REVIEW
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Too little, too late: The recurrent theme in maternal deaths due to sepsis

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Abstract
Background: Maternal sepsis accounts for 11% of direct obstetric deaths, making it the third commonest cause of death, after obstetric hemorrhage and hypertensive disorders.
Objective: To evaluate the risk factors and quality of care for maternal deaths due to sepsis.
Methods: Detailed secondary file review for all maternal deaths classified as pregnancy-related sepsis in South Africa between 2014-2016 and comparison of management with the Surviving Sepsis guidelines.
Results: There were 158 maternal deaths from sepsis. The postpartum period carried the greatest risk (94% of deaths), especially after caesarean delivery (50%). Adequate fluid resuscitation was done in only 25 cases (16%) and initiation of empiric antibiotics was often delayed (48% of those receiving antibiotics). Only 28% of women with possible source of infection in the uterus had a hysterectomy (39 cases).
Conclusion: Healthcare professionals often underestimate the severity of maternal sepsis and poorly adhere to treatment guidelines.

Introduction

The death of a woman during pregnancy, child birth or the puerperium is one of the greatest possible tragedies. On average every two minutes, somewhere in the world, a pregnant women dies.[1,2] Hemorrhage (27%), hypertensive disorders (14%) and sepsis (11%) are the three biggest causes of direct obstetric mortality.[1,2] With Sustainable Development Goal 3.1, the United Nations has pledged to reduce the global maternal mortality rate (MMR) to less than 70 per 100,000 live births by 2030, as opposed to the 216 deaths per 100,000 live births that occurred in 2015.[1,2]

In South Africa, a system of National Confidential Enquiries into Maternal Deaths exists to review maternal deaths.[3] The confidential enquiry identifies challenges in the health system and makes recommendations for improvement. These triennial ''Saving Mothers'' reports use the term ''pregnancy-related sepsis''.[3] Deaths from pregnancy related sepsis (PRS) are those caused by infections in the genital tract or in tissues involved in the birth process in viable pregnancies.[4] Deaths from septic miscarriage are classified as a separate category, as are non-pregnancy related infections (e.g. Tuberculosis,Pneumocystis jiroveci pneumonia).[3]

Worldwide, the use of varying (and often imprecise) definitions has hindered research into the particular burden of maternal sepsis. In 2017, the World Health Organisation (WHO) proposed a new definition of maternal sepsis as a ''life-threatening condition with organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or the postpartum period''.[5] This change is in line with the new Sepsis-3 definition for the general population.[6] The Sepsis-3 definition aimed to identify a subgroup with a mortality of at least 10% and uses the SOFA(Sequential or Sepsis-related Organ Failure Assessment) score to quantify organ dysfunction. Physiological changes in pregnancy (e.g. increased white cell count, increased respiratory rate, hyperdynamic circulation, changes in clotting etc.) cause classical predictive scores like the SOFA score to overpredict mortality in the obstetric population, thereby complicating the identification and diagnosis of sepsis.[4,5,6] Nevertheless, correct and early identification of maternal sepsis is paramount for successful treatment. The Global Maternal and Neonatal Sepsis Study (GLOSS) set out to develop a set of diagnostic criteria for maternal sepsis. Results are currently being analyzed and have not yet been published.[7]

Known risk factors for infections include pre-existing maternal conditions (obesity, diabetes, malnutrition, severe anaemia) and factors related to childbirth (caesarean section, prolonged rupture of membranes, multiple vaginal

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examinations, and placental retention).[8]

At present, no specific treatment guidelines exist for managing maternal sepsis in low-resource settings. We know from the adult population in high-income countries that the use of so called "bundles", like the Surviving Sepsis Campaign Guidelines, improves outcomes. Bundles are a small and straightforward set of evidence-based practices that need to be performed as a whole. A modified version of the Surviving Sepsis bundle for the obstetric population in low-resource settings, termed FAST-M, has recently been developed and is undergoing feasibility testing in Malawi. FAST-M is an acronym for Fluids, Antibiotics, Source Control, Transport and Monitoring.[9,10]

We aimed to characterise risk factors for septic deaths in the South African obstetric population and to assess whether real-life clinical management is compliant with current international treatment guidelines.

Methods

We performed a secondary file review under permission of the National Committee for the Confidential Enquiry into Maternal Deaths. The original confidential enquiry data mentioned 201 South African maternal deaths between 2014-2016 attributed to pregnancy-related sepsis. Upon review of the received files, we found 158 of 201 cases of pregnancy-related sepsis. Of these 158 cases, we examined the full clinical records in detail. Data were extracted using a standard data collection sheet and subsequently entered into an excel spreadsheet. Descriptive statistics (frequencies, averages, percentages) were calculated and reported. There is no control group. No additional ethical approval was required for this secondary review.

