

Characteristics and outcomes of obstetric patients with maternal sepsis requiring admission to a South African intensive care unit: A retrospective review

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Background. Maternal sepsis is a major cause of maternal mortality worldwide and constitutes one of the leading causes of preventable maternal mortality and morbidity. Puerperal sepsis following a caesarean delivery has been shown to be a leading cause of sepsis in women.

Objectives. To describe the epidemiology, risk factors, management interventions and maternal outcome of patients with maternal sepsis admitted to a South African (SA) intensive care unit (ICU) over a 2-year period.

Methods. We conducted a single-centre, retrospective review of data of 54 patients admitted to a tertiary referral ICU in SA with the diagnosis of maternal sepsis from 1 January 2015 to 31 December 2016. Clinical characteristics, management interventions and maternal outcomes of patients with maternal sepsis were described and assessed.

Results. There were 39 884 deliveries during the study period and 16 060 (40.3%) were by caesarean section (CS). Sepsis was diagnosed in 1.7% ($n=678$) of the patients and 8.0% ($n=54$) of these patients were admitted to ICU. The median (interquartile range (IQR)) maternal age was 30 (26 - 34) years. Sepsis post CS accounted for 50% ($n=27$), sepsis post vaginal birth for 12.9% ($n=7$), septic incomplete miscarriages for 24.0% ($n=13$), sepsis post preterm deliveries for 9.2% ($n=5$) and sepsis post exploratory laparotomy for ruptured ectopic pregnancy for 3.7% ($n=2$). Coagulase-negative *Staphylococcus* was the most commonly isolated organism. The median (IQR) duration of ICU stay was 4 (2 - 6) days. All patients required mechanical ventilation. The mean (standard deviation (SD)) duration of ventilation was 2.5 (1.7) days. More than a quarter of women (29.6%; $n=16$) required inotropic support, while 90.7% ($n=49$) required blood products and 9.2% ($n=5$) required renal replacement therapy. Complications in ICU were metabolic acidosis (46.3%), acute kidney injury (40.7%), coagulopathy (25.9%), circulatory shock (12.9%), acute respiratory distress syndrome (9.2%), cardiac arrest (9.2%) and abnormal liver enzymes (7.4%). Mortality was 11.1% ($n=6$).

Conclusions. Maternal sepsis remains a significant cause of morbidity and mortality. The identification of associated risk factors will help guide appropriate interventions.

Keywords. peripartum sepsis; critical illness.

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Sepsis is a major cause of maternal mortality and morbidity worldwide. Approximately 90% of all deaths related to pregnancy and childbirth occur in developing countries.^[1] Death rates due to sepsis are higher in Africa, Asia, and Latin America and the Caribbean than in developed countries.^[2] In the past three decades, efforts have been made by the World Health Organization (WHO) to standardise definitions of sepsis for the general adult population to address the difficulties around terminology in the field.^[3] According to the recent surviving sepsis campaign guidelines, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Peripartum sepsis is defined by the WHO as bacterial infection of the genital tract or its surrounding tissues occurring at any time between the onset of rupture of membranes or labour and day 42 postpartum in which two or more of the following are present: pelvic pain; fever; abnormal vaginal discharge; abnormal smell/foul odour discharge; or delay in uterine involution.^[4]

According to the confidential enquiry into maternal deaths, 28.1% ($n=100/356$) of women died owing to obstetric haemorrhage, 26.7% ($n=95/356$) died from hypertension, 12.6% ($n=45/356$) died from non-pregnancy related infection, 9.6% ($n=34/356$) died from medical and surgical disorders, 7.6% ($n=27/356$) died from pregnancy-related sepsis, 6.7% ($n=24/356$) died from anaesthetic complications, and 4.5% ($n=16/356$) died from pulmonary embolism between the periods of 2014 and 2016 in South Africa (SA).^[5]

Recently, the quick sepsis related organ failure assessment (qSOFA) score or the sepsis 3 consensus definitions have been used to identify patients at risk of sepsis and are at a higher risk of death in the hospital. The qSOFA score creates a standardised, numeric score that allows comparison of patient population groups and helps inform resource allocation and triage decisions. The score uses three criteria and assigns one point for low blood pressure (systolic blood pressure ≤ 100 mmHg), high respiratory rate (≥ 22 breaths per min)

or altered mentation (Glasgow Coma Scale (GCS) <15).^[6]

A large number of childbirths and pregnancy terminations still occur outside the healthcare system in developing countries. Additionally, health-seeking behaviour is also poor.^[7] Therefore, clinical data on patients presenting to the intensive care units (ICUs) with maternal sepsis are limited in developing countries. We aimed to describe clinical characteristics, management interventions and maternal outcomes of patients with maternal sepsis admitted to a tertiary ICU in SA.

