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Cerebro-placental ratio as a prognostic factor of fetal outcome in pregnancy complicated by maternal sickle cell disease

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Abstract

Objectives: To assess the role of the cerebro-placental ratio (CPR) in predicting adverse fetal outcomes among women with sickle cell disease (SCD).

Methods: A prospective cohort study at Korle-Bu Teaching Hospital, Accra, Ghana, between January and June 2016. Pregnant women with SCD at 34 gestational weeks or more underwent weekly fetal umbilical and middle cerebral artery Doppler assessment until delivery. Participants were categorized into two study arms based on CPR (<1.1 or ≥1.1). The primary outcome, a composite of adverse perinatal outcomes including intrauterine growth restriction, stillbirth, low birthweight, and neonatal intensive care unit admission, was compared between groups.

Results: Overall, 48 pregnant women with SCD were enrolled, and 5 had a fetus with CPR less than 1.1. Low CPR (<1.1) had a sensitivity and specificity of 29.4% and 100%, respectively, for predicting composite adverse perinatal outcomes. Sensitivity and specificity were, respectively, 100% and 93.5% for predicting stillbirth, and 40.2% and 97.4% for predicting low birthweight. Perinatal outcomes did not differ between the two major sickle cell genotypes (hemoglobin SS and hemoglobin SC).

Conclusions: Among women with SCD, CPR less than 1.1 was associated with adverse perinatal outcomes, particularly low birthweight and stillbirth.

KEYWORDS

Adverse neonatal outcome; Cerebro-placental ratio; Doppler; Fetal compromise; Sickle cell disease; Small for gestational age; Ultrasound

1 | INTRODUCTION

Pregnancies complicated by maternal sickle cell disease (SCD) are at risk of adverse maternal and perinatal outcomes.[1] Perinatal mortality and morbidity such as intrauterine growth restriction (IUGR), preterm delivery, and intrapartum fetal distress are higher in women with SCD than in those without SCD.[2–5] Over the years, improvements in obstetric outcomes have been observed for women with SCD owing to better fetal surveillance and multi-disciplinary care including hematology.[6]

The cerebro-placental ratio (CPR), a ratio of the middle cerebral artery (MCA) and umbilical artery (UA) Doppler indices, has been shown to improve accuracy in predicting adverse perinatal outcome as compared with MCA or UA Doppler indices alone.[7–9] Assessment of CPR at repeated intervals has been increasingly incorporated in the surveillance of fetuses at risk of hypoxemia.[10] Furthermore, recent studies have suggested that low MCA pulsatility index (PI) and high UA PI are associated with intrapartum fetal distress, low neonatal blood pH, and neonatal intensive care unit (NICU) admission, regardless of fetal size.[11–13]

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There have been numerous studies on the use of CPR in high-risk pregnancies; however, most of these studies were for conditions such as severe pre-eclampsia, prolonged pregnancy, and IUGR. To our knowledge, there are no published studies on the role of CPR in pregnancies complicated by maternal SCD, a condition associated with a high rate of adverse perinatal outcomes.

The aim of the present pilot study was therefore to assess the value of CPR measured in the late third trimester for predicting adverse fetal outcomes among pregnancies complicated by maternal SCD. The hypothesis was that low CPR (<1.1) is associated with an increased risk of adverse perinatal outcomes among women with SCD.

2 | MATERIALS AND METHODS

The present prospective cohort study was conducted between January 1 and June 30, 2016, among pregnant women with SCD receiving care at a specialized SCD Obstetric Clinic at Korle-Bu Teaching Hospital, the main referral center in the Greater Accra region of Ghana, which manages 12 000 deliveries annually including approximately 200 women with SCD. The study protocol was reviewed and approved by the Ethical and Protocol Review Committee of the College of Health Sciences, University of Ghana (no. MS-Et/M.3-P4.5/2015-2016). Written informed consent was obtained from women enrolled in the study.

