# Screening for pulmonary hypertension in pregnant women with sickle cell disease in sub-Saharan Africa



Alim Swarray-Deen, MD; Misturah Y. Adana, MD, PhD; Micheal A. Alao, MD; Victoria A.A. Agyen-Frimpong, MD; Adekunle Fakunle, PhD; Deda Ogum-Alangea, PhD; David N. Adjei, PhD; Kwame Yeboah, MD, PhD; Yemi Raheem Raji, MD; Samuel A. Oppong, MD; James A. Ogunmodede, MD; Kolawole Wahab, MD; Kola Okuvemi, MD

BACKGROUND: Sickle cell disease (SCD) has evolved from a condition predominantly fatal in childhood to a chronic illness impacting many adults, including women of reproductive age. For females with SCD, pregnancy represents one of the greatest health threats, exacerbating existing health challenges and introducing new risks. Despite advancements in healthcare, routine screening for existing complications like pulmonary hypertension (PH) remains inconsistent, particularly in low- and middle-income countries (LMICs), where the prevalence of SCD is highest.

**OBJECTIVE:** This study aimed to assess the feasibility of screening for PH in pregnant women with SCD in LMICs, with the goal of enhancing maternal health outcomes in this vulnerable population.

STUDY DESIGN: A prospective multi-center feasibility study was conducted from September 2022 to February 2023 at teaching hospitals in Ghana and Nigeria. The study included pregnant women with SCD between 28 and 34 weeks of gestation. Screening for PH utilized a tricuspid regurgitation velocity (TRV) criterion (>2.5 m/s), with adherence to American Society of Echocardiography guidelines. Statistical analysis included descriptive statistics and proportions.

RESULTS: Among 3091 pregnant women attending antenatal care, 88 had SCD (2.8%), and 55 were eligible for the study. We recruited 44 participants (mean age 28.9 years, SD 4.8), with 48% (21/44) SS genotype and 52% (23/44) SC genotype. Most participants (95.3%) had normal TRV (<2.5 m/s), with only one showing elevated TRV, successfully referred. Protocol adherence was 100%. Antenatal outcomes showed 95% echo uptake and 95.7% retention to term whilst postnatal echo follow-up was 43.5%. Notably, 27.1% (10/37) of deliveries required neonatal intensive care unit admission, and 18.2% were preterm. The sole participant with PH required intensive care unit care and experienced a preterm delivery with neonatal death on day 5.

**CONCLUSION:** Screening and referral for PH in pregnant women with SCD in LMICs are feasible but face challenges in early diagnosis, healthcare personnel availability, and postnatal follow-up. Strategic planning is crucial to address these challenges and improve outcomes in this high-risk population

Key words: feasibility study, low-middle income, pregnancy, pulmonary hypertension, screening referral system, sickle cell disease

From the Department of Obstetrics & Gynaecology, University of Ghana Medical School, Accra, Ghana (Swarray-Deen and Oppong); Department of Anatomy, University of Ilorin Teaching Hospital, Ilorin, Kwara State, Nigeria (Adana); Department of Pediatrics, University College Hospital, Ibadan, Nigeria (Alao); Department of Medicine & Therapeutics, Korle Bu Teaching Hospital, Accra, Ghana (Agyen-Frimpong); Department of Medicine, College of Medicine, University of Ibadan, Ibadan, Nigeria (Fakunle); Department of Population, Family and Reproductive Health, School of Public Health, University of Ghana, Accra, Ghana (Ogum-Alangea); Department of Medical Laboratory Sciences, School of Biomedical and Allied Health Sciences, College of Health Sciences, University of Ghana, Accra, Ghana (Adjei); Department of Physiology, University of Ghana Medical School, Accra, Ghana (Yeboah); Nephrology Unit, Department of Medicine, College of Medicine, University of Ibadan, Ibadan, Oyo State, Nigeria (Raji); Department of Medicine, University of Ilorin, Ilorin, Kwara State, Nigeria (Ogunmodede and Wahab); Department of Family Medicine, Indiana University School of Medicine, Indianapolis, IN (Okuyemi)

Patient Consent Statement: Informed consent was obtained from all participants included in the study. All procedures followed in this research were in accordance with the ethical standards of the institutional review board and the 1964 Helsinki Declaration and its later amendments. Written consent was provided by each participant before their inclusion in the study.

Funding: This project was funded by the Stroke and Cardiovascular Research Training (SCaRT) Institute in supported by the National Institutes of Health (NIH)/Fogarty International Centre (grant number 5D43TW009140-08) to Gbenga Ogedegbe The funding organization had no role in the design of the study, the collection, analysis, and interpretation of data, or in writing the manuscript. The authors had full access to all the data and assume responsibility for the integrity and accuracy of the data presented.