Methods

The study population included all obstetric patients admitted to Chris Hani Baragwanath Academic Hospital (CHBAH) ICU diagnosed with maternal and peripartum sepsis by the treating intensivist. CHBAH is a 3 200-bed hospital located in Johannesburg, SA, with a maternity unit that delivers an average of 24 000 babies every year. Patients whose names were captured in the ICU admission record ledgers and whose files were found in the ICU records room from 1 January 2015 to 31 December 2016 with the clinical diagnosis of maternal sepsis as per the admitting physician were included in the study. Data collected included demographic data, obstetric clinical details, maternal comorbidities and clinical details during ICU stay (Table 1). No files were excluded.

The total number of patients admitted to ICU with maternal and peripartum sepsis during the study period was 54. The primary objective of the case series review was to determine maternal outcomes as defined by discharge from ICU or mortality of patients admitted with the diagnosis of maternal sepsis to CHBAH ICU. Secondary objectives were to describe the demographic and clinical characteristics of maternal admissions to CHBAH ICU with the diagnosis of maternal sepsis using the qSOFA score to identify risk factors associated with peripartum sepsis and the most common organisms responsible for peripartum sepsis.

Data were entered into a password-protected Excel database (Microsoft Corp., USA) and were analysed using the STATA software, version 14 (STATA Corp., USA). Bivariate analyses were performed using Fisher's exact and χ^2 tests. The primary outcome variable was mortality. Exposure variables included sociodemographic and clinical data. For descriptive and analytical

Table 1. Demographic and clinical characteristics of patients on admission

Characteristic	Died, n (%)		Fisher's exact p-value
	Yes	No	
Age, years			
<35	3 (7.1)	39 (92.9)	1.000
≥35	0	9 (100)	
Premature labour, GA (weeks)			
≤28	1 (5.9)	16 (94.1)	1.000
>28 - 37	1 (6.7)	14 (93.3)	
>37	1 (5.3)	18 (94.7)	
Weight (kg)			
<80	1 (4.2)	23 (95.8)	0.708
80 - 100	2 (9.1)	20 (90.9)	
>100	0	5 (100)	
Chronic comorbid disease			
No	3 (13.0)	20 (86.96)	0.090
Yes	0	27 (100)	
Prolonged rupture of membranes			
No	2 (4.3)	45 (95.7)	0.221
Yes	1 (25)	3 (75)	
Retained products of conception			
Uterine evacuation	3 (10.0)	27 (90.0)	0.265
No uterine evacuation	0	20 (100)	
History of pelvic or other infection			
Septic miscarriage	1 (4.6)	21 (95.5)	1.000
Puerperal sepsis	2 (7.1)	26 (92.9)	
Diabetes			
No	3 (6.1)	46 (93.9)	1.000
Yes	0	2 (100)	
Parity			
1	0	14 (100)	0.383
2	3 (14)	17 (85)	
3	0	10 (100)	
4	0	6 (100)	
Length of stay in ICU, days			
≤6	1 (2.4)	40 (97.6)	1.000
>6	0	8 (100)	
Anaemia			
No	1(14.3)	6 (85.7)	0.370
Yes	2 (4.7)	41 (95.35)	
MAP			
No	3 (7.3)	38 (92.68)	1.000
Yes	0	10 (100)	
Duration of ventilation, days			
<5	1 (2.4)	41 (97.6)	1.000
≥5	0	7 (100)	
Renal replacement required			
No	2 (7.1)	26 (92.9)	1.000
Yes	1 (4.4)	22 (95.7)	
Culture			
No	1(2.7)	36 (97.3)	0.179
Yes	2 (14.3)	12 (85.7)	