Table 1: Demographics

	N (158)	%
Parity		
0	37	25%
1	46	21%
2	32	22%
3+	32	22%
Province		
Eastern Cape	20	13%
Free State	1	1%
Nothern Cape	2	1%
North West	14	9%
Gauteng	34	21%
Limpopo	28	18%
Mpumalanga	11	7%
Kwa Zulu Natal	41	26%
Western Cape	7	4%
Place of death		
Community Health Center	1	1%
District	34	22%
Regional	58	37%
Tertiary or above	62	39%
Private	2	1%

Results

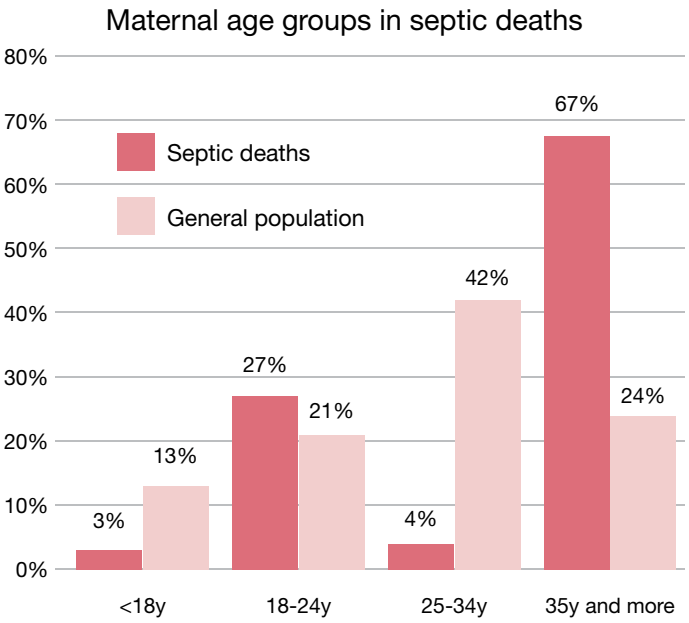
Demographics and risk factors

The average age of affected women is 29 years, with a majority (106/158, 67%) presenting at advanced maternal age, 35 years or older. This is in contrast to the general obstetric population (Figure 1). One quarter (37, 25%) were primigravidae. Most deaths occurred in KwaZulu-Natal (26%) and Gauteng (21%). Sixty percent were referred to a higher level of care, resulting in four out of five deaths to occur in facilities of at least level 2 (37% in regional hospitals, 39% in tertiary). Table 1 gives an overview of the demographics.

Risk factors like anaemia (Hb<10g/dL at booking) and overweight/obesity (BMI>25 or mid-upper arm circumference >27.1cm) should be documented in the maternity case records but were found to be unrecorded in 73% and 68% of cases, respectively. Of the women with available information on these parameters, 37% had anemia and 62% was overweight or obese.

An obvious and important risk factor in the South African context is HIV infection. Ninety percent of all women knew their status. More than half (57%) were HIV positive and 71% of these women were on antiretroviral treatment. Despite this, CD4-count was known to be below 350 for 53% of all HIV-positive women. In the general obstetric population, the proportion of HIV positive women is estimated to be around 24% of which 87% is receiving antiretroviral treatment (data extrapolated from Perinatal Problem Identification Programme).

Figure 1: Distribution of maternal age



Data for general pregnant population for 2014-2015, source: Recorded Live Births 2015, Statistical release P0305, Statistics South Africa

The postpartum period was the most dangerous period, with 94% of all deaths occurring after delivery. Half of all deliveries (50%) were by caesarean section (CS) and the majority of these were performed as an emergency procedure (77%); 7% had a CS in the second stage of labor. Use of prophylactic antibiotics, though recommended by all major guidelines, was documented in only one out of five caesarean deliveries (21%).

Diagnosis

We assessed the possible diagnostic criteria evaluated in the GLOSS study, namely respiratory rate (RR) between 21-24/min or above 24/min, pulse rate (PR) 100-119/min or at least 120/min, systolic blood pressure (SBP) of 90-99mmHg, a temperature of at least 38°C or less than 36°C, SBP less than PR (a so-called "shock-index" of >1), and anuria for more than 12hours.

Urine output was very poorly recorded so that we were unable to evaluate this criterion in 76% of the cases.

Temperature was another poorly monitored sign, with no records for 39% of all cases. The most sensitive parameter seems to be a tachycardia of at least 120/min, which was present at some point in 73% of all cases. Next is a shock-index of >1 which was present at some point in 59% of all cases. Whilst none of the criteria in itself appears to be very sensitive, a combination of abnormal vital signs was present in 88% of all cases. Table 2 presents an overview of the vital signs upon diagnosis and in the last 24h before death.