Conflicts of Interest: The authors declare that they have no conflicts of interest relevant to the content of this manuscript. There are no financial or personal relationships that could be perceived as influencing the research and its outcomes.

Corresponding author: Alim Swarray-Deen asdeen8@gmail.com

2666-5778/\$36.00

© 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/) http://dx.doi.org/10.1016/j.xagr.2024.100413

# AJOG Global Reports at a Glance

## A. What is the study about?

This study investigated the feasibility of screening for pulmonary hypertension (PH) in pregnant women with sickle cell disease (SCD) across low-middle-income countries (LMICs).

## B. Why is it significant?

Pregnant women with SCD face heightened risks, including pulmonary hypertension, which can significantly impact maternal health outcomes.

### C. What does it contribute to the literature?

This study contributes by demonstrating the practicality and effectiveness of PH screening protocols specifically tailored for LMICs, highlighting a crucial step toward improving maternal health in vulnerable populations.

### Introduction

Sickle cell disease (SCD) is one of the most prevalent single-gene disorders globally, with over 75% of the burden concentrated in sub-Saharan Africa.<sup>1-3</sup> While SCD traditionally was fatal in childhood, advances in healthcare have shifted its natural history to a chronic illness affecting adults.4 Among adults with SCD, secondary pulmonary hypertension (PH) is a significant complication, occurring in approximately 30% of patients and contributing to a high mortality rate of up to 40%. 5-8 For pregnant women with SCD, one of the greatest threats arises during pregnancy, as the risks of adverse outcomes are markedly elevated. These risks include neonatal mortality, admission to neonatal care units, anemia, preeclampsia, vaso-occlusive crises, and acute chest syndrome.<sup>9,10</sup> The presence of PH further exacerbates these risks, with nearly 25% of such pregnancies facing severe complications.11

Despite the established guidelines recommending routine PH screening every 1 to 3 years for adults with SCD, <sup>12</sup> such practices are rarely implemented in low- and middle-income countries (LMICs) where SCD prevalence is highest. In LMICs, prepregnancy screening and counseling for PH are often unavailable, and there is limited evidence on the benefits of systematic screening and referral systems. Therefore, it is crucial to develop and evaluate effective PH screening and referral protocols tailored for pregnant women with SCD in these settings to improve

maternal and perinatal health outcomes.

While the pathophysiology of PH in SCD is complex, persistent hemolysis and inflammation are thought to be the primary causes, leading to structural damage in the pulmonary blood vessels. This structural deterioration causes increased pressure in the pulmonary arteries, putting strain on the right ventricle and eventually causing it to fail. <sup>13</sup>

Pulmonary capillary wedge pressure (PCWP) is a key measure for evaluating PH and provides insights into left ventricular function. An elevated PCWP may indicate left heart dysfunction contributing to PH, but this invasive method is not recommended during pregnancy. <sup>14</sup>

Secondly, tricuspid regurgitation, assessed via transthoracic echocardiography, offers information about right ventricular function and the severity of PH. These measurements play a pivotal role in diagnosing the disease, tracking its progression, and guiding treatment decisions. Traditionally, a tricuspid regurgitant velocity (TRV) of  $\geq 2.5$  m/s detected through echocardiography has served as a surrogate marker for PH.15 This elevated TRV is linked to increased fetal loss rates, more frequent episodes of acute chest syndrome, heightened risk of fetal malformations, and elevated mortality and morbidity maternal rates. 13,16 Furthermore, the current guidelines endorsed by the European Society of Cardiology (ESC) and European Respiratory Society categorize the likelihood of PH based on TRV at rest as either high ( $\geq$ 3.5 m/s), intermediate (2.9–3.4 m/s), or low (2.8 m/s). <sup>17</sup> However, these guidelines have not been evaluated in our region, and the feasibility and effectiveness of implementing these screening criteria in LMICs remain unassessed compared to high-income countries.

To address this knowledge gap, our team of experts specialized in caring for pregnant women with SCD in Ghana and Nigeria conducted a "feasibility" study across two centers. The primary objectives of this study were to screen for PH among pregnant women with SCD and to assess the impact of the screening and referral system on pregnancy outcomes within this specific group of women.

