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Third trimester maternal anemia is associated with fetal cardiovascular compromise in Southwestern Uganda

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Abstract

Background Maternal anemia is still a global public health burden during pregnancy. It impairs fetal-placental perfusion leading to fetal hypoxia, that disrupts vital physiological and biochemical pathways. This affects fetal growth and developmental programming, resultant into advance. perinatal outcomes and susceptibility to various non-communicable diseases later in life. This study set out to established how clinical Doppler and other physiological cardio, cerebral and peripheral vascular parameters vary at various grades of maternal anemia.

Methods A cross-sectional study was conducted among women aged 20–35 years, with singleton third trimester pregnancies attending Mbarara Regional Referral Hospital between March 2023 and August 2023. These were grouped into non-anemic with Hemoglobin concentration ≥ 11 g/dL, while mild anemia (Hb:10–10.9 g/dL), moderate anemia (7–9.9 g/dL), and severe anemia Hb < 7 g/dL. Resistance to flow and flow distribution were assessed by Doppler-derived indices and ratios of the fetal middle cerebral artery (MCA) and umbilical artery (UA). Physiological parameters like volumetric flow were calculated from measurements. We compared means using ANOVA and evaluated the relationships between flow parameters and the severity of anemia using Spearman's correlation coefficient.

Results We enrolled 288 participants with a mean age of 27 ± 4.3 years. The UA resistance indices among the non-anemic were significantly lower than among the anemic and significantly escalated from among the mild to the severely anemic, for instance, UA-PI increased from (0.88 ± 0.18) among the mild, moderate (0.92 ± 0.24) to (1.09 ± 0.34) severe anemia, ($p < 0.001$), while the mean flow velocity decreased as anemia severity increased ($F [3,284] = 3.44, p = 0.017$). The mean cerebral flow velocity demonstrated an increasing trend with the severity of anemia ($p = 0.042$). Similarly a lower mean Cerebral placental Ratio was noted in the anemic group (1.87 ± 0.49) compared to the non-anemic group (2.15 ± 0.53) , ($p < 0.001$), while as maternal Hb concentration reduced, the CPR significantly decreased, ($r = 0.31, F[3,284] = 12.64, p < 0.001$). As the maternal hemoglobin concentration reduced, the fetal heart rate increased ($r = -0.06, p = 0.308$).

Conclusion Anemic women exhibited higher UA flow resistance, lower Cerebral placental ratio, suggestive of altered flow patterns with increasing severity of



maternal anemia. These findings suggest that maternal anemia influences umbilical artery hemodynamics, potentially responsible for compromised fetal well-being. Understanding these associations could contribute to enhanced antenatal care strategies, emphasizing the importance of monitoring maternal anemia and its potential implications on fetal cardiovascular health.

Keywords Third trimester pregnancy, Maternal anemia, Fatal cardio-vascular parameters

1 Background

Globally, anemia is one of the most silent critical public health burden affecting 38–56% of pregnant women [1]. In developing countries low social-economic, and poor health among other factors, escalate the burden. No wonder the Sub-Saharan Africa prevalence is 44% [2]. The overall prevalence in East Africa is 41.82%, lowest in Rwanda at 23.4%, and highest in Tanzania at 57.1% while the Ugandan prevalence is at 38.5% [3]. At Mbarara Regional Referral Hospital, studies have reported prevalence of 84.4% and 62.82% [4] and [5] respectively. Additionally, 5% of admitted pregnant women have moderate to severe anemia [6]. Besides physiological adaptations responsible for hemodilution anemia, microcytic anemia is the most common type of anemia during the 2nd or 3rd trimesters [7].

Epidemiological studies have underscored the profound impact of maternal anemia as a stressor, that alters the qualitative and quantitative health of the intrauterine environment, on fetal growth and developmental programming [8, 9]. Maternal anemia disrupts, placental perfusion, resulting in intra-placental or post-placental hypoxia [10]. Although during hypoxia, the carotid chemo reflex, and the vascular oxidant tone trigger a brain sparing reflex, resulting into significant cardiac output redistribution to vital organs away from the peripheral circulations [11], even brief episodes of fetal hypoxia can lead to diminished neuronal growth and death [12]. Chronic hypoxia is associated with long term cerebral vasodilatation leading to cerebral edema, and subsequent brain damage [13]. These alteration have profound perinatal to postnatal adverse outcomes inclusive but not limited to perinatal mortality, increased susceptibility to non-communicable diseases and long-term disabilities later in life, associated with social-economic and health burdens [14–16].

The high rates of maternal anemia related perinatal morbidities and mortality have not spared, Mbarara Regional Referral Hospital, with notable elevated stillbirth of 5.9%, equivalent to 90.9 per 1000 births and in-hospital neonatal death rates among anemic women stand at 11.8%, in contrast to 2.7% among non-anemic women [17–19]. If not addressed, this may hinder attainment of the 2030 sustainable development goal (SDG 3). This is partly contributed due to poor utilization of high risk screening modalities like Doppler derived flow parameters for feta-placental surveillance. These are capable of demonstrating fetal oxygenation, cardiac output distribution, and prediction of adverse perinatal outcomes aiding possible appropriate clinical management [20, 21].

