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A Case Series Describing Causes of Death in Pregnant Women with Sickle Cell Disease in a Low-Resource Setting

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To the Editor,

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AUTHORSHIP CONTRIBUTIONS

S.A.O., M.R.D., A.K., and E.O. designed the study; E.V.A., T.K.B. and S.A.O. collected the data; S.A.O., E.O., Y.D.A., T.K.B., C.H.B., E.V.A., M.R.D., A.K. and A.J. adjudicated on the case files; and E.V.A., M.R.D., M.R. performed the analyses; M.R.D., E.V.A and S.A.O. interpreted the results. All authors participated in writing the article, all authors reviewed and approved the manuscript before submission.

DISCLOSURES OF INTERESTS

Full disclosure of interests available to view online as supporting information.

Sickle cell disease (SCD) is most prevalent in sub-Saharan Africa with 15,000 newborns per year in Ghana.[1, 2] Pregnant women with SCD have increased risks of both SCD-specific and pregnancy-related complications, compared to pregnant women without SCD.[3] In a recent meta-analysis, our team reported that SCD in pregnancy increases the risk of maternal death by over 20-fold compared to pregnant women without SCD, in low- and middle-income countries.[4] In sub-Saharan Africa, maternal death rate of SCD is 7–12%,[3, 5, 6] without clearly identifiable etiologies.

Following our before and after study that demonstrated a 89% relative risk reduction in maternal death in women with SCD with our combined SCD-obstetric team care model,[7] we undertook a medical records and autopsy review of all SCD maternal deaths over a seven-year period from 2010 to 2016, at the Korle-Bu Teaching hospital (KBTH), in Accra, Ghana. Ethical approval was obtained from the institutional review boards of the College of Health Sciences, University of Ghana and Vanderbilt University Medical Centre. At the KBTH, about 11,000 deliveries occurred annually including 200 women with SCD, and about two-thirds are HbSC.

We conducted a combined retrospective (January 2010 to April 2015) and prospective case series (May 2015 to December 2016) of all maternal deaths in women with SCD at KBTH. All deaths that occurred prior to arrival at the hospital, and those without documented evidence of hemoglobin phenotype, were excluded. Our research team, including obstetricians, hematologists, a pediatrician, anesthesiologists and nurses, adjudicated all cases of SCD maternal deaths to reach a consensus on the cause of death. Pathologists performed autopsies. In this series, we defined maternal death, direct and indirect obstetric cause of death according to WHO ICD-10 classification (WHO 2012).[8]

The maternal mortality records, patients' admission and discharge files, and death certificates of all SCD-related maternal deaths within the study period were retrieved and reviewed by the team.

Data were summarized as simple descriptive statistics. The Mann-Whitney U-test and Fisher exact test were used to evaluate differences between pregnant women with HbSS versus HbSC. A p-value of <0.05 was considered statistically significant. SPSS version 24 (IBM Corp, USA) was used for analysis.

Over the seven years, there were 56 SCD maternal deaths; 44 cases were included in the analysis and 12 excluded because of incomplete documentation of SCD status, suspected but not confirmed. The median age of the deceased women was 30 years (range 19–43). There was no significant difference in age between HbSS and HbSC phenotypes ($p=0.225$). One woman had HbS β^+ -thalassemia. There was no significant difference in parity between HbSS and HbSC ($p=0.156$). Median gestational age at hospitalization prior to death was 33 weeks (range 14–40), and the median interval from hospitalization to death was 3.5 days (range 1–21). Of the available records, approximately 83% (26/31) of the maternal deaths in women with SCD occurred in the third trimester or postpartum period. Table 1 summarizes the demographic characteristics.

Approximately 60% (28/44) of the maternal deaths were in women with HbSC disease, one death occurred in a women with HbS β^+ -thalassemia. Of all the maternal deaths, 86.4% (38/44) had SCD-related complications. Autopsy records of the maternal deaths were retrieved for approximately 82% (36/44) of the cases. Table S1 provides details for each case including the underlying causes of death.

In all, 75% (33/44) of the pregnant women who died were admitted for acute vaso-occlusive pain events and nearly 80% of these developed other SCD-related complications prior to death. Among the women that died, no difference was observed in rate of hospitalization for acute pain episodes between HbSS (86.7%) and HbSC (71.4%); $p=0.45$.

Nearly 87% (33/38) of the SCD-related maternal deaths were caused by ACS; 19 (57.6%) cases were confirmed with autopsy records. There was no statistical difference in maternal death rate due to ACS between HbSS and HbSC phenotypes (80% versus 71.4% respectively; $p=0.719$). One pregnant woman with HbS β^+ -thalassemia also died of ACS. The majority (80%; 26/33) of pregnant women who died from ACS had a preceding acute pain episode.