# Materials and methods **Study design and sites**

This prospective multi-center feasibility study was conducted over 6 months, from September 2022 to February 2023, at two sites. The first site was the Korle Bu Teaching Hospital (KBTH) in Accra, Ghana, which has a dedicated clinic for obstetric care for individuals with SCD. The SCD Obstetric Clinic has been offering comprehensive multidisciplinary SCD obstetrics care since 2015.18 The second site, the University of Ilorin Teaching Hospital (UITH) in Ilorin, Nigeria, which provides comprehensive level 3 maternal-fetal care but does not have a dedicated SCD Obstetric Clinic. This study was approved by the ethics committees of both KBTH and UITH (KBTH-IRB/00080/2022 and UITH/ CAT/189/219/312, respectively). Each participant provided written informed consent before participating in the study and the study was conducted in accordance with the ethical standards and principles of the Declaration of Helsinki.

### **Study participants**

The following were the inclusion criteria for screening: age above 18 years; singleton pregnancies with gestational age confirmed through first or second-trimester ultrasound scan; gestational age between 28 and 34 weeks; and documented SCD genotype of SS or SC

confirmed through medical records and Hb electrophoresis using alkaline pH using cellulose acetate paper. Women with SCD with complicated pregnancies, such as multiple gestations or fetal abnormalities, and SCD women admitted for acute complications were not included in the study.

For this study, we decided to enlist participants who were between 28 and 34 weeks pregnant. Our decision was in line with the ESC guidelines, which suggest that if PH is detected before the age of viability (set at 28 weeks of gestation in both facilities as in most LMIC), terminating the pregnancy may be advisable. Moreover, we selected the upper limit of 34 weeks to ensure that there was enough time for effective referral and intervention, which would maximize their potential impact on the study's results.

# Sample size estimation

According to hospital records, an average of 150 pregnant women with SCD attend the antenatal clinic annually. We estimated that about 15 SCD patients would attend per month. To account for factors such as uneven attendance, presence of other diseases, and potential loss to follow-up, we decided that a sample size of 50 participants over 6 months (25 from each site) would be sufficient for this feasibility study.

# Sampling technique

The sampling technique employed in this study was purposive sampling, where participants were intentionally selected based on specific criteria and objectives, rather than through random selection.

# Conduct of the study and intervention

At each study site, a research assistant screened pregnant women attending antenatal care (ANC) to determine their eligibility for the study. Women with SCD who met the criteria were counseled and enrolled after obtaining written consent. Following enrolment, demographic data, medical records, and detailed obstetric histories were

collected. A standard 2D transthoracic echocardiogram (ECHO) was then performed on the participants at no additional cost. Echocardiographic assessments were carried out by a dedicated cardiologist at each site, adhering to the American Thoracic Society Clinical Practice Guidelines. 15 At KBTH, ECHO were conducted on the same day as recruitment, while at UITH, they were scheduled for a later date, with an average interval of 2 weeks from enrolment to the scan to ensure retention. A General Electric Logiq-e ultrasound unit was used at KBTH, and a Sonoscape SS1-8000 was utilized at UITH. The Tricuspid regurgitation was assessed in the parasternal right ventricular inflow, parasternal short-axis, and apical fourchamber views to determine the highest velocity. If the tricuspid regurgitant jet velocity was greater than 2.5 m/s, the participant was considered to have elevated systolic pulmonary artery pressure. 15 Participants with normal screening results (TRV<2.5 m/s) continued to receive routine care from dedicated obstetricians and hematologists at their respective sites. Those identified with PH (TRV>2.5 m/s) were referred to the study cardiologist for appropriate care while continuing their routine care with dedicated obstetricians and hematologists.

All participants were followed up until delivery, and a repeat echo assessment was requested after their 6-week postpartum visit.

### **Study outcomes**

The following primary study outcomes were prespecified and based on a combination of practical considerations and industry standards for assessing the feasibility and reliability of clinical studies. <sup>18,20</sup> They represent reasonable benchmarks that, if achieved, indicate that the study can be conducted effectively, participants can be retained throughout the study period, and data collection procedures are adhered to at a high level.

1. Recruitment rate: A minimum of 75% of eligible individuals agreeing to participate signifies feasibility.

- 2. Retention rate: A minimum of 75% of enrolled participants completing all scheduled visits and adhering to the protocol until 6 weeks postpartum demonstrates feasibility.
- 3. Adherence rates: A minimum of 90% completion of ECHO, according to ECS recommendations, evidenced by comprehensive echo reports, illustrates feasibility.

The secondary outcomes include the detection of PH using TRV criteria, maternal and perinatal outcomes such as preterm delivery, incidence of maternal SCD vaso-occlusive crisis, hospital admission, maternal mortality, and fetal outcomes including low birthweight, stillbirth, fetal distress, and birth asphyxia.