Our study explores this important clinical question of how severity of maternal anemia during the last trimester, influences fetal cardiovascular hemodynamics in the umbilical and middle cerebral arteries representative of peripheral and cerebral circulations respectively. We compared Doppler flow indices as markers of vascular resistance while the Cerebro-placental ratio (CPR) was a predictive and quantifying measure for

cardiac output flow distribution, as a response to hypoxia and reflecting placental status. The study also explored application of physiological concepts like volumetric flow per minute, which could provide valuable insights into estimating individual organ perfusion, oxygen consumption rates and energy metabolism. Such insights are crucial for understanding the clinical origins of fetal comorbidities, ultimately reducing perinatal and neonatal morbidity and mortality.

2 Methods

2.1 Study design, duration and setting

A cross-sectional study was carried out at Mbarara Regional Referral Hospital (MRRH), between February 2023 and August 2023. MRRH is a tertiary government hospital in southwestern Uganda, and also doubles as a training facility for Mbarara University of Science and Technology. Participants were recruited from the antenatal out-patient clinic and high-risk obstetrics ward of MRRH. Averagely, 7082 women attend ANC, with 3418 of these booking in the 2nd and 3rd trimesters, and 1076 considered high risk pregnancies.

2.2 Study population

We included gravid women aged 20–35 years, with singleton pregnancies in the third trimester (28–40 weeks). Although the World Health Organization defines reproductive age between 15 and 49 years teenager pregnancies (< 20 years) and advanced maternal age (> 35 years) were considered high risk. Teenage pregnancies are associated with risks such as low birth weight, and preterm birth, while advanced maternal age is linked with increased arterial stiffness, decreased compliance, reduced placental transport, placental insufficiency, risk of preeclampsia, and fetal complications like IUGR, attributed to increased utero-placental vascular resistance and decreased blood flow [22]. These were grouped into the non-anemic group with Hb \geq 11 g/dL and the anemic women, Hb < 11 g/dL. Women with multiple pregnancies, congenital cord abnormalities, in labor, oligohydramnios, polyhydramnios and those with known conditions such as preeclampsia and gestational diabetes were excluded.

2.3 Sample size calculation

Sample size estimation was by using a formula designed to compare means of populations [23].

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times [(\delta_1)^2 + (\delta_2)^2]}{(p_1 - p_2)^2}$$

Where; n is the minimum sample size of thanemic or non-anemic groups. $Z_{\alpha/2}$ is the critical value of normal distribution at $\alpha/2$ for a confidence level of 95%, α is 0.05 the critical value is 1.96. Z_{β} is the critical value of the normal distribution at β for a power of 90%, critical value is 1.28. P_1 and δ_1 are the expected mean MCA S/D ratio = 3.82 and standard deviation = 0.51 of non-anemic women respectively. P_2 and δ_2 are the expected average MCA S/D = $(3.86 + 3.64 + 3.33) \div 3 = 3.61$ and standard deviations = $(0.61 + 0.62 + 0.49) \div 3 = 0.573$ among anemic (mild, moderate and severe) women [13]. The sample size for each group was 144, with a total of 288 participants inclusive of 10% non-satisfactory results.

2.4 Study procedure

Informed consents were obtained from eligible participants by the research assistants (midwife) after detailed explanation of the study's purpose at the antenatal outpatient clinic and high-risk ward.

2.5 Data collection

Questionnaires and checklist instructions were employed to collect social demographic and obstetric data. Fetal age relied on the known last normal menstrual period (LNMP) or first-trimester biometric measurements. Maternal anthropometrics and vital signs were measured. All investigations were carried out under room temperature and moderate lighting to ensure accuracy and reliability.

2.6 Hb estimation

Hb estimation and other RBC indices, were done in the hospital laboratory accredited by the Uganda National Accreditation System (UGANAS), and the South African National Accreditation system (SANAS), ISO 15189:2012, accreditation number M0861.

Laboratory technician performed the phlebotomy under standard aseptic techniques and samples were Subsequently, analyzed using the automated Sysmex hematology analyzer.

2.7 Fetal studies

2-D Screening for fetal and cord abnormalities was performed first, then color and Pulse Doppler ultrasound examinations were performed with a 3.5MHZ curvilinear transducer of the Alpinion ultrasound imaging system by a radiology resident and sonographer.

All procedures were done in the supine position with the back tilted at about 45° to prevent compression of maternal IVC and effects on utero placenta perfusion, and reduce effects of maternal supine position on fetal UA and MCA parameters as documented by [24].

All measurements were performed during periods of no fetal movement or apnea as possible because fetal respiratory movements alter UA size and blood flow velocity.