All study women had SCD (genotype hemoglobin SS [HbSS] or hemoglobin SC [HbSC] based on acid–agar electrophoresis) and were receiving care at the SCD Obstetric Clinic. The inclusion criteria were singleton pregnancy and gestational age 34^{+0} weeks or more based on an early ultrasound scan before 12 gestational weeks. The exclusion criteria were pregnancy with aneuploidies or major fetal abnormalities, history of smoking and/or alcoholic consumption, diabetes mellitus, pre-eclampsia, prepartum hemorrhage, and hydrops fetalis.

Study participants completed a structured pre-tested questionnaire to collect demographic data. The women underwent weekly Doppler assessments from recruitment until delivery, which were all performed by the same researcher (AS-D). The last measurements before delivery were used for analysis.

The Doppler examinations were performed by using a ClearVue 350 Ultrasound instrument (Phillips, Eindhoven, The Netherlands) with a 3.5-MHz curvilinear transducer. In brief, UA Dopplers were measured in free loops of the umbilical cord. MCA Dopplers were measured by using an image of the fetal head obtained at the level of the sphenoid bone in the transverse plane. Color flow Doppler was used to visualize the Circle of Willis, and the measurement was taken approximately 1 cm distal to the point where it branches from the internal carotid artery, with the angle of insonation kept as close as possible to 0^0. The mean of three optimal measurements taken during periods of fetal apnea was used to calculate the PI and resistivity index of each artery. The cerebral/placental ratio was calculated from the MCA-PI and UA-PI.

Perinatal outcomes were assessed at the postnatal clinic from delivery to 6 weeks postpartum. Perinatal and delivery variables were collected, including mode of delivery, indication for cesarean delivery (if applicable), fetal distress, meconium staining of liquor, birthweight, Apgar scores at 1 and 5 minutes, birth asphyxia, respiratory distress syndrome, convulsions, NICU admission, duration of NICU stay (if applicable), stillbirth, and neonatal death. The primary outcome was a composite of adverse perinatal outcomes, including IUGR, stillbirth, low birthweight, and NICU admission.

Data analysis was performed by using SPSS version 22 (IBM, Armonk, NY, USA). A CPR cutoff of 1.1, the fifth centile of the study population, was used to categorize the cohort into low (<1.1) and normal (≥1.1) CPR. Continuous variables were compared by using Student *t* test or Mann-Whitney *U* test, and categoric variables were compared by using Fisher's exact test for independence. Differences were considered significant for *P* values of less than 0.05.

Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive performance of CPR for composite adverse perinatal outcomes. The area under the ROC curve (AUC) and the corresponding sensitivity, specificity, and negative and positive predictive values for the CPR cutoff of less than 1.1 were calculated.

3 | RESULTS

During the study period, 48 pregnant women with SCD met the inclusion criteria and were available for postnatal review. Of these, 25 (52.1%) were SS genotype, and 23 (47.9%) were SC genotype. The women were divided into those with a fetus with low CPR (<1.1; n=5), and those with a fetus with normal CPR (≥1.1; n=43). Table 1

TABLE 1 Demographic and prenatal characteristics of the study women.[a]

Variable	CPR<1.1 (n=5)	CPR> 1.1 (n=43)	*P* value
Educational level			0.602
Low	2 (40.0)	11 (25.6)	
High	3 (60.0)	32 (74.4)	
Marital status			0.011
Unmarried	4 (80.0)	8 (18.7)	
Married	1 (20.0)	35 (81.3)	
Parity			>0.99
Nulliparous	3 (60.0)	23 (53.5)	
Multiparous	2 (40.0)	20 (56.5)	
GA at enrollment, wk	35.4 ± 1.9	35.7 ± 1.5	0.633
No. of prenatal visits	5.8 ± 2.5	6.6 ± 1.7	0.384
No. of admissions	1.4 ± 1.1	0.7 ± 0.9	0.131
GA at delivery, wk	37.6 ± 1.3	37.8 ± 1.4	>0.99

Abbreviations: GA, gestational age.
[a]Values are given as mean ± SD or number (percentage).

summarizes the maternal demographic and prenatal characteristics of the two study groups.