## **Analysis plan**

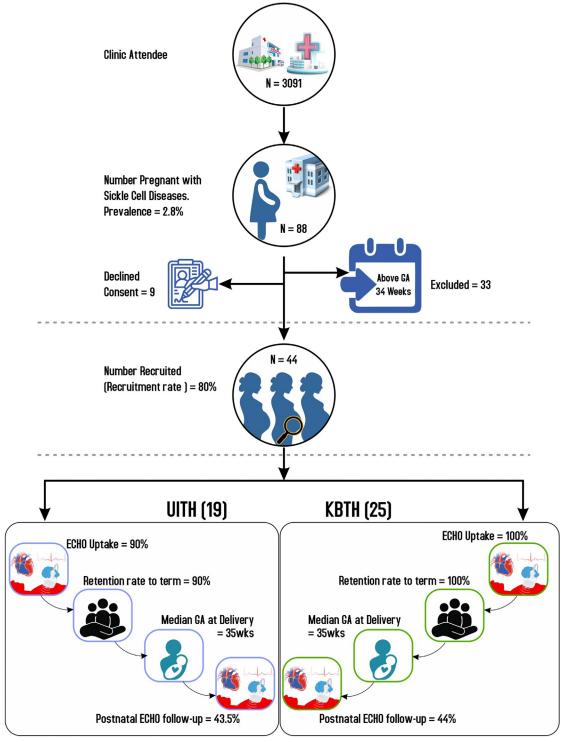
All data were entered into Excel spreadsheets, validated, and exported to SPSS (version 25). All outcome measures were summarized using proportions and percentages. Other variables, such as socio-demographic characteristics, were summarized using appropriate descriptive statistics. Participants with TRV<2.5 m/s were categorized as no PH, while those with TRV≥2.5 m/s were grouped as PH.

### Results

A total of 3091 pregnant women attended ANC at both sites during the study period. Out of these, 88 (2.8%) were pregnant women with SCD. We recruited 44 out of 55 eligible pregnant women with SCD (25 from KBTH and 19 from UITH), achieving a recruitment rate of 80.0%. The most common reason for exclusion was that participants exceeded 34 weeks of gestation during the study period (Figure 1). The recruited participants had a mean (SD) age of 28.9 (4.8) years. Most participants (91%) had education beyond the primary level, and about 77.3% were employed (as shown in Table 1). None of the participants had any prior knowledge about PH or had been previously screened for it.

Among the women, 48% had an SS genotype and 52% had an SC genotype.

FIGURE 1 Study flow diagram illustrating participant recruitment and screening processes from both sites (KBTH and UITH).



Swarray-Deen. Screening for pulmonary hypertension in pregnant women. AJOG Glob Rep 2024.

The mean TRV was 1.43 m/s, with most participants (95.3%) having normal ventricular function and TRV<2.5 m/s. Only one participant had an elevated

TRV and was referred to the cardiologist. Protocol adherence was 100%.

The antenatal outcomes included achieving an echocardiography uptake

of 95% (antenatal echocardiography KBTH 100.0% and UITH 90.0%). Retention to term was 95.7%, (KBTH [100%]; UITH [90.5%]). Two

TABLE 1 Socio-demographic and obstetric characteris	tics of study participants
Demographic variables	Frequency (%)
Age, mean (SD)	28.9 (±4.9)
Range	19-37
BMI, mean (SD)	26.4 (±5.3)
Range	19.8-41.2
Gestational age at enrolment, mean (std. dev)	29.8 (±1.9)
Range	28-34
Parity	
0	16 (%)
1	13 (%)
2	10 (%)
3	5 (%)
Marital status	
Married	37 (84.1%)
Single	7 (15.9%)
Education	
None	2 (4.5%)
Primary	2 (4.5%)
Junior high school	4 (9.1%)
Senior high school	7 (15.9%)
Tertiary	29 (66.0%)
Employment status	
Formal	10 (22.7%)
Informal	24 (54.6%)
Unemployed	10 (22.7%)
Phenotype	
HbSC	23 (52.3%)
HbSS	21 (47.7%)
Religion	
Christian	21 (47.7%)
Muslim	23 (52.3%)
Routine attendance at adult SCD clinic	
Yes	25 (56.8%)
No	19 (43.2%)
Number pain crisis in past year	
0	15 (34.1%)
1–2	16 (36.4%)
3–5	7 (15.9%)
6–9	2 (4.5%)
>10	4 (9.1%)
Swarray-Deen. Screening for pulmonary hypertension in pregnant wom	en. AJOG Glob Rep 2024.

participants (4%) from UITH were lost to follow-up in the 2-week waiting period for the ECHO (one voluntary withdrawal and one preterm delivery).

The dedicated study cardiologists at each site followed the study protocol with 100% adherence and evaluated both antenatal and postnatal ECHO (Table 2). The assessment per participant took approximately 25 minutes on average and no challenges were reported. The mean TRV for the entire study population was 1.80 ( $\pm 0.6$ ) m/s.