The average fetal heart rate FHR was calculated from 3 separate measurements, obtained in M-mode. The normal FHR was 120–160 bpm. UA and MCA Doppler procedures were performed as described by Maulik and Lees (2005). A 2-D fetal brain axial section demonstrating the thalami and the sphenoid wings was obtained. Color flow was used to demonstrate the circle of Willis and the proximal MCA portion, where a small Doppler gate approximately the width of the vessel was placed close to the internal carotid artery origin, since its PSV decreases with distance from point of origin. The angle between the beam and flow was set close to 0°. UA flow measurements were done in a free floating cord segment. This is because the end-diastolic flow at the fetal end is lower, hence impedance is higher than at the placental cord insertion. The angle of insonation was set as low as possible less than 60° [25].

The MCA and UA peak systolic velocity (PSV), end diastolic velocity (EDV) and the average velocity over a cardiac cycle, time-averaged maximum velocity (TAMXV) were obtained from the flow velocity waveforms. The measure of microvascular bed resistance

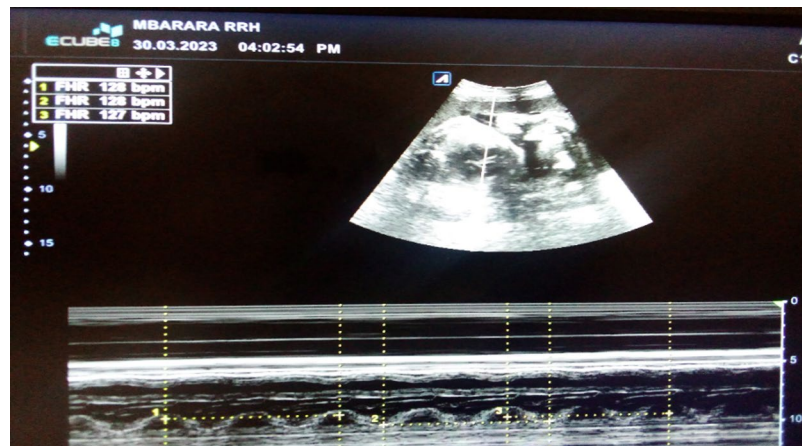


Fig. 1 Assessment of the fetal heart rate (FHR)

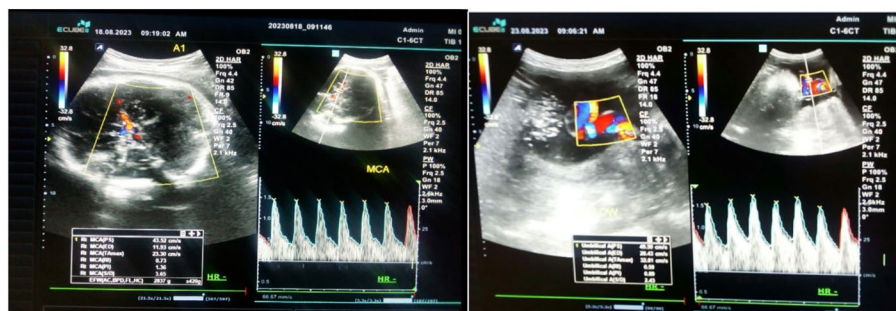


Fig. 2 Doppler assessment of: **a** middle cerebral artery. **b** Umbilical artery

to flow distal to the point of assessment was determined by the pulsatility index (PI), resistive index (RI), and Systolic/Diastolic ratio (S/D) (Figs. 1 and 2).

The Cerebro-placental ratio (CPR) was calculated as a ratio between MCA PI and UA PI, representing fetal cerebral and peripheral resistance respectively. A CPR value < 1.08 , indicated possible pathological state [26, 27].

The mean flow velocities (V_{UA}) and (V_{MCA}) equivalent to $\frac{TAMXV}{2}$ (cm/s) were calculated [28]. Since the fetal MCA diameter is too small for accurate measurements, the mean flow velocity (VMCA) was considered as the quantitative flow volume in the MCA (Fig. 3).

Three separate measurements of the UA diameter (**D**) were measured in transverse and longitudinal sections. The average **D** was calculated and used to obtain the cross-sectional area (**CSA**). The vessel was assumed to be cylindrical in nature where; $D = \frac{D1+D2+D3}{3}$ $CSA = \frac{\pi}{4} \times D^2$ (cm²).

Volumetric blood flow (**Q**) back to the placenta, through one UA was calculated by; $Q = CSA \times VUA$, (ml/s), then multiplied by 60 to convert seconds to minutes (ml/min). The Reynold number (**RE**) was calculated to establish the nature of umbilical flow or turbulence transition, $RE = \frac{VD\rho}{\eta}$ where: v is the mean UA velocity (cm/s), D is the UA diameter (cm), ρ the density of blood and η the viscosity of blood. Although blood is a non-Newtonian fluid, it was assumed to have a constant Viscosity (η) of 0.0033 kg/m/s and density (ρ) of 1050 kg/m³. Flow was considered laminar when the $RE < 2300$.



Fig. 3 Measurement of umbilical artery diameter

2.8 Data analysis

The data was entered into Excel and then imported into STATA 15.0 software, (College Station, Texas, USA) for analysis. Normality was graphical tested. Continuous variables and descriptive data, were presented as central tendency (means and percentages) and dispersion indices (standard deviation) in tables. Anemic participants were categorized as mild anemia (Hb 10–10.9 g/dL), moderate anemia (7–9.9 g/dL), or severe anemia (Hb < 7 g/dL) basing on WHO standards [29].