GA = gestational age; ICU = intensive care unit; MAP = mean arterial pressure.

purposes, age, weight, parity, gestational age (GA), qSOFA score, admission heart rate, temperature and respiratory rate were categorised to allow for calculations of frequencies and proportions as well as χ^2 analysis. The use of inotropic support,

the presence of hypotension on admission, chronic comorbid disease, hypertensive disorders of pregnancy, cardiac arrest, acute kidney injury (AKI) and acute respiratory distress syndrome were binary variables. The GCS was recorded on admission and

on discharge. Data were reported as medians and interquartile ranges due to non-normality.

Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (ref. no. M170687). This was a retrospective review of data and the requirement for consent was waived by the ethics committee.

Results

There were 39 884 deliveries during the study period and 16 060 (40.3%) were by CS. Of the 1.7% ($n=678$) of patients who were diagnosed with sepsis, 8.0% ($n=54$) were admitted to ICU.

The median (IQR) maternal age was 30 (26 - 34) years. More than three-quarters of women (87%; $n=46$) had between 1 and 3 live births, and 13% ($n=7$) had 4 previous live births. The mean (standard deviation (SD)) GA at delivery was 30.5 (1.3) weeks.

Half of the patients (50%; $n=27$) had puerperal sepsis post CS and 12.9% ($n=7$) had puerperal sepsis post normal vaginal birth. Two patients were in the first trimester (GA <13 weeks) while 14 were in the second trimester (GA between 13 and 27 weeks). About a quarter of the patients (24.0%; $n=13$) had sepsis post incomplete miscarriages, 9.2% ($n=5$) had post preterm deliveries and 3.7% ($n=2$) had post exploratory laparotomy for ruptured ectopic pregnancy.

Fifty percent of the patients ($n=27$) were HIV-positive and 51.85% ($n=14$) of these patients did not attend antenatal care prior to hospital admission. Moreover, 48.14% ($n=13$) of HIV-positive patients were on antiretroviral therapy. Less than a quarter of women (20.37%; $n=11$) had pregnancy-related hypertensive disorders. These included gestational hypertension ($n=7$), defined as high blood pressure $\geq 140/90$ mmHg after 20 weeks' gestation with no target organ dysfunction, and pre-eclampsia ($n=4$). One (1.85%) woman had cardiac disease (peripartum cardiomyopathy) and one (1.85%) had antiphospholipid syndrome as per laboratory markers and treating physician diagnosis. More than three-quarters of patients (88%; $n=46$) had hypotension and 19% ($n=10$) had hypertension. The majority of the women (63%; $n=34$) had a normal temperature (36 - 38°C) on admission. Less than a tenth (9%; $n=5$) had acute respiratory distress syndrome. All patients presented with a qSOFA score of at least 2. More than one-third of patients (42.1%; $n=16$) had a qSOFA of 3 and 2 patients had a qSOFA score of 6. Clinical characteristics as well as the qSOFA scores are shown in Table 2.

All patients required mechanical ventilation. The mean (SD) duration of ventilation was 2.5 (1.7) days. More than a quarter of the patients (29.6%; $n=16$) required inotropic support, 90.7%

($n=49$) required blood products (packed red cells, fresh frozen plasma, platelets, cryoprecipitate) and 9.2% ($n=5$) required renal replacement therapy.

The median and mean (SD) length of stay in the ICU were 5 and 3.9 (1.9) days, respectively.

There were 6 deaths (11.1%) and 4 (67%) of these were patients referred from local clinics. Half of these patients (50%; $n=3$) had positive blood cultures and were HIV-positive and another 50% ($n=3$) had puerperal sepsis post CS. Table 2 shows the maternal complications and interventions in ICU.

Maternal complications of sepsis were acute kidney injury (40.7%), coagulopathy (25.9%), circulatory shock (12.9%), acute respiratory distress syndrome (9.2%), cardiac arrest (9.2%) and abnormal liver enzymes (7.4%). Blood cultures were positive in 25.9% of cases ($n=14$).