One participant exhibited an elevated TRV of 3.6 m/s and abnormal ventricular systolic function. She required intensive care unit (ICU) admission and had a preterm delivery at 35 weeks gestation, which tragically resulted in a neonatal mortality on day 5 of life.

All other participants had TRV values below 2.5 m/s. A total of 37 spontaneous deliveries were recorded, with 25 (67.6%) occurring at KBTH and 12 (32.4%) at UITH. These deliveries occurred at a median gestational age of 35 weeks, with an interquartile range of 2 weeks. The average birth weight was 2.7 kg ( $\pm 0.5$  kg). Most deliveries were vaginal (16, 43.2%), with cephalic presentation being the most common (30, 90.0%). Among these deliveries, 27.1% required admission to the neonatal ICU (NICU), and 18.2% were preterm (Table 3).

The overall postnatal ECHO followup rate was 43.5%, with 44.0% and 43.5% follow-up at KBTH and UITH, respectively. The primary challenge encountered during the study was the intermittent unavailability of cardiologists.

### Discussion

Principal findings: Our study highlights the feasibility of implementing a screening and referral system for PH among pregnant women with SCD in West African countries with a high burden of SCD. Despite facing challenges typical of LMICs, such as limited healthcare infrastructure and logistical hurdles in postnatal care, our findings demonstrate promising results. We

			Antenatal echoes (N=44)				Postnatal echoes (N=20)			
Variables	Min	Max	Mean	±SD	Min	Max	Mean	±SI		
Aortic root diameter	1.8	3.5	2.7	0.3	1.7	3.1	2.4	0.5		
Aortic cusp distance	1.4	3.3	1.9	0.3	1.6	2.2	1.8	0.2		
Aortic annulus diameter	1.5	3.2	2.1	0.4	1.6	2.4	1.8	0.2		
Right ventricular diameter	0.9	4.5	2.9	0.6	1.6	4.2	2.9	0.6		
Right ventricular anterior wall thickness	0.3	3.2	0.4	0.2	0.4	0.6	0.4	0.1		
Interventricular septal thickness in diastole	0.6	1.3	1.0	0.2	0.7	1.3	0.9	0.3		
Left ventricular internal diameter in diastole	2.4	6.7	4.9	0.7	3.7	6.3	5.0	0.7		
Left ventricular internal diameter in systole	0.8	4.7	3.3	0.6	2.3	4.4	3.4	0.6		
Left ventricular posterior wall thickness in diastole	0.5	1.4	0.9	0.2	0.6	1.1	0.9	0.1		
Left ventricular ejection fraction	47.2	79.0	60.4	6.8	48.0	77.0	59.4	6.9		
Fractional shortening	24.1	46.0	32.3	7.2	24.0	46.0	28.8	6.1		
Main pulmonary artery diameter	1.4	6.7	2.8	1.6	1.8	6.1	2.6	2.1		
Mitral valve E velocity	0.6	1.4	0.9	0.2	0.6	1.0	8.0	0.2		
Mitral valve deceleration time	45.0	369.0	143.4	43.9	100.0	205.0	155.6	25.		
Mitral valve a velocity	0.2	1.0	0.6	0.2	0.3	0.7	0.5	0.3		
E/A ratio (early diastolic filling velocity to late diastolic filling velocity ratio)	0.9	8.5	1.6	0.7	1.0	3.1	1.4	0.7		
Septal e' velocity (early diastolic tissue Doppler velocity of the septal mitral annulus)	0.1	0.2	0.1	0.0	7.0	17.0	9.0	2.8		
Lateral e' velocity (early diastolic tissue Doppler velocity of the lateral mitral annulus)	0.0	16.0	0.2	0.0	0.1	19.0	8.0	13.		
Ratio of early diastolic filling velocity to septal e' velocity	3.2	10.8	7.1	1.9	2.4	8.9	7.2	2.6		
Mitral valve peak velocity	0.5	4.9	1.2	0.7	0.9	1.3	1.1	0.1		
Mitral valve pressure gradient	1.2	68.2	4.3	3.8	3.1	6.6	4.5	1.1		
Aortic valve peak velocity	1.2	1.9	1.5	0.2	1.1	1.6	1.4	0.3		
Aortic valve pressure gradient	6.0	14.9	9.7	2.3	4.7	10.8	8.4	3.4		
Tricuspid valve peak velocity	0.3	3.8	0.6	0.2	0.5	169.8	0.6	0.1		
Tricuspid valve pressure gradient	0.1	2.2	1.1	0.5	0.9	11.5	1.2	0.4		
Tricuspid regurgitant velocity <sup>a</sup>	0.5	3.4	1.8	0.6	1.6	2.6	2.1	0.3		
Pulmonary valve peak velocity	0.6	1.4	1.0	0.2	0.7	1.2	0.9	0.1		
Pulmonary valve pressure gradient	1.3	12.5	3.8	2.4	1.7	6.2	3.3	1.1		
Tricuspid annular plane systolic excursion	2.0	3.9	2.7	0.4	1.9	2.9	2.5	0.3		

achieved high recruitment rates and excellent protocol adherence, indicating that engaging eligible pregnant women with SCD in comprehensive healthcare programs is achievable with appropriate strategies and dedication from healthcare teams.