A quarter (9/36) of maternal deaths with autopsy report were from venous thromboembolic (VTE) events. Pulmonary embolism was responsible for 24.2% (8/33) of cases of ACS and almost 40% (8/19) of autopsy-confirmed pulmonary deaths; 75% (6/8) of pulmonary emboli were massive and bilateral. One maternal mortality in a woman with HbSS was attributable to stroke. Two-thirds (6/9) of venous thromboembolism occurred in women with HbSC disease. There was no statistically significant difference in VTE as cause of death between HbSC and HbSS ($p=0.69$).

In our case series of maternal death among pregnant women with SCD at a single centre in Accra, Ghana, the main causes of death were related to SCD complications. Most maternal deaths were preceded by acute pain episodes; the commonest cause of death was ACS (86%). The number of deaths from venous thromboembolism was similar in pregnant women with HbSC and HbSS. In our cohort, 60% of the maternal deaths are associated with HbSC disease, and likely reflects the phenotypic distribution of SCD in Ghana.[2]

The results of our study have significant public health importance for pregnant women in both high and low-income settings. ACS is potentially preventable and a leading cause of death in pregnant women with SCD. The pathophysiology of ACS is complex, including venous thromboembolic disease, pulmonary infection, and fat embolism. Our group demonstrated that multi-modal approach for the management of acute pain episodes and prevention of ACS could be replicated during pregnancy with balloons instead of incentive spirometry, along with anticipatory guidance and adherence to written protocols for the multi-disciplinary health care team. Our intervention resulted in the reduction of maternal mortality by almost 90%.[7] Together, this study and our prior work [7] provide compelling evidence that a significant proportion of maternal deaths in SCD can be prevented with a multi-modal approach to either decrease the incidence rate of acute pain or decrease its common sequelae, ACS, or both. Unfortunately, successful strategies to decrease the

incidence of thromboembolism are unclear in pregnant women with SCD and will require further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Comparison of baseline and clinical characteristics of all cases of maternal death with SCD categorized by SCD phenotype

Characteristic	HbSS (N 5 15) ^a	HbSC (N 5 28)
Age (n 5 43)		
< 20 years	1 (6.7)	0 (0.0)
20–34 years	11 (73.3)	20 (71.4)
2: 35 years	3 (20.0)	8 (28.6)
Median age (years)	28.0 (6.0)	31.5 (9.0)
Parity (n 5 41)		
0–1	12 (85.7)	16 (59.3)
2–4	2 (14.3)	11 (40.7)
Gestational age at hospitalization (n 5 30)		
First trimester (up to 13 weeks)	0 (0.0)	0 (0.0)
Second trimester (13 weeks 1 day up to 26 weeks)	3 (37.5)	3 (13.6)
Third trimester (26 weeks 1 day up to 40 weeks)	5 (62.5)	19 (86.4)
Median gestational age at hospitalization (weeks)	30.0 (19.0)	33.5 (7.0)
Approximate time of death (n 5 31)		
Prepartum (first trimester)	0 (0.0)	0 (0.0)
Prepartum (second trimester)	2 (25.0)	3 (13.0)
Prepartum (third trimester)	3 (37.5)	5 (21.7)
Postpartum (< 1 week)	2 (25.0)	14 (60.9)
Postpartum (1–2 weeks)	1 (12.5)	1 (4.3)
Duration of hospitalization (n 5 43)		
< 1 day	2 (13.3)	5 (17.9)
1–2 days	4 (26.7)	8 (28.6)
3–5 days	5 (33.3)	6 (21.4)
> 5 days	4 (26.7)	9 (32.1)
Median duration of hospitalization (days)	4.0 (7.0)	3.0 (8.0)
Type of delivery (n 5 30)		
Vaginal delivery	2 (25.0)	6 (27.3)
Caesarean delivery	1 (12.5)	8 (36.4)
Not delivered ^b	5 (62.5)	8 (36.4)
Fetal outcome (n 5 30)		
Alive	3 (37.5)	13 (59.1)
Intra-uterine fetal death (IUFD)	3 (37.5)	9 (40.9)
Spontaneous abortion	2 (25.0)	0 (0.0)
Causes of maternal death		
Indirect obstetric (SCD-related) deaths (n 5 37)	14 (93.3)	23 (82.1)
Acute chest syndrome (ACS)	12 (80.0)	20 (71.4)
Venous thromboembolism (VTE)	3 (30.0)	6 (24.0)
Acute vaso-occlusive pain crisis (VOC)	1 (6.7)	0 (0.0)

Characteristic	HbSS (N 5 15) ^a	HbSC (N 5 28)
Direct obstetric deaths (n 5 6)	1 (6.7)	5 (17.9)
Pregnancy-related infection	0 (0.0)	2 (7.1)
Hypertensive disorders in pregnancy, childbirth and the puerperium	0 (0.0)	1 (3.6)
Obstetric haemorrhage	1 (6.7)	2 (7.1)

^aCount (percentage) for categorical variables, median (Interquartile range) for continuous variables.

^bNot delivered includes IUFD and spontaneous abortions (< 28 weeks gestation). There were no statistically significant differences between SS and SC.

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