Table 2: Presence of selected diagnostic criteria as percentage of all cases (N=158)

	RR21-24	RR>24	p100-119	p>120	BP90-99	T>38°C	T<36°C	annuria	SBP<PR
At diagnosis	7	39	19	58	40	30	12	4	44
Last 24h	4	43	16	60	49	30	12	7	43
Any point	11	57	27	73	59	40	20	9	59

RR = respitory rate/min; p = pulse rate/min; BP = systolic blood pressure in mmHg; anuria = for at least 12h

Management
Vital signs were recorded less than once a day for 8% of all cases, 1-2x/day in 29%, every eight hours in 6% of all cases, and at least every six hours in 46% of all women. Adequate fluid resuscitation was performed in only 16% of cases, with 27% receiving inadequate (23%) or delayed fluids (4%). In more than half of all deaths (54%) fluid resuscitation was not attempted at all. Parental broad-spectrum antibiotics were initiated in 81% of all cases, although delayed in 48% of those receiving antibiotics. Cultures were sent off for microbiological assessment in only 26% of all cases. Thirty-nine hysterectomies were performed, making up 28% of all cases with possible source of infection in the uterus

Box 1: Key findings
- Hb was not recorded in 73%
- MUAC was not recorded in 68%
- 79% were not given prophylactic antibiotics before CS
- 77% had inadequate or no fluid resuscitation
- Temperature was never measured in 39%
- 48% of all antibiotics were started too late
- Only 26% of women had cultures sent off
- 28% had a hysterectomy done as source control

DISCUSSION

Interpretation of the findings
Prevention is always better than treatment. Especially in times of rising antimicrobial resistance, infection prevention and control should be a priority. Besides reinforcing hospital policies on hand hygiene and cleaning, eliminating or optimizing risk factors in individual patients deserves more attention. We found poor recording of Hb and BMI at booking, which means opportunities for e.g. iron supplementation and screening for and treatment of gestational diabetes are likely to be missed. The proportion of deliveries by CS was twice as high as in the general obstetric population over that same period of time (50% vs. 26%). Caesarean section is known to be an important risk factor for peripartum infections.[9] There is overwhelming evidence for the effectiveness of prophylactic antibiotics before incision and administration is recommended by all major guidelines but was documented in only 21%. Undoubtedly, there is room for improvement here. The upscaling of voluntary counselling and testing and universal treatment for all people living with HIV has been impressive. Pregnant women are a key intervention group. It is uplifting that HIV status was documented for 90% of the cases and 71% of positive women had been receiving treatment. Nevertheless, the high prevalence (57%) of HIV amongst these deaths shows that continued efforts to improve HIV-care remain important to reduce maternal mortality.

As mentioned previously, the diagnosis of maternal sepsis is problematic because of lack of a gold standard and accepted diagnostic criteria. Recently, the SOFA score has been proposed for the general adult population. An increase of the score with two or more is needed for the diagnosis of sepsis and is associated with a mortality of at least 10%. However, the formal SOFA score requires multiple laboratory measurements, reducing its usefulness at the bedside and in resource-restrained settings. A simplified version of this score is known as quick-SOFA (qSOFA) and has only three parameters that are readily available: systolic blood pressure ≤100mmHg, respiratory rate ≥22/min and altered mentation (GCS<15). Presence of at least two parameters is associated with worse outcomes. Whilst not able to formally evaluate this diagnostic score in our obstetric population, the finding that 88% of women had more than one abnormal vital sign, supports the principle of this score. The same principle is applied in early warning charts to record vitals, where a combination of abnormal parameters should prompt immediate action. Of course, any diagnostic score will only be useful if vital signs are accurately recorded and charted. It is therefore worrying that simple clinical observations like temperature and urine output were missing for 39% and 76% of cases respectively. A basic assessment of the level of consciousness like the AVPU scale (Awake, responsive to Voice, responsive to Pain or Unresponsive) should be included in early warning charts to alert healthcare workers to patients with altered mentation.

In terms of management, the surviving sepsis campaign recommends that fluid resuscitation should consist of at least 30 mL/kg of intravenous crystalloid fluid within the first 3 hours and additional fluid administration be guided by frequent reassessment of hemodynamic status. This assessment should include a thorough clinical examination and evaluation of available physiologic variables such as heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and lactate levels etc. In the reviewed files, administration of resuscitation fluids was adequate in only 16% of women.