**Results:** Screening for PH in pregnant women requires careful consideration of diagnostic tools. While

biomarkers like N-terminal pro-b-type natriuretic peptide (NT-proBNP) and the 6-minute walk test offer supplementary information, they have limitations. NT-proBNP levels can be affected by pregnancy-related changes, and the 6-minute walk test assesses cardiorespiratory fitness rather than directly measuring pulmonary pressures. Each method has its own strengths and weaknesses,

emphasizing the need for a tailored approach in suspected PH cases during pregnancy.

Among noninvasive methods, echocardiography, specifically the measurement of TRV, is a commonly used tool. The American Thoracic Society Clinical Practice Guidelines recommend a TRV>2.5 m/s as an indicator of increased mortality risk

Perinatal outcomes	<i>N</i> =37			
Gestational age at delivery, <i>median (IQR)</i>	37 (2)			
Range	28-39			
Mode of delivery				
SVD	16 (43.2%)			
C/S	21 (56.7%)			
Onset of labor				
Spontaneous	15 (93.7%)			
Induced	1 (6.3%)			
Indication for C/S				
Failed induction	3 (14.3%)			
Fetal distress	1 (4.7%)			
Fetal macrosomia	1 (4.7%)			
Maternal bleeding	1 (4.7%)			
Recurrent crisis	1 (4.7%)			
Previous C/section	14 (66.7%)			
Livebirth	37 (100%)			
Birth weight, mean (SD)	2.7 (0.5)			
Range	1.5-3.6			
NICU admission	10 (27.1%)			
Reason for NICU admission				
Asphyxia	1 (3.0%)			
Indrawing chest	1 (3.0%)			
Prematurity/preterm	6 (18.2%)			
Vomiting	1 (3.0%)			
Monitoring	1 (3.0%)			

in SCD.15 Despite its value, TRV is not without limitations. It can produce false positives, and its accuracy is influenced by factors such as operator skill and patient positioning. A TRV≥2.5 m/s has a low positive predictive value, with only 31% of these patients showing a mean pulmonary artery pressure ≥25 mm Hg on right heart catheterization (RHC).21 In contrast, a TRV≥3 m/s, which is three standard deviations above the mean, demonstrates higher specificity, confirming PH in 66% to 77% of patients undergoing RHC.22 While RHC provides precise measurements, it is

invasive and not always available in all healthcare settings.

The increasing affordability and accessibility of ultrasound make it a practical screening method, particularly in LMICs, where it may be the only viable option due to healthcare delivery constraints.

Determining the optimal timing for TRV screening in pregnant women with SCD is complex and raises ethical concerns. Preconception screening is recommended by guidelines such as those from the Royal College of Obstetricians and Gynaecologists and the American Thoracic Society, 15,23 but

implementing this in LMICs poses significant challenges. These guidelines stress early detection and management, but pregnancy introduces dynamic physiological changes that complicate the establishment of an optimal screening time.

A study by Soh et al<sup>24</sup> recommended pregnancy termination in cases of identified PH due to high risks. However, our study included participants beyond the age of viability, requiring a more nuanced approach to decision-making. Rather than relying solely on TRV cutoffs, we considered both obstetric and cardiac status. This reflects the ethical complexities in LMICs where preconception screening may not be feasible, and decisions must balance the risks and benefits for both the mother and the fetus.

The study's recruitment rate, which is crucial for determining feasibility, exceeded expectations with an impressive 90.7% across all participating facilities. This shows that eligible pregnant women with SCD can be engaged in LMICs with proper communication strategies and the dedication of health-care teams involved. Additionally, the study showed remarkable retention rates, with 100% retention rate up to the delivery, indicating that participants were effectively engaged.