ANOVA was used to compare means of groups based on severity of anemia and F value obtained. Spearman's rank correlation coefficient (r) gauged the relationships between fetal flow parameters and the severity of anemia, with scatter graphs and lines of best fit illustrating the results. A statistically significant p -value was considered when < 0.05.

3 Results

3.1 Sociodemographic characteristics of the study participants

A total of 288 pregnant women, (144 in each group) were recruited. The mean age of the study participants was 27.08 ± 4.28 years. Majority 54.2% of participants were at or above 34 weeks of gestation. Highest level of Educational attained varied, with the majority having attained secondary education.

The mean hemoglobin (Hb) level for the study participants was 10.54 ± 2.52 g/dL. Specifically, the anemic participants recorded a mean Hb of 8.58 ± 1.94 g/dL, which was substantially lower than the non-anemic group's mean Hb of 12.49 ± 1.14 g/dL ($p < 0.001$). The anemic group exhibited significantly lower values across various indices compared to the non-anemic group. Similar trends were observed in hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), with all these indices showing statistically significant differences between the anemic and non-anemic groups ($p < 0.001$), as shown in Table 1.

Table 1 Socio demographic characteristics and red blood cell indices of the participants

Characteristic	Total N= 288(mean ± SD)	Non-anemic ≥11 g/dL N= 144 (mean ± SD)	Anemic < 11 g/dL N= 144(mean ± SD)	p-value
Age (years)	27.08 ± 4.28	27.09 ± 4.36	27.06 ± 4.22	0.930
Gestational age (weeks)				0.480
< 34	132 (45.8%)	63 (43.8%)	69 (47.9%)	
≥ 34	156 (54.2%)	81 (56.3%)	75 (52.1%)	
Education				0.067
None	22 (7.6%)	7 (4.9%)	15 (10.4%)	
Primary	96 (33.3%)	50 (34.7%)	46 (31.9%)	
Secondary	108 (37.5%)	49 (34.0%)	59 (41.0%)	
Tertiary	62 (21.5%)	38 (26.4%)	24 (16.7%)	
Marital status				0.210
Married	253 (87.8%)	130 (90.3%)	123 (85.4%)	
Unmarried	35 (12.2%)	14 (9.7%)	21 (14.6%)	
Gravidity				0.640
Primi-gravida [1]	68 (23.6%)	34 (23.6%)	34 (23.6%)	
Multi-gravida [2–4]	166 (57.6%)	86 (59.7%)	80 (55.6%)	
Grand multigravida (≥ 5)	54 (18.8%)	24 (16.7%)	30 (20.8%)	
MUAC (cm)				0.024*
< 19 (severe)	3 (1.0%)	0 (0.0%)	3 (2.1%)	
19–<22 (moderate)	16 (5.6%)	4 (2.8%)	12 (8.3%)	
≥ 22 (normal)	269 (93.4%)	140 (97.2%)	129 (89.6%)	
Red blood cell indices				
Hb (g/dL)	10.54 ± 2.52	12.49 ± 1.14	8.58 ± 1.94	< 0.001*
HCT (%)	38.01 ± 2.82	40.02 ± 2.43	36.00 ± 0.39	< 0.001*
MCV (fL)	87.94 ± 9.70	88.17 ± 6.09	87.72 ± 12.31	0.690
MCH (pg)	28.54 ± 3.82	29.27 ± 2.44	27.80 ± 4.71	< 0.001*
MCHC (g/dL)	32.37 ± 2.64	33.23 ± 1.80	31.52 ± 3.05	< 0.001*

* $p < 0.05$; MUAC: Middle Upper arm circumference, Hb: hemoglobin concentration, HCT: hematocrit, MCV: mean corpuscular hemoglobin, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration

Table 2 Comparison of UA Doppler flow parameters and severity of maternal anemia

Parameter	No anemia (≥ 11 g/dL) N= 144	Anemia			F	p-value
		Mild (10.0–10.9 g/dL) N= 45	Moderate (7.0–9.9 g/dL) N= 76	Severe (< 7 g/dL) N= 23		
S/D	2.49 ± 0.73	2.46 ± 0.59	2.75 ± 1.22	3.29 ± 1.37	5.96	< 0.001*
RI	0.58 ± 0.09	0.58 ± 0.08	0.60 ± 0.09	0.66 ± 0.10	6.41	< 0.001*
PI	0.87 ± 0.21	0.88 ± 0.18	0.92 ± 0.24	1.09 ± 0.34	6.77	< 0.001*

* $p < 0.05$; PI: pulsatility index, RI: resistive index, S/D: Systolic/Diastolic ratio

In Table 2, notably all UA indices exhibited significant differences ($p < 0.05$). Generally, the non-anemic group (≥ 11 g/dL), exhibited lower UA indices compared to anemic group (< 11 g/dL).