Administration of intravenous antimicrobials must be initiated within the first hour after recognition of possible sepsis. Initial therapy should include one or more broad spectrum antimicrobials to cover all likely pathogens (including bacterial and potentially fungal or viral coverage). Delays in giving antimicrobials have been proven to be associated with increased mortality. Empiric broad spectrum antibiotics were indeed administered in 81%, but initiation was delayed in at least 48% of those receiving antibiotics

Key recommendations of the Surviving Sepsis campaign
1. If hypoperfusion present: resuscitate with 30mL/kg of IV crystalloids within the first 3h
2. Reassess perfusion status frequently using dynamic clinical parameters (heart rate, blood pressure, urine output, lactate levels, passive leg raising test)

3. Initiate broad-spectrum antimicrobials within the first hour
4. Obtain routine cultures before starting antimicrobial therapy
5. Identify site of infection and perform source control as soon as feasible

Furthermore, the guidelines state that appropriate routine microbiologic cultures (including blood cultures) should be obtained before starting antimicrobial therapy in all patients with suspected sepsis. This should however not lead to delay in initiation of antimicrobial therapy. Pathogen identification and sensitivity testing will allow the clinician to select the appropriate (narrow) spectrum antimicrobial. Unfortunately, microbiology testing was done in only 26% of women.

Rapid identification or exclusion of a specific anatomical site of the infection should be sought and any required source control intervention should be implemented as soon as medically and logistically practical. In contrast to this recommendation, only 39 hysterectomies were performed, or a mere 28% of all cases with the possible source of infection in the uterus.

In general, the disease severity of these women was often underestimated and management was not aggressive enough. Vital signs were incompletely or infrequently recorded and there was poor monitoring of resuscitation end-points like urine output, lactate clearance and mean arterial pressure etc. Antibiotic therapy was often delayed and too few attempts at source control were made.[10]

Strengths and limitations

This study is valuable as it provides insights in demographics, risk factors and real-life management of women with pregnancy-related sepsis, which is an important cause of maternal mortality both globally and in South Africa. The original files were exhaustively reviewed and 158 cases that occurred in the entire nation over a three-year period were included. The inclusion of possible diagnostic criteria ties in neatly with the recent evolution in diagnosis of (maternal) sepsis and pointed out possible problems with applying the new criteria (e.g. urine output seldom recorded). An audit of this kind is important to detect where opportunities are missed and suggest possible solutions in order to reduce maternal mortality and achieve Sustainable Development Goal 3.1.

However, as we only reviewed cases where the outcome was a maternal death, this study does not tell us how the average patient with maternal sepsis is managed. It might be that the vast majority of women do receive adequate care and have good outcomes. Also, although every attempt was made to extract data as completely as possible, it could be that certain actions (like giving prophylactic antibiotics before caesarean section or sending of cultures) were actually performed but not noted in the file. Moreover, it is important to bear in mind that avoidable factors may be present on the patient-side as well (most importantly patients who are not booked, refuse treatment or present only in a critical condition) thereby making it impossible for health care workers to act according to protocol. Lastly, the initial NCEMD data mentioned 201 cases of PRS whereas we only found 158 cases sent to us for review to concern PRS. However, we think it unlikely that the missing files would significantly alter these findings.

CONCLUSION

Maternal sepsis remains one of the leading causes of maternal mortality. In order to reduce the burden of maternal deaths due to pregnancy-related infections, infection prevention needs to be a priority and risk factors for infection should be managed accordingly. The disease severity of these women was often underestimated and management was not aggressive enough. Vital signs were incompletely or infrequently recorded and there was poor monitoring of resuscitation end-points like urine output, lactate clearance and mean arterial pressure. Antibiotic therapy was often delayed and too few attempts at source control were made.

RECOMMENDATIONS

Box 2: Practical recommendations

- All women must have Hb and MUAC recorded at first visit.
- All women undergoing caesarean section must have prophylactic antibiotics
- Adhere to protocols for observations of vital signs post-delivery (especially caesareans)
- Adjust Early Warning Charts to include neurological assessment (AVPU)
- Raise awareness on the use of qSOFA and its possible implications for mortality
- Any woman with suspected sepsis should be started on the Surviving Sepsis protocol immediately, see Figure 2
- ESMOE Sepsis module should be changed to reflect these new insights
- Maternity Care Guidelines need to be adjusted to meet new requirements

Healthcare workers should be updated on the diagnosis and management of sepsis and the severity of the condition should be emphasised. Public awareness should be raised about the dangers of infection during the postpartum and women should be encouraged to seek care early. The most practical way to implement this is through an updated sepsis module, which incorporates the sepsis bundle of care, in the existing ESMOE (Essential Steps in Managing Obstetric Emergencies) framework and to adjust maternity care guidelines to meet the new requirements.

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