In terms of protocol adherence, which is essential for ensuring data quality, the study achieved an impeccable 100% adherence rate for ECHO procedures. This outcome highlights the feasibility of implementing complex diagnostic tests in resource-constrained settings, reflecting the expertise of healthcare teams and the comprehensive training provided. However, the intermittent unavailability of cardiologists and challenges with postnatal follow-up underscore the need for consistent staffing and strategies to enhance accessibility. The low postnatal turnout was similar in both sites, even at KBTH which is well-known for its multidisciplinary SCD Obstetric care that has been operational since 2015.25,26

We noticed that many mothers preferred to opt for clinics closer to their

homes for postpartum care, resulting in decreased attendance at our study site. Despite providing stipends to subsidize transportation, the distance to the hospital remained a significant barrier for many, ultimately leading to their nonattendance on their scheduled follow-up dates

Clinical implications: Our findings hold significant implications for clinical practice in LMICs. Integrating PH screening into routine ANC for pregnant women with SCD could potentially mitigate the risks associated with undiagnosed PH, including maternal mortality. Clinicians should consider implementing standardized protocols and enhancing healthcare accessibility to ensure timely PH detection and intervention.

Research implications: Longitudinal studies are needed to evaluate the effectiveness of interventions following early PH detection during pregnancy. Additionally, investigating the long-term impacts of PH screening on maternal and fetal outcomes could provide further insights into optimizing care strategies for this vulnerable population.

**Strengths and limitations:** The study benefits significantly from its dual-site approach, offering a broader scope for data collection and enriching the understanding of how the screening protocol operates in diverse settings. However, the sample size, though adequate for a feasibility study, limits the extent to which findings can be generalized beyond the two specific sites. Additionally, the echocardiography machines used at the KBTH and UITH were of different makes, which could have introduced variability in TRV readings. To address this, standardized protocols, consistent training, and calibration checks were implemented to minimize potential discrepancies, and no significant differences related to equipment were observed in the results. Challenges in retaining participants for postpartum echocardiography also present a potential limitation, affecting the comprehensive assessment of outcomes across the study cohort. These considerations underscore the need for cautious interpretation of the study's findings and highlight areas where future research could further elucidate the effectiveness and scalability of PH screening strategies in similar settings. The single-case incidence of PH in our study limits generalizability, highlighting its rarity in our cohort. Despite these constraints, our findings underscore the urgent need for targeted interventions and policy initiatives to enhance PH screening and management strategies specifically tailored for LMIC settings.

#### Conclusion

This study highlights the importance of screening for PH in pregnant women with SCD in LMICs. It shows that it is feasible to include routine PH screening in prenatal care, but there are challenges in postpartum retention. The study emphasizes the need for specialized care and long-term management to improve outcomes for this vulnerable population. Healthcare systems in LMICs should integrate comprehensive care for individuals with SCD into routine prenatal services, address logistical barriers, and optimize resource allocation to ensure timely diagnosis and intervention of PH amongst other SCD complications.

# CRediT authorship contribution statement

**Alim Swarray-Deen:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. Misturah Y. Adana: Writing – review & editing, Writing - original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. Micheal A. Alao: Writing review & editing, Writing - original draft, Visualization, Validation, Funding acquisition, Formal analysis, Data curation, Conceptualization. Victoria A.A. Agyen-Frimpong: Writing review & editing, Writing - original Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. Adekunle Fakunle: Writing - review & editing, Writing - original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. Deda Ogum-Alangea: Writing - original draft, Supervision, Methodology. David N. Adjei: Writing - review & editing, Writing original draft, Project administration. Kwame Yeboah: Writing – review & editing, Writing - original draft, Project administration. Yemi Raheem Raji: Writing - review & editing, Writing original draft, Project administration. **Samuel A. Oppong:** Writing – review & editing, Writing - original draft, Visualization, Validation, Supervision, administration, Resources, Project Methodology, Formal analysis. James **A. Ogunmodede:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. Kolawole Wahab: Writing - review & editing, Writing - original draft, Project administration. Kola Okuyemi: Writing - review & editing, Writing original draft, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization.

## **ACKNOWLEDGMENTS**

We extend our heartfelt thanks to Dr Sorie Conteh and Dr Emmanuella Tagoe for their invaluable contributions in performing the echocardiograms. Special appreciation goes to John Ayete-Nyampong, the project manager, and the staff of the Fetal Assessment Centre at the Korle Bu Teaching Hospital in Ghana. We also acknowledge the administrative members of the SCART team, Sylvia Darko Osei and Abigail Addison, for their vital support.

### REFERENCES

- **1.** Piel FB, Patil AP, Howes RE, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet 2013;381(9861):142–51.
- **2.** Mogann PT, Hernandez AG, Ware RE. Sickle cell anemia in sub-Saharan Africa: advancing the clinical paradigm through partnerships and research. Blood 2017;129 (2):155–61.
- **3.** Collaborators GBDSCD. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000-2021: a systematic analysis from the Global Burden of Disease Study 2021. Lancet Haematol 2023;10(8): e585–99.