The two groups were similar with respect to maternal age, parity, marital status, and educational level. Overall, 26 (54.2%) of the participants were nulliparous. The mean ± SD gestational age was 35.7 ± 1.5 weeks at recruitment, and 37.8 ± 1.5 weeks at delivery (Table 1). On average, the participants had two Doppler scans from the point of recruitment to delivery.

All study women delivered within 7 days of the last scan, and 28 (56.3%) delivered by day 5 (interquartile range [IQR], 3–6) after the last Doppler scan. The mean pre-delivery hemoglobin level of the participants was 9.2 ± 1.4 g/dL; in total, 15 (31.1%) women had a blood transfusion in the perinatal period.

Twenty-nine (60.4%) of the participants delivered by cesarean; the most common indication was previous cesarean (10, 34.5%), followed by failed induction (5, 17.2%), IUGR (4, 13.7%), fetal distress (3, 10.3%), malpresentation (2, 6.9%), and maternal request (1, 3.4%). Of the 19 vaginal deliveries, 11 had spontaneous labor onset and 8 had labor induction. The two common indications for induction of labor were SCD at term and recurrent vaso-occlusive crisis.

Neonatal outcomes are summarized in Table 2. There were no significant differences in neonatal outcomes between women with HbSS and those with HbSC genotypes (data not shown).

The median (IQR) CPR among all women was 1.6 (1.2–1.9). The 5th and 95th centiles of CPR within the study group were 1.1 and 2.3, respectively. CPR less than 1.1 was significantly associated with an increased risk of composite adverse perinatal outcomes (P=0.004). Among the individual components of the composite outcome, CPR less than 1.1 was associated with an increased likelihood of stillbirth (P=0.009) and low birthweight (odds ratio [OR], 15.20; 95% confidence interval [CI], 1.90–121.38; P=0.005). Other factors, including mode of delivery, fetal distress, Apgar score, NICU admission, and duration of NICU admission, had no significant association with CPR (Table 2).

Low CPR was predictive of composite adverse perinatal outcomes (AUC, 0.8; 95% CI, 0.6–0.9; P=0.002) (Fig. 1). CPR less than 1.1 had a sensitivity of 29.4%, specificity of 100%, positive predictive value of

TABLE 2 Relationship between CPR and perinatal outcomes.[a]

	CPR				
Variable	**<1.1 (n=5)**	**≥1.1 (n=43)**	**Total (n=48)**	***P* value**	**OR (95% CI)**
Composite adverse outcome					
No	0 (0)	31 (72.1)		0.004	[e]
Yes	5 (100)	12 (27.9)			
Mode of delivery					
Cesarean	3 (10.3)	26 (89.7)	29 (60.4)	>0.99	[e]
Vaginal	2 (10.5)	17 (89.5)	19 (36.6)		
Fetal distress					
No	5 (11.1)	40 (88.9)	45 (93.8)	>0.99	[e]
Yes	0 (0)	3 (100)	3 (6.3)		
Live birth					
No	2 (100)	0 (0)	2 (4.2)	0.009[b]	[e]
Yes	3 (6.5)	43 (93.5)	46 (95.8)		
Birthweight, kg					
<2.5	4 (40.0)	6 (60.0)	10 (20.8)	0.005[b]	15.21 (1.90–121.38)
≥2.5	1 (2.6)	37 (97.4)	38 (79.2)		
Apgar score 5 min					
≤6	0 (0)[d]	1 (100)	1(2.2)	0.931[b]	[e]
≥7	3 (6.5)	42 (91.3)	45 (97.8)		
NICU admission					
No	1 (2.9)	33 (97.1)	34 (73.9)	0.162[b]	[e]
Yes	2 (16.7)	10 (83.3)	12 (26.1)		
Duration of NICU admission, d	5 (4–5)	4 (2–5)		0.758[c]	[e]

Abbreviations: CI, confidence interval; CPR, cerebro-placental ratio; NICU, neonatal intensive care unit; OR, odds ratio.
[a]Values are given as median (range) or number (percentage).
[b]By Fisher exact test.
[c]By Mann-Whitney *U* test.
[d]Two cases of intrauterine fetal death were not included in Apgar score data.
[e]OR was not calculated owing to a "zero" value in one group.

