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RESEARCH ARTICLE

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Implementation of multidisciplinary care reduces maternal mortality in women with sickle cell disease living in low-resource setting

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Abstract

Sickle cell disease (SCD) is associated with adverse pregnancy outcome. In women with SCD living in low-resource settings, pregnancy is associated with significantly increased maternal and perinatal mortality rates. We tested the hypothesis that implementing a multidisciplinary obstetric and hematology care team in a low-resource setting would significantly reduce maternal and perinatal mortality rates. We conducted a before-and-after study, at the Korle-Bu Teaching Hospital in Accra, Ghana, to evaluate the effect of a multidisciplinary obstetric-hematology care team for women with SCD in a combined SCD-Obstetric Clinic. The pre-intervention period was assessed through a retrospective chart review to identify every death and the post-intervention period was assessed prospectively. Interventions consisted of joint obstetrician and hematologist outpatient and acute inpatient reviews, close maternal and fetal surveillance, and simple protocols for management of acute chest syndrome and acute pain episodes. Primary outcomes included maternal and perinatal mortality rates before and after the study period. A total of 158 and 90 pregnant women with SCD were evaluated in the pre- and post- intervention periods, respectively. The maternal mortality rate decreased from 10 791 per 100 000 live births at pre-intervention to 1176 per 100 000 at post-intervention, representing a risk reduction of 89.1% ($P = 0.007$). Perinatal mortality decreased from 60.8 per 1000 total births at pre-intervention to 23.0 per 1000 at post-intervention, representing a risk reduction of 62.2% ($P = 0.20$). A multidisciplinary obstetric and hematology team approach can dramatically reduce maternal and perinatal mortality in a low-resource setting.

1 | INTRODUCTION

Sickle cell disease (SCD) is the most common genetic disorder in the world and a public health problem in sub-Saharan Africa.[1] Over the past four decades, medical advances have led to improved survival in high-income countries,[2] with most children with SCD now reaching their reproductive ages.[3] However, an emerging new health challenge is pregnancy in women with SCD, particularly in low-resource settings. Pregnant women with SCD are at an increased risk for both pregnancy and SCD-related morbidity and mortality.[4–6] In sub-Saharan Africa, in women with SCD, maternal mortality rate ranges from 7 to 12%.[5–8] A previous meta-analysis comparing maternal mortality rates in women

with and without SCD living in high-income countries did not demonstrate increase in the odds of maternal mortality (Odds Ratio 3.54, 95% confidence interval (CI) [0.63, 51.59]).[9] However, pregnant women with SCD in low- and middle-income countries have significantly higher odds of maternal mortality compared to those without SCD in the same setting (Odds Ratio 22.8, 95% CI [14.67, 35.46], $P < 0.001$)[9] suggesting that improved medical support may decrease the maternal mortality rate in pregnant women with SCD.[9] The perinatal mortality rate was similar and significantly higher in women with SCD in both high- and low to middle-income countries when compared to those without SCD in each region, (Odds Ratio 3.76, 95% CI [2.12, 6.68], $P < 0.001$) and (Odds Ratio 3.75, 95% CI [1.59, 8.82], $P = 0.002$), respectively.[9]

In a large teaching hospital in Accra Ghana, based on the high maternal and perinatal mortality rates, an obstetrician (SAO) initiated a clinic for women with SCD in 2011. After observing no significant reduction in the maternal and perinatal mortality rates after 3 years, in 2014, the SCD-Obstetric Clinic expanded to include a multidisciplinary care team consisting of obstetricians, hematologists, a pediatrician, nurses, and an intensivist with expertise in pulmonology. The primary basis to form the multidisciplinary care team was to test the hypothesis that co-managing of pregnant women with SCD and implementing standard protocols would significantly reduce maternal and perinatal mortality rates in women with SCD living in a low-income setting.