- 4. Lanzkron S, Carroll CP, Haywood Jr. C. Mortality rates and age at death from sickle cell disease: U.S., 1979-2005. Public Health Rep 2013:128(2):110-6.
- 5. Aliyu ZY, Kato GJ, Taylor Iv J, et al. Sickle cell disease and pulmonary hypertension in Africa: a global perspective and review of epidemiology, pathophysiology, and management. Am J Hematol 2008;83(1):63-70.
- 6. Krishnan S, Fricke EM, Cordoba M, Chalifoux LA, Girgis RE. Pulmonary hypertension complicating pregnancy. Curr Pulmonol Rep 2021;10(2):71-83.
- 7. Zimbarra Cabrita I, Mohammed A, Layton M, et al. The association between tricuspid regurgitation velocity and 5-year survival in a North West London population of patients with sickle cell disease in the United Kingdom. Br J Haematol 2013;162(3):400-8.
- 8. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004;350(9):886-95.
- 9. Boafor TK, Olayemi E, Galadanci N, et al. Pregnancy outcomes in women with sicklecell disease in low and high income countries: a systematic review and meta-analysis. BJOG: Int J Obstet Gynaecol 2016;123 (5):691-8.
- 10. Oteng-Ntim E, Meeks D, Seed PT, et al. Adverse maternal and perinatal outcomes in pregnant women with sickle cell disease: systematic review and meta-analysis. Blood 2015;125(21):3316-25.
- 11. Karimi MB. Neglected pulmonary arterial hypertension in sickle cell anaemia during

- prenatal care. Eur J Case Rep Intern Med 2020;7(6):001532.
- 12. Willen SM. Gladwin MT. What is the role of screening for pulmonary hypertension in adults and children with sickle cell disease? Hematol Am Soc Hematol Educ Program 2017;2017(1):431-4.
- 13. Gordeuk VR, Castro OL, Machado RF. Pathophysiology and treatment of pulmonary hypertension in sickle cell disease. Blood 2016;127(7):820-8.
- 14. Sheikh AB, Nasrullah A, Lopez ED, et al. Sickle cell disease-induced pulmonary hypertension: a review of pathophysiology, management, and current literature. Pulse (Basel) 2021;9(3-4):57-63.
- 15. Klings ES, Machado RF, Barst RJ, et al. An Official American Thoracic Society Clinical Practice Guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med 2014;189(6):727-40.
- **16.** Gladwin MT. Cardiovascular complications and risk of death in sickle-cell disease. The Lancet 2016;387(10037):2565-74.
- 17. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2015;46(4):903-75.
- 18. Asare EV, Olayemi E, Boafor T, et al. Implementation of multidisciplinary care reduces maternal mortality in women with sickle cell disease living in low-resource setting. Am J Hematol 2017;92(9):872-8.
- 19. Oppong SA, Asare EV, EOAjo, et al. Undefined. Multidisciplinary care results in similar maternal and perinatal mortality rates

- for women with and without SCD in a lowresource setting. Am J Hematol 2019;94: 223-30.
- 20. Desai M. Recruitment and retention of participants in clinical studies: critical issues and challenges. Perspect Clin Res 2020;11(2): 51-3.
- 21. Niss O, Quinn CT, Lane A, et al. Cardiomyopathy with restrictive physiology in sickle cell disease. JACC Cardiovasc Imaging 2016;9 (3):243-52.
- 22. Mehari A, Gladwin MT, Tian X, Machado RF, Kato GJ. Mortality in adults with sickle cell disease and pulmonary hypertension. JAMA 2012;307(12):1254.
- 23. Royal College of Obstetricians and Gynaecologists. Management of sickle cell disease in pregnancy. Green-top Guideline No. 61. London: RCOG; 2011.
- 24. Soh MC, Sankaran S, Chung NYA, et al. Mildly raised tricuspid regurgitant velocity 2.5-3.0 m/s in pregnant women with sickle cell disease is not associated with poor obstetric outcome - an observational cross-sectional study. Obstetric Medicine 2016;9(4):160-3.
- 25. Oppong SA, Olayemi E, Adomakoh Y, et al. Multi-disciplinary obstetrics and sickle cell disease clinic in low resource setting lowers maternal and perinatal death rates to the same levels as those without sickle cell disease. Blood J 2017;130(Suppl 1):616.
- 26. Swarray-Deen A, Asare EV, Ayettey Brew R, et al. Sustainability of low maternal mortality in pregnant women with SCD in a low-resource setting. Blood Adv 2022;6(7):1977-80.