The systolic/diastolic (S/D) ratio progressively increased with anemia severity, that is 2.49 ± 0.73 in the non-anemic group, 2.46 ± 0.59 in mild anemia, 2.75 ± 1.22 in moderate anemia, and 3.29 ± 1.37 in severe anemia, ($p < 0.001$). A similar trend was observed for the resistive index (RI), where the non-anemic and mild anemic groups had RI of 0.58 ± 0.08 , compared to 0.60 ± 0.09 in moderate anemia, and 0.66 ± 0.10 in severe anemia ($p < 0.001$). The pulsatility index (PI) also exhibited a significant increase with anemia severity, with values of 0.87 ± 0.21 in the non-anemic group, 0.88 ± 0.18 in mild anemia, 0.92 ± 0.24 in moderate anemia, and 1.09 ± 0.34 in severe anemia ($p < 0.001$) (Table 2).

Table 3 Nature, characteristics of umbilical artery flow and comparison of umbilical artery flow parameters with severity of maternal anemia

Parameter	No anemia (≥ 11 g/dL) N=144	Anemia			F	p-value
		Mild (10.0–10.9 g/dL) N=45	Moderate (7.0–9.9 g/dL) N=76	Severe (<7 g/dL) N=23		
UAV (cm/s)	16.8 \pm 5.02	16.03 \pm 3.52	15.63 \pm 4.30	13.79 \pm 4.31	3.44	0.017*
UA D (cm)	0.46 \pm 0.06	0.47 \pm 0.08	0.47 \pm 0.07	0.44 \pm 0.08	2.03	0.109
UA Q (ml/min)	175.63 \pm 78.59	172.73 \pm 70.42	168.39 \pm 71.01	132.84 \pm 64.49	2.22	0.086
RE number	2,498,841.9 \pm 904,671	2,411,963.8 \pm 655,454.41	2,357,830.3 \pm 782,288.27	1,957,911.8 \pm 765,656.89	2.93	0.034*

* $p < 0.05$; UAV Umbilical artery mean flow velocity, UAD Diameter, UAQ Volumetric flow, RE Reynold number

Table 4 Comparison between MCA Doppler flow parameters and severity of maternal anemia

Parameter	No anemia (≥ 11 g/dL) N=144	Anemia			F	p-value
		Mild (10.0–10.9 g/dL) N=45	Moderate (7.0–9.9 g/dL) N=76	Severe (<7 g/dL) N=23		
S/D	6.08 \pm 2.11	6.29 \pm 2.78	5.59 \pm 2.14	6.15 \pm 6.73	0.73	0.533
RI	1.38 \pm 0.85	0.79 \pm 0.13	0.80 \pm 0.08	3.35 \pm 1.23	1.21	0.306
PI	3.13 \pm 1.61	1.75 \pm 0.39	1.65 \pm 0.36	1.59 \pm 0.42	0.39	0.757
MCA V (cm/s)	11.31 \pm 3.54	11.70 \pm 3.36	12.79 \pm 3.72	11.99 \pm 4.52	2.76	0.042*

* $p < 0.05$; PI pulsatility index, RI resistive index, S/D Systolic/Diastolic ratio, MCAV middle cerebral artery flow velocity

The mean umbilical artery flow velocity (UA V) decreased as severity of anemia increased ($p = 0.017$). Similarly, the variation in the umbilical artery diameter (UA D) showcased a trend of increase from 0.46 ± 0.06 in the non-anemic group to 0.47 in the mild and moderate anemic groups, followed by a reduction to 0.44 ± 0.08 in the severely anemic group. The Reynolds number (RE number) exhibited a significant decrease with decreasing maternal hemoglobin levels ($F [3,284] = 2.93$, $p = 0.034$) as shown in Table 3.

The mean flow velocity in the middle cerebral artery (MCA V) significantly increased with the severity of maternal anemia ($p = 0.042$).

There were no statistically significant differences in the mean values of MCA indices that is ($p > 0.05$). However the mean values of MCA PI reduced as the severity of maternal anemia increased, that is 3.13 among nonanemic compared to, 1.75 among mild anemia compared to, 1.65 among moderate anemia and compared to 1.59 among severely anemic women, Table 4.

There is a non-significant weak positive relationship between maternal Hb level and umbilical artery flow volume, ($r = 0.08$, $p = 0.157$). As the severity of maternal anemia reduced, the UA flow volume increased, as shown in Fig. 4.

In Fig. 5 above, there's a significant ($p < 0.001$), weak positive relationship ($r = 0.31$) between the maternal hemoglobin concentration and cerebral placenta ratio (CPR). As the severity of maternal anemia reduced, the CPR increased.

Further analysis using ANOVA, emphasized the significant association. The CPR increased from 1.54 ± 0.48 among the severely anemic compared to, (1.86 ± 0.47) among moderate compared to (2.03 ± 0.47) among the mild anemia and 2.15 ± 0.53 among the non-anemic, ($F[3,284] = 12.64$, $p < 0.001$).

In both the non-anemic and anemic groups, the FHR was with in normal range. There is a non-significant weak negative ($r = -0.06$) relationship between maternal hemoglobin concentration and fetal heart rate (FHR), $p = 0.308$ (Fig. 6).