2 | METHODS

2.1 | Study design and setting

We conducted a single-center retrospective and prospective study comparing the outcomes before and after implementing a multidisciplinary care team for pregnant women with SCD from January 2014 to May 2016. The study was conducted at the Department of Obstetrics and Gynecology, Korle-Bu Teaching Hospital, the national referral center in Accra, Ghana. The study protocol was reviewed and approved by the Ethical and Protocol Review Committee, College of Health Sciences, University of Ghana (MS-Et/M.12-P4.2/2013–2014) and Vanderbilt University Medical Center (VUMC) Institutional Review Board (VUMC IRB141050).

2.2 | Pre-intervention phase

In 2014, the KBTH team team in Accra and the VUMC team, in Nashville TN, met to discuss strategies to reduce maternal and perinatal mortality. Ultimately, a pre- and post-intervention design was decided because a randomized controlled trial was deemed unethical based on the high maternal mortality rate. The pre-intervention period of the study from January 2014 to April 2015 was approved by the Institutional Review Boards. During the pre-intervention period, obstetricians and midwives assessed and managed all pregnant women with SCD at the SCD-Obstetric Clinic and during acute admissions with standard departmental protocol. Inpatient consultations were sought for critically ill patients based on hospital policy of inpatient referrals. Inpatient admissions of pregnant women with SCD were scattered among five different wards in the department. The pre-intervention period was assessed through retrospective review of all SCD-related admissions, delivery, and discharge records. During the same period, both the KBTH and VUMC teams reviewed all of the SCD-related maternal and perinatal deaths and autopsy records. The date of termination of the pre-intervention study coincided with the commencement of the post-intervention phase.

2.3 | Post-intervention phase

The post-intervention period was from May 2015 to May 2016. A multidisciplinary care team consisting of obstetricians, hematologists, a pediatrician, nurses, and an intensivist with training in pulmonology was formed to address the immediate needs of pregnant women with SCD and anticipate strategies for acute inpatient management with the various specialists. The KBTH team had weekly face-to-face meetings to assess and refine standard protocols for management of pregnant women with SCD and discuss all prior deaths and ongoing challenges with clinical care. The VUMC team visited the program three times within 18 months to assist with reviews of research governance files, patient care protocols, and death events. Participants included pregnant women with SCD (HbSS and HbSC), confirmed by hemoglobin electrophoresis, who attended antenatal care at the hospital and provided written informed consent. Strategies used at VUMC to treat and prevent acute chest syndrome in adults with SCD were discussed and adapted to KBTH (Supporting Information Figure S1).

2.4 | Maternal assessment in post intervention phase

The hematologists and obstetricians evaluated all pregnant women with SCD in the joint SCD-Obstetric Clinic after obtaining consent. Simplified protocols were implemented for diagnosis and prevention of acute chest syndrome during hospitalizations for vaso-occlusive pain episodes or post-surgery (Supporting Information Table S1). Latex balloons were used routinely on the obstetric wards in place of incentive spirometers, at the same frequency as previously described.[10] Two obstetric wards were designated for admission and treatment of pregnant women with SCD throughout the study period. Measurement of hemoglobin oxygen saturation was integrated into routine clinical care. Protocols were established for the transfer of patients with acute chest syndrome to the Intensive Care Unit (ICU) for ventilatory support when indicated. As standard care, stable participants were followed bi-weekly at the outpatient clinic until 34 weeks gestation and weekly until delivery. Those with complications were seen more frequently as required. Simple blood transfusion was used in the treatments of symptomatic anemia, recurrent acute vaso-occlusive pain episodes, and acute chest syndrome.

2.5 | Fetal assessment in post-intervention phase

Serial obstetric ultrasounds were performed bi-weekly in the third trimester to monitor fetal growth. Umbilical artery Doppler studies were performed in those with suspected intrauterine growth restriction (IUGR).