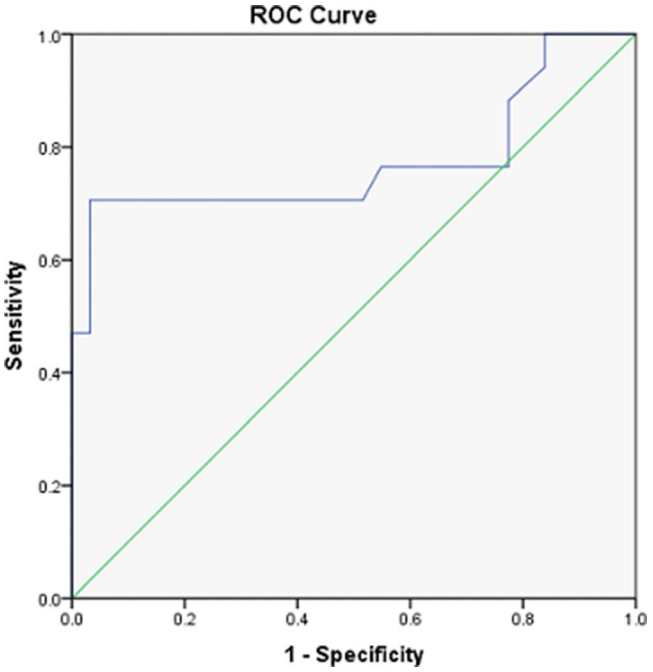

FIGURE 1 Receiver-operating characteristic curve for predicting adverse outcomes.

100%, and negative predictive value of 72.1% for predicting composite adverse perinatal outcomes. Among the individual components, CPR less than 1.1 had a sensitivity and specificity of, respectively, 40.2% and 97.4% for predicting low birthweight, and 100% and 93.5% for predicting stillbirth (Table 2).

Bivariate analysis comparing obstetric outcomes was performed separately for preterm and term deliveries to account for the potential confounding role of gestational age at delivery. The association between stillbirth and CPR was significant for preterm deliveries (P=0.047), but not for term deliveries (P>0.99) (data not shown). By contrast, CPR was not associated with low birthweight among preterm deliveries (P=0.428), but was significantly associated with low birthweight among term deliveries (P=0.035). Other factors, including mode of delivery, fetal distress, APGAR scores, NICU admission, and duration of NICU admission, were not associated with CPR in either the term or preterm group (data not shown).

The two cases of stillbirth reported were both associated with severe maternal anemia with hemoglobin levels of 6.7 and 7.1 g/dL. The normal CPR (≥1.1) group had a significantly higher mean hemoglobin level as compared with the low CPR (<1.1) group (P=0.022) (data not shown). Women with CPR less than 1.1 were more likely to have had a blood transfusion (OR, 11.63; 95% CI, 1.17–115.59; P=0.028). Low pre-delivery maternal hemoglobin was associated with low birthweight (P=0.043) and NICU admission (P=0.024).

4 | DISCUSSION

The main findings of the present pilot study suggested that CPR less than the 5th centile (1.1) was associated with adverse perinatal outcomes among women with SCD. This association was most significant for low birthweight (<2.5 kg) and stillbirth, and was observed for both sickle cell genotypes (HbSS and HbSC).

Cerebro-placental ratio is accepted as a reliable indicator of blood flow redistribution in the brain. Low CPR can be attributed to either a rise in UA resistance (reflecting placental resistance) or a drop in cerebral vascular resistance (resulting from a brain-sparing effect).[14] The appropriate CPR threshold to use is currently still unclear, with various investigators using cutoff values from <1 to 1.1, or 5th and 10th centile cutoffs and even multiples of medians.[15] Research by Gramellini et al.[7] reported that CPR values remain constant in the last 10 weeks of pregnancy, and they used a value of 1.08 as a cutoff for predicting adverse fetal outcomes. A similar report was made by Devine et al.,[16] who stated that CPR less than 1.05 was the best predictor of adverse perinatal outcomes. By contrast, Prior et al.[11] reported that, although mean CPR is relatively constant at term, the 5th percentile continues to decrease as a consequence of increasing standard deviation and thus would be a more reliable cutoff. In the present pilot study of 48 women with SCD, there were no cases of CPR <1, even though 25 adverse perinatal outcomes were recorded. Thus, the cutoff was based on a previous study that used the threshold for abnormal CPR as the 5th centile of the study population.[11] The 5th centile from the present dataset was computed as 1.1.