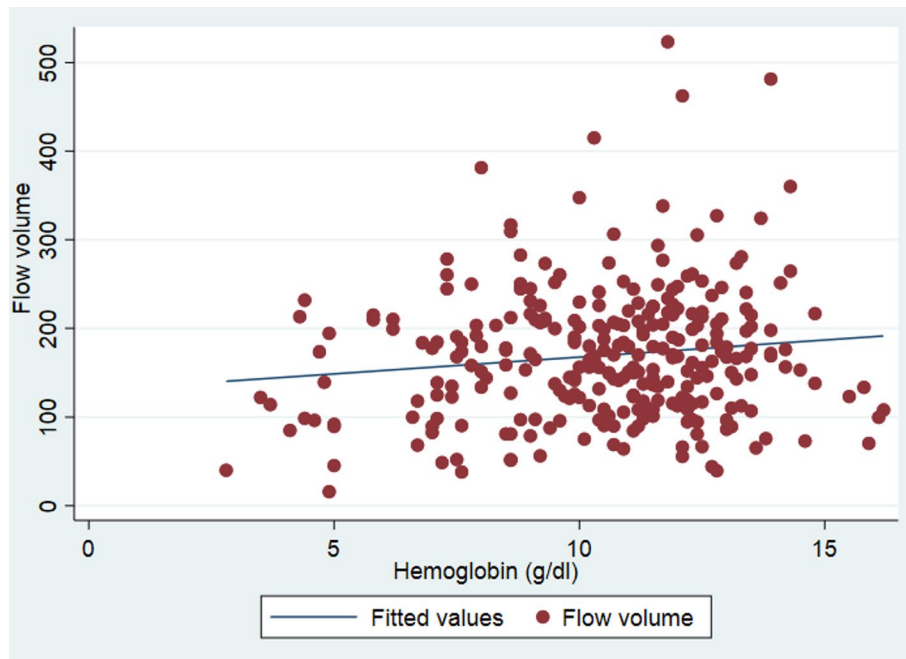


Fig. 4 Correlation between maternal hemoglobin concentration and UA volume flow

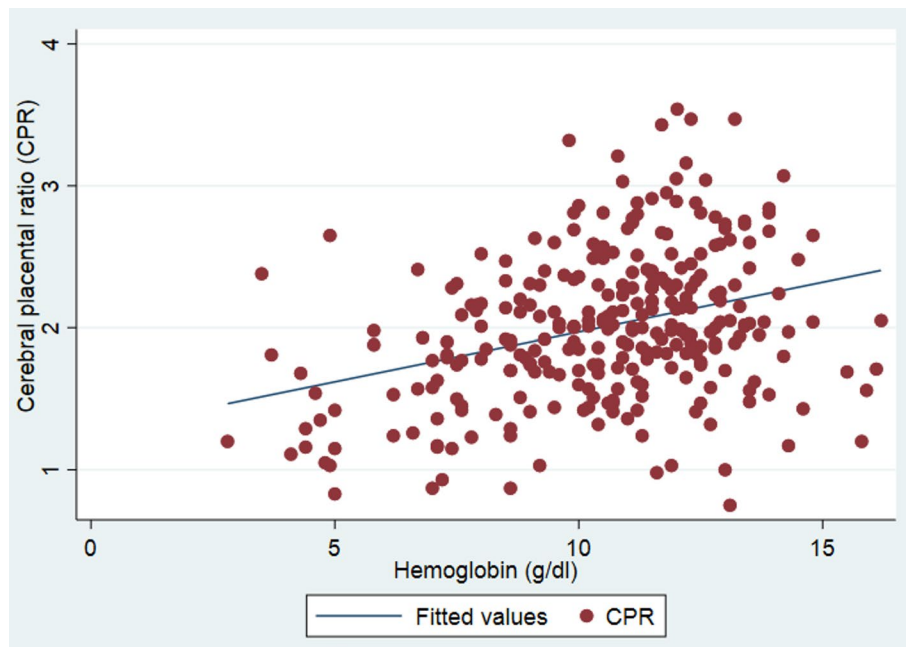


Fig. 5 Correlation between maternal hemoglobin concentration and cerebral placental ratio

Among the non-anemic and Mild anemia group, the mean fetal heart rate is slightly the same that is 143.95 ± 11.25 bpm and 143.67 ± 11.10 bpm respectively. It slightly increased as the maternal Hb level reduced moderate (144.80 ± 11.88 bpm) and 149.69 ± 0.47 bpm among the severely anemic.