TABLE 1 Baseline characteristics and pregnancy outcomes of women with sickle cell disease in the pre-intervention period ($n = 158$) consisting of Obstetric Clinic of 16 months and post-intervention period ($n = 90$) consisting of a combined Sickle Cell Disease Obstetric Clinic of 13 months

Patient characteristic	Pre- intervention period ($n = 158$)	Post-intervention period ($n = 90$)	*P*-value[b]
Age—*n* (%)			
< 20 years	5 (3.2)	4 (4.4)	
20–34 years	128 (81.0)	73 (81.1)	
≥ 35 years	25 (15.8)	13 (14.4)	
Age (years), median (range)	29.0 (18–43)	29.0 (18–41)	0.468
Phenotype—*n* (%)			
HbSS	20 (12.7)	35 (38.9)	
HbSC	57 (36.1)	55 (61.1)	
Not indicated	81 (51.3)	0	
Parity—*n* (%)			
0–1	113 (71.5)	70 (77.8)	0.401
2–4	40 (25.4)	19 (21.1)	
≥ 5	2 (1.3)	1 (1.1)	
Not indicated	3 (1.9)	0	
Maternal Outcome			
Maternal deaths—*n* (%)	15 (9.5)	1 (1.1)	0.009
Maternal deaths per 100 000 live births	10 791	1176	0.007
Type of Delivery[a]			0.054
Caesarean—*n* (%)	90 (57.0)	42 (46.7)	
Vaginal—*n* (%)	57 (36.1)	45 (50.0)	
Spontaneous abortion	6 (3.8)	3 (3.3)	
Deaths with fetus in-utero	1 (0.6)	0	
Mode of delivery not documented	4 (2.5)	0	
Perinatal Outcome			
Spontaneous abortion	6 (3.9)	3 (3.3)	1.000
Perinatal deaths—*n* (%)	9 (5.8)	2 (2.2)	0.337
Perinatal deaths per 1000 births	60.8	23.0	0.200

[a]Outcome available for 147 and 87 participants during pre- and post-intervention periods, respectively. During the pre-intervention era, there were 6 spontaneous abortions, 1 mother died with the fetus in-utero, and mode of delivery and fetal outcome were not documented in 4 patients. During the post-intervention period, there were 3 abortions.
[b]*P*-values from comparison of the pre-intervention and post-intervention cohorts based on the Chi-square test for categorical variables, the t-test for normally distributed continuous variables, and the Mann-Whitney-U test for non-normally distributed continuous variables.

2.6 | Labor and delivery and post-intervention phase

Delivery was planned between 38 and 39 weeks gestation unless the mother or fetus were at risk. During labor, all participants were admitted to a high-risk labor ward and closely monitored on partograph until delivery. Adequate hydration, pain relief, and frequent monitoring of their oxygen saturation with a goal of maintaining the hemoglobin oxygen saturation greater than 95% were ensured. Elective and emergency cesarean sections were performed for obstetric indications. Supportive blood transfusion therapy was given to participants with symptomatic anemia or postpartum hemorrhage with reduction in hemoglobin of > 2 g/dL below baseline.

2.7 | Data collection

Retrospective chart review of all SCD-related admissions, deliveries, and discharges were performed during the pre-intervention period. The KBTH and VUMC teams adjudicated all SCD-related maternal and perinatal deaths during the period to establish the clinical cause of death. During the post-intervention period, participants' demographic, obstetric, and medical data were recorded prospectively. The only death during the post-intervention period was also adjudicated by the team.

2.8 | Data analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt University Medical Center.[11] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. Differences in demographic characteristics and pregnancy outcomes between the pre- and post-intervention groups and between the HbSS

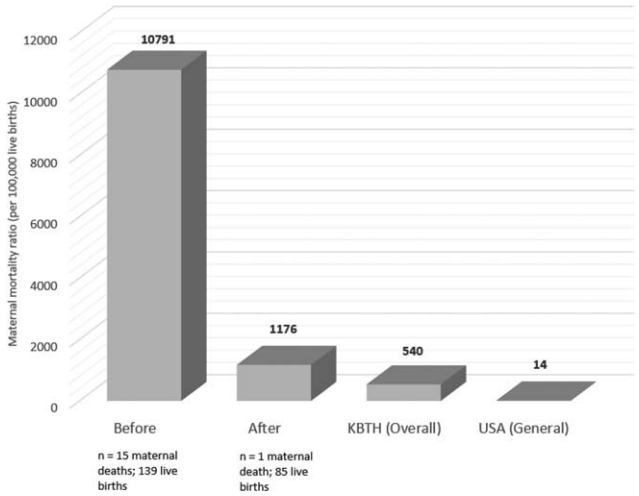

FIGURE 1 Maternal mortality rates in pregnant women with sickle cell disease before and after intervention at Korle Bu Teaching Hospital compared to maternal mortality rates in pregnant women without sickle cell disease at Korle Bu Teaching Hospital, in Accra Ghana[19]; and maternal mortality rates in pregnant women living in the United States of America, general population.[20]

