodemographic group. Clinical and sociodemographic details are computerised at the first prenatal visit and again after delivery.

National guidelines for the prevention and management of infection and critical illnesses are followed. The Hospital has, like all other maternity units in the country, implemented the Irish Maternity Early Warning System (IMEWS) for the early identification of critical illnesses in pregnant and post-partum women [8].

Our study included women admitted to the High Dependency Unit (HDU) with suspected severe infection in the three years 2015–7. There were no set criteria for admission and the decision to admit was taken on clinical grounds by a senior obstetrician. The women were identified from the HDU Register. The individual medical records were reviewed. Infections were classified according to the national Clinical Practice Guideline for Bacterial Infections Specific to Pregnancy [9]. There is also immediate access, if clinically required, to a nearby large acute hospital with an Intensive Care Unit (ICU).

The four criteria developed for the early identification of severe maternal infection were based on an adjusted qSOFA, a review of the literature, and the IMEWS guideline. The respiratory rate criteria was lowered to ≥ 20 bpm to allow for physiological changes in pregnancy as per the current IMEWS criteria [8]. The systolic blood pressure at ≤ 100 mmHg is that recommended by the qSOFA. The main purpose of identifying low blood pressure is to diagnose clinical shock due to infection. Obstetric early warning scores focus on hypertension for the early identification of preeclampsia. Using this cut off also facilitated comparison with qSOFA. Temperature \geq

37.5°C and heart rate ≥ 100 bpm were added to the qSOFA indicators. Temperature was reduced to 37.5°C from 38.0°C as a previous study of IMEWS found that not all cases of bacteraemia triggered a review based on the current parameters [10]. Heart rate > 100 bpm as per the current IMEWS (2014) was chosen to allow for the physiological changes in pregnancy. Altered mental status was excluded because a preliminary study of our data found that none of the women presented with a GCS < 15 and given the physiological changes of pregnancy, altered mentation is not an early feature of severe infection. The EMIPs index was completed retrospectively from the set of observations that prompted a review by a senior obstetrician and the decision that the women had a severe infection requiring admission to the HDU. As this was a clinical audit, approval by the Research Ethics Committee was not required.

Results

Of the 73 women admitted to the HDU with suspected severe infection, the case records were retrieved in 69. The characteristics of the study population are shown in Table 1. Of the 69, 75.4% were antenatal admissions, the mean age was 31.3 years, 71% were multiparous and 26.1% were obese. The causes of the suspected infection before HDU admission are shown in Table 2.

The results of the four Early Maternal Infection Prompts (EMIP) are shown in Table 3. One of the prompts was abnormal in 91.3% (n = 63) of cases, two in 80% (n = 53) and three or more in 33.3% (n = 23). The recordings of the maternal vital signs was incomplete in a number of cases. The respiratory rate was not recorded before HDU admission in 24.6% (n = 17) cases, temperature in one case, and systolic blood pressure in two cases.

There were six women (8.7%) admitted with a severe infection clinically who scored zero on the EMIP based on the parameters measured before admission. Of these 6 women, four were

Table 1
Characteristics of the study population.

Mean age (+/- SD) years	31.3 (+/- 6.33)
Nulliparas	29% (n = 20)
Obese	26.1% (n = 18)
Current smokers	8.7% (n = 6)
Irish-born	62.3% (n = 43)
Preterm deliveries	68% (15/22)
Caesarean deliveries	41% (9/22)

Table 2
Causes of suspected maternal infection (n = 70).*

Chorioamnionitis/ pPROM	24.6% (n = 17)
Post Caesarean section	15.9% (n = 11)
Influenza	15.9% (n = 11)
Urinary Tract Infection	15.9% (n = 11)
Respiratory Tract Infection	8.7% (n = 6)
Other	8.7% (n = 6)
Unknown	11.5% (n = 8)

PPROM = Prolonged preterm rupture of the membranes.

* Although total patients were 69, one woman was admitted with both chorioamnionitis and influenza, so the total number was 70.

Table 3
Abnormal parameters at the time of decision to admit woman to the High Dependency Unit because of suspected maternal infection (n = 69).