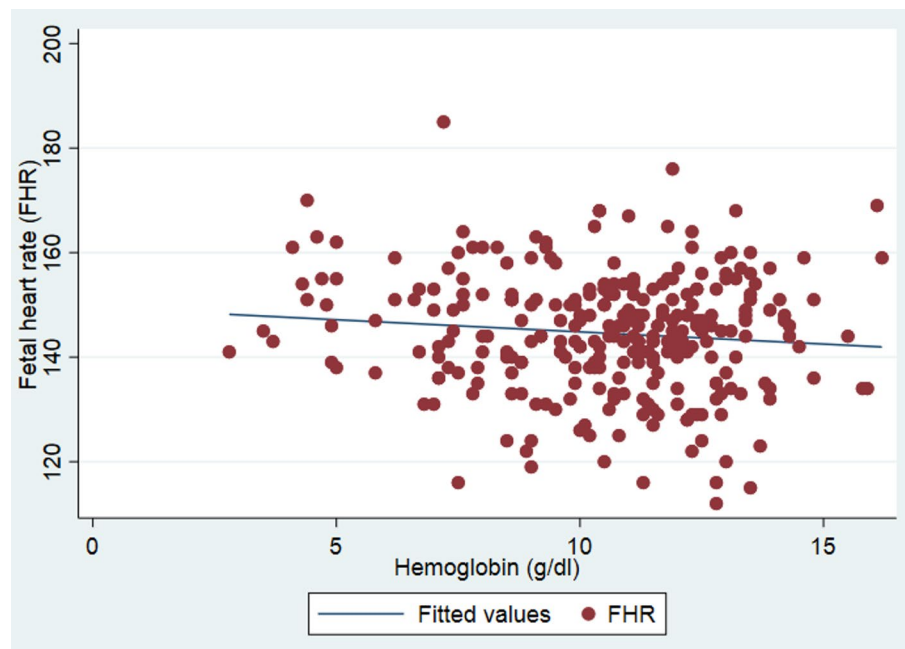


Fig. 6 Correlation between maternal hemoglobin concentration and fetal heart rate

4 Discussion

Notably, all UA indices exhibited significant differences ($p < 0.05$), highlighting the distinct hemodynamic profiles associated with anemia during pregnancy. Among the anemic, the Umbilical artery PI, RI and S/D, were higher than among the non-anemic women; similar findings have been reported by Ali and colleagues [30]. However parameters in both groups lay within gestational age-specific percentile references established by multi-racial prospective longitudinal studies on low risk singleton pregnancies, between the 28th–40th weeks, where; RI (0.66 to 0.53), S/D ratio (3.02 to 2.18) and PI (1.00 to 0.75) [28, 31].

Similarly, as the severity of maternal anemia increased progressively, UA indices and S/D ratio displayed a highly significant upward trend. Studies from Egypt and India, mirroring our study in maternal characteristics inclusion/exclusion criteria, and study site setting, reported analogous findings [32–34]. In a normal third-trimester pregnancy, as gestational age advances, UA flow velocities are high while resistance is low. The volume and numbers of tertiary stem placental villi increase, resistance reduces and subsequently increasing forward flow during the cardiac cycle. In contrast during pathological states affecting placental morphological, villi hemodynamics are altered suggesting potential alterations in vascular elastic and compliance properties, which lead to increased resistance downstream, elevating UA (RI, PI, S/D) as indicators of heightened resistance to flow [35]. For instance, RI approaches zero as resistance decreases and approaches one as resistance increases [28, 32, 36, 37].

Contrary to our findings, a study in Turkey observed a decreasing trend in the UA PI and RI as the severity of maternal anemia increased [38]. This discrepancy could be attributed to the acknowledged limitations in assessing the effects of altitude, smoking, and the unknown impacts of maternal severe acute respiratory syndrome coronavirus-2 on fetal parameters. Racial variations in fetal flow parameters particularly between 30th–36th weeks, have also been documented [39].

As the severity of maternal anemia increased, the mean UA velocity significantly reduced, lowest among the severe anemic. Similarly, although the Mean UA diameter and quantitative Volumetric flow were non-significant, they also decreased as the severity of maternal anemia increased.

Umbilical flow increases with velocity and Cross-sectional area. However, the most important determinate of flow is placental resistance. This re-affirms the potential effect of our study's documented highly significant UA indices. Increase in placental arterial stiffness, increases UA PI (an indicator of resistance) subsequently reducing flow [40, 41].

Under normal circumstances, the placenta is a low resistance organ hence most flow should always be directed towards the placenta away from the high resistance fetal circulations like the pulmonary circulation. However as placental resistance increases, UA flow towards the placenta reduces [13]. The small UA-diameter among the severely anemic group, offers more resistance to flow, subsequently decreasing flow, a relationship base on Poiseuille's equation [42]. Studies have reported significant positive correlation between maximum UA flow velocity and placental flow volume [28, 43]. Fetus with growth restriction due to maternal anemia have been reported to have 70% reduction in umbilical flow volume entirely attributed to decrease in velocity rather than vessel diameter, compared to normal fetus and in fetal anemia where flow volume increases [28, 44].

In all the study groups, UA flow was turbulent, with Reynolds number > 2300. The RE significantly increased as severity of maternal anemia decreased, highest among non-anemic group and lowest among the severely anemic. This also may indicates increased pressure, since turbulent flow requires greater pressure to push a given flow volume [45, 46]. While our study demonstrated the impact of vascular diameter on resistance and flow, providing valuable insights into physiological concepts like vascular tone and pathological narrowing, it is essential to acknowledge that fetal blood viscosity may pose a limiting factor. A third trimester study, established that maternal and umbilical cord Hb concs have a significant positive relationship, translating into increased hematocrit, viscosity and resistance to flow [47]. It's important to note that blood is a shear-thinning non-Newtonian fluid, whose viscosity (resistance to flow) changes with shear rate [48].