and HbSC groups were assessed by chi-square test or *t*-test for categorical or continuous covariates, respectively, or the Mann-Whitney *U*-test for covariates not normally distributed. The relative risk reductions between pre- and post-intervention periods for primary outcomes were calculated. A *P* value of less than 0.05 was considered statistically significant.

3 | RESULTS

The baseline characteristics of the study participants are summarized in Table 1. The median age and parity, as well as other clinical features of participants in the pre- and post-intervention periods, were similar.

During the post-intervention period, the maternal mortality ratio dramatically declined. The rate decreased from 10 791 (15 of 139) per 100 000 live births to 1176 (1 of 85) per 100 000 live births (risk ratio 0.103, 95% CI [0.014, 0.779]), representing an 89.1% risk reduction within 13 months of implementing the intervention ($P = 0.007$), Table 1 and Figure 1. The case fatality rates in the pre- and post-intervention periods were 9.5% (15 of 158) and 1.1% (1 of 90), respectively. The baseline demographic and clinical characteristics of participants with HbSS and HbSC in the post-intervention period were compared and the age, parity, and median duration of follow-up were similar between individuals with the two phenotypes. Participants with HbSS received their first prenatal visit earlier than those with HbSC. Similarly, participants with HbSS also delivered about a week earlier than those with HbSC [median 37.0 weeks (IQR 31–40) versus 38.0 weeks (IQR 30–41), respectively; $P = 0.006$].

During the post-intervention period, the multidisciplinary care team also decreased the perinatal mortality rate from 60.8 (9 of 148) per 1000 births to 23.0 (2 of 87) per 1000 births, representing a relative risk reduction of 62.2% ($P = 0.20$), Figure 2. The decline in the mortality rate was not significantly different during the pre and post intervention periods; however, the relative risk reduction in perinatal rate was clinically relevant and consistent with the dramatic decline in maternal mortality rate. There was an associated marginal increase in the live birth rate, from 88.0% (139 of 158) to 94.4% (85 of 90) ($P = 0.098$), Table 1.

A clinically relevant, but not statistically significant reduction in the cesarean delivery rate occurred from pre- to the post-intervention period, from 61.2% to 48.3% ($P = 0.054$) respectively, Table 1. Spontaneous vaginal deliveries correspondingly increased from 38.8% to 51.7%, respectively. There was no difference in spontaneous abortions during the pre- and post-intervention periods (4% vs 3%), respectively. During the pre-intervention period, one participant died before delivery and delivery data were missing for four pregnant women with SCD and excluded from the analysis.

During the pre-and post-intervention periods, autopsy examination was performed for all mortality cases, as per hospital policy, to establish the cause of death, Table 2. Cardiopulmonary complications were the cause of death in 60% (9 of 15) of cases in the pre-intervention and the only death in the post-intervention period. Adjudication of the maternal mortality in the pre-intervention period showed that 60.0% (9 of 15) had acute chest syndrome and all received simple blood transfusion therapy as part of management of acute chest syndrome. During the post-intervention period, 15.6% (14 of 90) had an episode of acute chest syndrome and all received simple blood transfusion therapy.