Table 3 shows the cultured organisms. Coagulase-negative *Staphylococcus* was the most frequently isolated organism ($n=4$).

Bivariate analysis by Fisher's exact test was carried out to identify variables with a potential independent effect on mortality. Age (years), premature labour (GA in weeks), weight (kg), chronic comorbid disease, prolonged rupture of membranes, retained products of conception, history of pelvic or other infection, diabetes, parity, length of stay in ICU (days), anaemia, mean arterial pressure, ventilation duration and renal replacement therapy were not statistically significant in predicting mortality.

Discussion

Maternal deaths from sepsis remains a major cause of death in SA women. In the present study, maternal sepsis was associated with preterm birth and constituted 25% of sepsis cases admitted to ICU. Maternal sepsis following preterm deliveries occurred post-partum (66.6%) while one case (1.8%) was associated with chorioamnionitis. Preterm birth has been associated with increased risk of maternal and neonatal infection.^[8]

Maternal sepsis was responsible for 5.9% of ICU admissions during the study period. A study conducted in the Limpopo Province of SA reported a similar finding (6.7%).^[9] Similar studies conducted in other African countries have reported that between 1 and 10% of ICU admissions were due to obstetric indications.^[9-11] In the present study, 11.1% of obstetric patients admitted to the ICU with sepsis died. This is lower than the mortality rate (21%) reported in a study conducted in Durban, SA.^[12] The reasons for this could be variable transport or ambulance availability in different regions of the country and lack of specialist obstetrician and critical care.

Table 2. Maternal complications and interventions in ICU

Variable	Description	n (%)
Inotropic support	Yes	16 (30)
	No	35 (70)
Cardiac arrest prior to admission	Yes	6 (11.1)
	No	48 (88.9)
Acute kidney injury	Yes	32 (59.3)
	No	22 (40.7)
Acute respiratory distress syndrome	Yes	5 (9.3)
	No	49 (90.7)

ICU = intensive care unit.

Table 3. Cultured organisms

Causative organism	n (%)
Coagulase-negative <i>Staphylococcus</i>	4 (23.3)
<i>Klebsiella oxytoca</i>	2 (11.8)
<i>Escherichia coli</i>	2 (11.8)
<i>Prevotella</i> spp.	2 (11.8)
<i>Enterococcus faecalis</i>	2 (11.8)
Group G <i>Streptococcus</i>	1 (5.9)
<i>Strep. aeruginosa</i>	1 (5.9)
<i>Staph. aureus</i>	1 (5.9)
<i>Pseudomonas aeruginosa</i>	1 (5.9)
<i>Corynebacterium</i> spp.	1 (5.9)

The median maternal age was 30 years. Some studies have shown that teenage mothers have an elevated risk of sepsis during labour, while other studies have shown an increased risk of sepsis with maternal age >39 years.^[13] Age did not have any significant correlation with mortality in the present study.

Multiple studies have shown an increased rate of sepsis post CS at term and sepsis was attributed to emergency CS compared to elective CS.^[13,14] Deliveries by CS in the present study were for fetal distress, prolonged second stage of labour, cephalopelvic disproportion, severe pre-eclampsia and haemolysis, elevated liver enzymes, and low platelets syndrome.

Prolonged labour has been identified as a risk factor for sepsis; however, the duration of labour was not taken into consideration in the present study. Of note, 40.7% ($n=22$) of the patients had 2 or more children. Multiparous women have been shown to be at an increased risk of sepsis and mortality.^[15]

The majority of patients (87%; $n=48$) were diagnosed with anaemia (haemoglobin <10 g/dL) during their stay in ICU. On average, these patients received 2 units or more packed red cells and fresh frozen plasma, while 6 patients received platelets. Anaemia in pregnancy can be physiological and/or attributed to iron, folate and vitamin B12 deficiency, and has a prevalence of 35 - 75%.^[16] The high percentage of anaemia noted in our study could be due to the fact that 43.6% ($n=24$) of women did not attend antenatal clinics. Half of the patients (50%) had retroviral disease, which was associated with anaemia of chronic disease, late presentation at health facilities, lack of compliance with haematinics and haemorrhage secondary to miscarriages.