Respiration Rate ≥ 20 rpm	51.9% (27/52)
Temp ≥ 37.5 C	69.1% (47/68)
HR ≥ 100 bpm	81.2% (56/69)
Systolic BP ≤ 100 mmHg	25.4% (17/67)

admitted for monitoring after delivery for suspected chorioamnionitis. Two had infection confirmed subsequently. A fifth woman was admitted for observation after excision of a large cervical polyp at 12 weeks gestation who became pyrexial after admission to HDU. Vaginal swabs were positive for Group B beta-haemolytic *Streptococcus*. One woman admitted directly to HDU with normal vital signs after transfer from another hospital with prolonged preterm rupture of membranes

Of the 69 cases, altered mentation was not recorded in any case, a respiratory rate ≥ 22 breaths per minute was recorded in 33.3% ($n=23$) of cases and a systolic BP ≤ 100 mmHg was recorded in 24.6% ($n=17$). Only 10.2% (7/69) of women with suspected severe infection, therefore, met the qSOFA criteria for sepsis with >1 abnormal parameters.

Infection was confirmed on microbiological culture in 56 women. Microbiology cultures returned positive in 85 samples. Of the 17 cases of suspected chorioamnionitis, 14 were confirmed by either cultures or evidence of ascending infection on histology. On admission only 20 (30%) of cases had an abnormal (<4.0 or $>16.9 \times 10^9/L$) leukocyte count.

A total of 13 cases had no microbiological growth to confirm infection, 11 of these recovered well after intravenous antibiotic therapy, one was a case of suspected chorioamnionitis after miscarriage, and one was a woman admitted with suspected chorioamnionitis who had colitis. Five were already on antibiotics before the septic workup in HDU. Of these, two had negative blood cultures and septic workups. No woman was diagnosed with a disseminated intravascular coagulopathy and two required vasopressors to maintain blood pressure. The admission parameters of the women with confirmed bacteraemias were 54.5% (6/11) had a RR ≥ 20 rpm, 57.1% (8/14) had a temperature $\geq 37.5^\circ\text{C}$, 85% (12/14) had a heart rate ≥ 100 bpm, and 16% (2/12) had a systolic blood pressure ≤ 100 mmHg.

Of the 52 antenatal admissions, the time of delivery was related to the infection in 22 (42.3%) cases. The mean gestation at delivery was 28 weeks. Nine of 22 (41%) were delivered by Caesarean section, 11 (50%) had labour induced with a subsequent vaginal delivery, and 2 (9%) had a spontaneous vaginal delivery. Of the 22 antenatal admission that delivered while in HDU, 15 (58%) were preterm. One of the antenatal admissions was colitis. Of the 30 (57.7%) remaining antenatal admissions all recovered quickly after antibiotics. Five were transferred to the general hospital for consideration of respiratory support. Of the 17 postnatal admissions, 8 (11.5%) women recovered quickly after 48 h of intravenous antibiotics, 8 (11.5%) had a prolonged admission for antibiotics, and one was transferred to the general hospital for management of a pelvic abscess.

Discussion

This retrospective audit evaluated a novel suite of four bedside clinical criteria in identifying women with severe infection who were at risk of developing maternal sepsis. At least one of the criteria was positive in 91.3% ($n=63$) of cases immediately before admission to the HDU. Prospective studies are now required to evaluate this suite of criteria in different settings, to evaluate whether the measurements need to be adjusted to balance sensitivity with specificity, to evaluate the criteria for different infections and to determine whether pregnancy outcomes can be improved.

It is notable that the EMIPs criteria were more sensitive than the proposed qSOFA index in women with severe infection clinically, which may be explained if the qSOFA criteria only become abnormal in the later stages of infection. It has been acknowledged that SOFA and qSOFA may only be of benefit when used on patients

with a significant degree of organ dysfunction [7]. SEPSIS-3 may in turn exclude patients who are in the transition from non-severe to severe infection and who may yet not be unwell enough to have a low GCS, low blood pressure or high respiration rate. The concept of "Pre-sepsis" may be a useful in previously healthy critically ill pregnant women who compensate easily after infection [7]. If we delay interventions until there is some form of organ dysfunction, there is a risk that the implementation of treatment may be too late.