4 | DISCUSSION

As efforts are made to reduce mortality among children with SCD in Africa through improved newborn screening, vaccination and effective treatment of malaria and other infections, as well as partnership in research and policies,[12,13] we can expect an increase in the number of

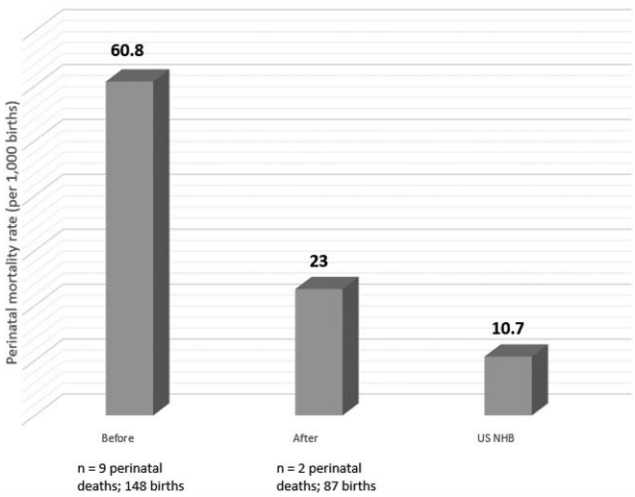

FIGURE 2 Perinatal mortality rates in pregnant women with sickle cell disease before and after intervention at Korle Bu Teaching Hospital, in Accra Ghana compared to Non-Hispanic Black (NHB) population of pregnant women in the United States.[21]

TABLE 2 Clinical profile of 16 women that died with sickle cell disease during the pre-intervention period (16 months) of an Obstetric Clinic and a post-intervention period (13 months) of a combined Sickle Cell Disease-Obstetric Clinic

Phenotype	Age	Parity	Clinical cause of death
Pre-intervention period			
HbSC	34	0	1. Acute Chest Syndrome 2. Pre-eclampsia
Not indicated in clinical notes	31	0	1. Acute Chest Syndrome 2. Pulmonary edema 3. Acute Kidney Injury 4. Septicemia 5. Sickle Cell Anemia[a]
Not indicated in clinical notes	27	3	1. Acute Kidney Injury 2. Septicemia 3. Sickle Cell Disease[a]
Not indicated in clinical notes	28	0	1. Acute Chest Syndrome in a known SCD patient[a] 2. Septicemia 3. Septic incomplete abortion
HbSS	27	0	1. Congestive cardiac failure 2. Severe anemia
HbSC	30	2	1. Acute Chest Syndrome 2. Pulmonary edema 3. Congestive cardiac failure 4. Acute Kidney Injury
HbSC	32	0	1. Acute Chest Syndrome 2. Bilateral Lobar Pneumonia 3. HELLP Syndrome
Not indicated in clinical notes	29	0	1. Severe anemia 2. Hyperhemolytic crisis 3. Vaso-occlusive crisis in a known SCD patient[a] 4. Puerperal sepsis
HbSC	28	0	1. Severe Anemia 2. Sequestration crisis
HbSC	39	3	1. Hypovolemic shock 2. Severe anemia 3. Hyperhemolytic crisis
HbSC	43	2	1. Acute Chest Syndrome 2. Pre-eclampsia
HbSS	26	1	1. Acute Chest Syndrome 2. Vaso- occlusive crisis
HbSS	32	1	1. Acute Chest Syndrome 2. Hyperhemolytic crisis 3. Vaso-occlusive crisis
HbSS	26	0	1. Severe anemia 2. Hyperhemolytic crisis 3. Vaso-occlusive crisis
Not indicated in clinical notes	26	0	1. Acute Chest Syndrome in a known SCD patient[a] 2. Pneumonia
Intervention period			
HbSC	27	1	Acute Chest Syndrome (pulmonary embolus)

[a]Autopsy report confirmed SCD diagnosis.

pregnant women with SCD. However, currently pregnancy in women with SCD in Africa is associated with a high mortality rate of between 7 and 12%[5–8] with a 22-fold increase in odds of death among women with SCD compared to those without SCD in the same setting.[9] We have demonstrated that a multidisciplinary care team dedicated to the active perinatal care of pregnant women with SCD, in a joint SCD-Obstetric Clinic, resulted in 89.1% reduction in maternal mortality and 62.2% reduction in perinatal mortality. We are unable to isolate which of the multiple interventions made the greatest impact in decreasing the maternal and perinatal mortality rates. We developed and used simple, scalable, and sustainable multimodal strategies to change clinical practice[14] as listed in Table SI and Figure SI, (Supporting Information).