A CPR cut-off of 1.1 was also recommended by Arbeille et al.,[17] who investigated pregnancies complicated by IUGR and/or hypertension. Low CRP predicted the occurrence of abnormal fetal heart rate 6–8 days before it happened.[17] Ropacka-Lesiak et al.[18] also used a cutoff of 1.1 in uncomplicated term pregnancies, showing that it had good sensitivity in predicting both fetal distress and adverse neonatal outcomes.

Flood et al.[19] examined composite adverse outcomes among fetuses with early-onset small for gestational age. They compared adverse outcomes using different cutoffs for abnormal CPR (PI <5th centile, PI <1, and PI <1.08), finding that all CPRs had lower sensitivities but higher specificities. This was also found in the present study, where low CPR had a sensitivity of 29.4% and specificity of 100% for composite adverse outcomes. It has been suggested that, instead of a fixed cutoff value for determining fetuses at risk of complications, the 5th centile might have higher predictive value.[14]

With regard to CPR and composite adverse perinatal outcomes, studies done on specific medical conditions in pregnancy have reported higher sensitivities as compared to the present study. For example, studies on CPR in women with preeclampsia by Shahinaj et al.[20] from Albania and Parshuram et al.[21] in Kenya reported sensitivity values of 98.0% and 93.3% respectively.

In the present study, CPR less than 1.1 had a higher specificity (100%) and lower sensitivity (29.4%). The conflicting results may be due in part to the different CPR cutoff values, sample sizes, population characteristics, definitions of observed adverse outcomes, and selection criteria used in the three studies.

In the present study, the AUC for CPR less than 1.1 was 0.8, indicating that this cutoff is statistically useful for correctly identifying cases that are likely to have an adverse perinatal outcome. Because

pregnant women with SCD are a high-risk group, improved test sensitivity is desirable; however, high specificity is also appropriate to avoid unnecessary interventions such as iatrogenic premature delivery. Although CPR may increase the identification of women at risk of adverse perinatal outcomes, other parameters such as absent or reversed UA Doppler flow may be more useful for avoiding unnecessary interventions in high-risk cases.

In terms of the individual perinatal outcomes assessed in the study, only low birthweight and stillbirth showed a significant association with CPR. To our knowledge, there are no other studies on CPR among pregnant women with SCD with which to compare the present data. Previously, Anyaegbunam et al.[22] only commented on the abnormal UA doppler velocimetry observed among women with SCD, which may be attributed to the increased rates of IUGR experienced by this group of women.

The limitations of the present study include the small sample size with its relatively low numbers of adverse perinatal outcomes. As a result, it was not possible to use logistic regression analysis to determine whether maternal demographic or prenatal characteristics had confounding effects. To reduce the effect of the relatively small sample size, a composite of adverse perinatal outcomes was used in the present analysis. The fact that the findings are comparable with those of previous studies supports the robustness of the present conclusions.

In conclusion, the risk of adverse perinatal outcomes among pregnant women with SCD is known to be greater than that among pregnant women without SCD. Low CPR was found to be associated with adverse perinatal outcomes. Further studies involving a larger sample size are required to demonstrate the utility of the CPR as a useful tool for prenatal monitoring of fetuses in high-risk pregnancies. The high specificity of CPR makes it a useful screening tool to determine if and when other intensive methods of fetal surveillance should be used. The present findings may greatly simplify fetal surveillance for women with SCD, which in turn might have significant implications for resource utilization in contemporary obstetric practice.

AUTHOR CONTRIBUTIONS

AS-D, JDS, and SAP contributed to study conception and design; AS-D and SAM-B collected the data; AS-D, KM, and KN analyzed the data; and all authors interpreted the data and reviewed the final version of the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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