This study was limited because it is retrospective and the clinical observations were sometimes incomplete. Respiratory rate in particular has been previously documented as being a commonly omitted vital sign despite its usefulness as a predictor of critical illness [11]. Our study was also limited to the setting of a HDU in a stand-alone maternity hospital where the decision to admit was based on the clinical judgement of a senior obstetrician. Thus, our findings may not be applicable in other settings or in other countries.

While maternal infection during pregnancy is common, the woman may be asymptomatic with no changes in her vital signs, for example, a urinary tract infection diagnosed on culture of a mid-stream specimen of urine. In contrast, a maternal infection may be so severe that the woman does not survive long enough to be admitted to an ICU or HDU. Our study has the advantage of being confined to suspected maternal infections severe enough for a senior obstetrician to be concerned about sepsis developing.

There is also little consensus about the definitions and classification of maternal infections. In particular, chorioamnionitis may be diagnosed on clinical, microbiological, and histopathological grounds or a combination of the three. Clinically it may be florid or it may present subtly [9]. It is strongly associated with cervical dilatation and rupture of the amniotic sac thus placing the woman at high risk of septicaemia.

A retrospective American study analysed 913 women with chorioamnionitis [12]. It found that existing SIRS and Modified Early Warning Scores (MEWS) did not accurately identify women at risk of admission to ICU, sepsis or death. A subsequent report on the same cohort of women evaluated the performance of six different early warning systems specifically designed for obstetric care, but not including IMEWS [13]. The systems varied widely in terms of their thresholds, format and predictive power. All six performed poorly in predicting severe sepsis and, in general, it was over-detected. It concluded that further research was required into an effective standardised system.

In a systematic review and meta-analysis to establish the normal maternal range in healthy pregnant women for each component of the SIRS criteria, 87 studies including 8834 patients were included [14]. It found that the physiological values for respiratory rate, heart rate and white blood cell count but not temperature met the criteria for SIRS during the second and third trimesters as well as labour. It was concluded that novel criteria were required to facilitate early diagnosis and prevent maternal sepsis.

In the development of a standardised Irish Maternity Early Warning System (IMEWS), the maternal parameters on the chart were customised for pregnancy [10]. In a retrospective review of 93 women with proven bacteraemia, 66% ($n=61$) would have been diagnosed as maternal sepsis based on the SIRS criteria and 56% ($n=52$) based on the new customised criteria. However, the SIRS criteria were based usually on a leucocytosis which was physiological, whereas the customised criteria were based on a pyrexia or tachycardia. An advantage of the customised criteria was that the diagnosis could be made at the bedside without laboratory investigations. In practice, criteria based on bedside triggers should expedite the administration of intravenous antibiotics and improve pregnancy outcomes.

A major problem in clinically validating early warning systems for critical illnesses or sepsis complicating pregnancy is that existing scoring systems were developed for prognostic rather than diagnostic purposes, particularly in the setting of intensive care in academic hospitals [1–3]. It is now accepted that outside pregnancy the SIRS criteria are not fit for purpose and that new bedside criteria need to be developed to make the diagnosis of sepsis [15]. The Task Force concluded that although SIRS was not helpful in identifying patients with organ dysfunction, non-specific SIRS criteria still might help identify patients with infection [15]. Likewise, the World Health Organisation (WHO) concluded that new bedside criteria need to be developed to diagnose organ dysfunction with maternal sepsis [16].

Conclusion

However, this emphasis on sepsis may hinder the diagnosis and treatment of infections before organ dysfunction, and thus the opportunity for early intervention, particularly appropriate intravenous antibiotics, may be lost. Our audit shows that this novel bedside index has potential in identifying maternal infection early before sepsis develops. The results suggest it is more sensitive than the qSOFA score for maternal infection. Prospective studies are required to evaluate the index in different settings, for different infections and at the different stages of maternal infections.

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