To our knowledge, the only other prospective cohort study describing improved management of pregnant women with SCD in Africa demonstrated that enhanced prenatal care specific for the region lowered maternal mortality from 26.7% to 1.8%, which was comparable to the 1.2% rate found in pregnant women without SCD in the same setting.[15] Similar to our study, a multidisciplinary approach was used, but the study did not have a systematic evaluation of the deaths prior to the intervention, and was limited in describing reproducible protocols for management of SCD-related complications, including vaso-occlusive pain and acute chest syndrome.[15]

A recent systematic review of prophylactic blood transfusion and transfusion-on-demand showed a potential benefit for prophylactic blood transfusion in pregnant women with SCD.[16] Though most

maternal and perinatal clinical outcomes, including mortality, were improved with prophylactic regular blood transfusion, the small number and low quality of studies limited any inference on the translational value of this treatment for our setting in Ghana. More importantly, the resource constraints in low-resource settings prohibit prophylactic red blood cell transfusion as a plausible long-term strategy for women with SCA in Africa.

The reason for the decline in our perinatal mortality rate is also unclear. We reported a reduction in perinatal mortality rate from 60.8 per 1000 live births in the pre-intervention period to 23.0 per 1000 live births in the post-intervention period, that was comparable to the 21.0 per 1000 live births reported in pregnant women with SCD living in Paris, France,[17] and the 29 per 1000 reported from a UK national cohort study.[4] In the post-intervention period, the live births rate in our study was higher than that reported in the Cooperative Study of Sickle Cell Disease in 1996 (94.4% versus 89.3%, respectively).[18] Potential reasons for the decrease in perinatal mortality coupled with the increase in live birth rate include: (a) a reduction in the maternal mortality, (b) serial ultrasound performed in the third trimester to monitor fetal growth and well-being, (c) umbilical artery Doppler studies for those with suspected intrauterine growth restriction, and (d) rigorous monitoring of mother and fetus during labor.

As expected, limitations are inherent in a before-and-after study design. Specifically, the lack of prospective data collection in the pre-intervention period limited data quality for co-morbidities such as acute pain and acute chest syndrome. For example, the SCD phenotypes in most cases were recorded during the post-intervention period, but not all participants in the pre-intervention period had them recorded uniformly. However, all women had some form of SCD based on their extensive medical record review, and autopsy findings documented the presence of SCD in women who died. The dramatic reduction in the mortality rate is not attributable to a known shift in the SCD phenotypes over a course of 18 months. A perceived limitation in a before-and-after study is unintended bias in the primary outcome measurement. However, the primary outcome measure was death, an immutable outcome, was recorded uniformly. Furthermore, the death rate in the pre-intervention period is similar to that of other studies in Africa (7–12%)[5–8] and a recent report by Wilson et al. in Ghana.[7] These data suggest no significant bias in pre-intervention period maternal mortality rate.

In conclusion, we have demonstrated that a multidisciplinary care team consisting of hematologists, pediatrician, and obstetricians, applying simple, reproducible and inexpensive standard care protocols, in the care of pregnant women with SCD significantly decreases maternal and perinatal mortality in a low-resource setting. In Africa, further strategies must be employed to decrease the SCD-related maternal and perinatal mortality rates to levels expected in the non-SCD population. Widespread use of these strategies provide a reasonable point for decreasing maternal and perinatal mortality rates in other low-resource settings. Further, given the high number of pregnant women in Africa, opportunities to better understand optimal strategies for healthcare delivery may educate high-resource setting where SCD is a rare disease, such as in the United States.

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CONFLICT OF INTERESTS

Full disclosure of interests is available to view online as Supporting Information.

AUTHOR CONTRIBUTIONS

SAO, MRD, AAK, and EO conceived the idea.

EVA, EM, SC, YOB, HG, LM, BC, CHB, YDA, EO, TKB and SAO performed the data search.

EVA, CHB, MD, MR and SAO analyzed the data.

All authors participated in writing the article, and reviewed and approved the final version before submission.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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