As maternal Hb reduced, the CPR also significantly reduced. However notably, all CPR values were above 1.08, indicating no clinical significance. The observed CPR reduction was because the measured MCA PI reduced while the UA PI increased. A similar pattern with a positive correlation ($r=0.407$, $p<0.001$), has been reported by Agrawal and colleagues [34]. that is Clinically significant low CPR values have been reported among high risk pregnancies CPR compared to normal pregnancy. It's 6.37 times likely to get a CPR of ≤ 1.32 in high-risk pregnancy than among normal pregnancy [49]. Mostafa et al. reported a CPR of 0.99 ± 0.12 among the severely anemic group [32]. In a normal pregnancy, fetal cerebral resistance is high during hypoxia, cerebral artery A2 receptors are activated by adenosine and hypoxia-induced nitric oxide leading to vasodilation and reduced cerebral resistance [50]. It's worth noting that CPR decreases proportionally with fetal partial pressure of oxygen, that is the lowest CPR corresponds to the lowest PO₂ level. This phenomenon reflects an augmented preferential flow redistribution to the fetal brain, a mechanism employed to sustain the requisite oxygen and nutrient supply [30, 51].

In contrast to our findings, KIRLANGIÇ et al. reported a significant weak negative correlation between maternal Hb and CPR [38]. This divergence maybe attributed to the MCA PI increasing while the UA PI decreased with decreasing maternal Hb levels and observed changes reflective of fetal vascular adaptive responses following the treatment of maternal anemia.

Since the mean MCA flow velocity was representative of the quantitative blood flow volume, MCA V increase with severity of anemia indicates increased flow volumes as a result of redistribution, concurrent with reduced MCA resistance exhibited by a decreasing trend of the MCA PI. During hypoxia, fetal cerebral vessels demonstrate variability (vasoconstriction and vasodilatation) [52].

Majority of the fetus in our study were 34 weeks and greater. As fetal age advances, the proportion of the combined cardiac output perfusing the increasing brain size increases, to compensate for the progressive fetal blood PO₂ decrease. The hypoxemia, in turn contributes to the “brain sparing reflex” [11, 50, 53, 54]. This aligns with documented positive correlations between fetal partial pressure of oxygen (PO₂) and MCA resistance index (RI) [13, 28, 55].

4.1 Study limitation and strength

The main limitations of the study were the cross-sectional design, lack of information on duration of the maternal anemia, and specific causes of anemia. These have documented impacts on placental perfusion and Doppler flow parameters. During the third trimester, particularly after 34 weeks of gestation fetal physiological cerebral vascular dilatation, may introduces potential bias impacting parameters like the CPR. Assumptions such as constant viscosity and density, used in calculations may not universally apply to the entire study population.

Our strength lies in contribution to existing literature, addressing the knowledge gap on fetal Doppler parameters for Ugandan population. The study also explores novel parameters, including volumetric flow per minute, hence comprehensive understanding beyond traditional flow indices and ratios.

5 Conclusion

Anemic women exhibited higher Umbilical artery resistance, worsening with increasing severity of maternal anemia suggestive altered flow patterns and hemodynamics.

However considering the short duration and cross-sectional study design, we propose implementation of longitudinal study design to facilitate tracking of cases over an extended period, exploration of modifier effects like duration of anemia and the impact of mitigating interventions like transfusions. This coupled with studies of fetal vessels like the ductus venosus, correlating findings with outcomes like fetal weight, placental and cord studies at delivery for insights into other cardiovascular parameters, such as fetal hemoglobin, could contribute to enhanced antenatal care strategies, emphasizing the importance of monitoring maternal anemia and its potential implications on fetal cardiovascular- placental health during pregnancy.

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Author contributions

JS: original idea, data analysis and first manuscript draft, YLFT: proposal writing, data analysis and editing manuscript, SLM: proposal writing and editing manuscript.

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Data availability

The dataset "Sociodemographic characteristics of study participants" is available upon request. The dataset of "Maternal hemoglobin levels" is available upon request. The dataset "Doppler-derived indices and ratios of the fetal middle cerebral artery and umbilical artery" can be requested by reaching out to the corresponding author. The dataset of "Physiological parameters" is accessible through a request to the corresponding author. The dataset "Cerebro-placental ratio (CPR) values" is available for request. The dataset of "Fetal heart rate measurements" is accessible upon request. To obtain dataset, please contact the corresponding author; on jonathanj094@gmail.com.

Declarations

Ethics approval and consent to participate

The ethical clearance was obtained from Mbarara University of Science and Technology Research and Ethics committee (MUST-REC; 2022 – 693) before the data was collected. Administrative clearance was sought from the Hospital Director of Mbarara Regional Referral Hospital and the Heads of Laboratory, Radiology and Obs-Gyn departments. All study procedures were performed in accordance with the relevant guidelines and recommendations and all participants provided written informed consent. This study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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