Half of the women (50%; $n=27$) were HIV-positive and 51.85% ($n=14$) of these women did not attend any antenatal clinics and were not on antiretrovirals. SA has a large number of people living with HIV and although deaths owing to non-pregnancy-related infections associated with HIV/AIDS have decreased, HIV remains a major risk factor for sepsis in our setting.^[2]

All patients had a qSOFA score of 2 or more, suggesting that the score may be a good triage tool for the admission of septic obstetric patients to ICU.

Globally, Gram-negative bacteria are the leading cause of maternal mortality from sepsis.^[17] However, the most frequently cultured organism in the present study was coagulase-negative *S. aureus* (CNS). CNS is relatively indolent organism, which acts as frequent coloniser and may have been a contaminant.^[18] Evidence of sepsis and chorioamnionitis following fetoscopy caused by *S. epidermidis*, a common skin flora, has been described.^[19] The finding of a low positive culture rate in the present study could be attributed to multiple factors such as the administration of antibiotics prior to cultures being taken and cultures being taken after the bacteraemic period. Most of the patients received a combination of ampicillin, gentamycin and metronidazole, which were later escalated depending on the culture results and illness progression.

All patients were sedated, intubated and mechanically ventilated on admission. Positive pressure ventilation delivered either non-invasively or invasively is a common therapeutic intervention in this group of patients.^[20]

More than a third of patients (44.4%; $n=24$) admitted to the ICU were pyrexial with temperatures above 38°C. Furthermore, the majority of the patients (85.2%; $n=46$) had tachycardia (heart rate >100 bpm), which could be indicative of sepsis. Tachycardia independent of temperature has previously been shown to be significantly associated with an increased mortality rate.^[21]

Less than a tenth of the women (3.7%; $n=2$) were admitted with a pre-existing diagnosis of cardiomyopathy, had cardiac arrests in ICU, and were successfully managed with cardiopulmonary resuscitation and inotropic support. Sepsis-induced cardiomyopathy has been shown to have a mortality rate of 70% in general cases.^[22]

More than half of the women (59.3%; $n=32$) had AKI on admission to ICU. Geraldo *et al.*^[23] showed AKI to be the main complication (24%) among critically ill obstetric patients admitted with hypertensive syndromes, haemorrhage and haemorrhagic shock, heart disease, respiratory insufficiency and sepsis. These conditions were also associated with increased mortality.^[23] The higher rate of AKI in our setting could be attributed to factors such as the presence of pre-existing renal disease, increased comorbidities such as HIV, and poor health-seeking behavior.^[23] The majority of the patients (81.2%; $n=26$) responded to fluid therapy while 11.1% ($n=6$) of the patients received renal replacement therapy.

The mortality rate was 10.9% ($n=6$) in our study and this was comparable to the reported 11% in global studies.^[24]

Study strengths and limitations

We conducted a small retrospective study in a high-volume (>20 000 deliveries per year) tertiary academic maternity centre in SA. The present study was limited by its retrospective design. The clinical diagnosis of maternal sepsis was made by the treating physician on admission and may have been subject to clinician variability. Sepsis is diagnosed in a minority of patients in the unit.

Many of the critically ill maternity patients are not admitted to ICU and are managed in the obstetric high-care unit owing to limited resources and a high demand for ICU beds. Therefore, their data was not included in the present study. Furthermore, the hospital is a tertiary referral centre and the population studied may not be representative of the general national group of septic obstetric patients in the community.

Conclusion

Maternal sepsis remains a major cause of mortality and a major contributor to mortality is puerperal sepsis post CS. The present study describes the characteristics, interventions and outcomes of patients admitted with a diagnosis of maternal sepsis to a tertiary academic ICU in SA. More than half of the women who died from sepsis had preterm delivery and did not attend antenatal clinics. Furthermore, half of the patients in the present study were HIV-positive. CNS was the most commonly cultured organism.

Declaration. None.

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Author contributions. JYL performed the literature review, collected data, was involved in the analysis and interpretation of data and drafted the manuscript. GDN conceptualised the research project. GDN and ECB supervised the literature review, interpretation of the results, and reviewed the manuscript. All authors approved the manuscript for publication.

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