Prenatal Hemoglobin Levels and Early Cognitive and Motor Functions of One-Year-Old Children

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abstract

OBJECTIVE: To explore the relationship between prenatal hemoglobin (Hb) concentration and infant cognitive and motor functions.

METHODS: Our prospective cohort study included 1-year-old children born to women enrolled at their first antenatal care (ANC) visit in Allada, Benin, before 29 weeks of pregnancy, within a trial comparing the efficacy of sulfadoxine-pyrimethamine and mefloquine. Hb concentrations of pregnant women were determined from venous blood samples collected at first and second ANC visits of at least 1-month interval and at delivery. Women were prescribed oral iron, folic acid, and anthelminthics after the first ANC visit. A total of 636 children (76.8% of eligible children) were assessed by trained research nurses for cognitive and motor functions by using the Mullen Scales of Early Learning.

RESULTS: Prevalence of anemia (Hb < 110 g/L) decreased from 67.0% at first ANC visit (mean gestational age [SD], 22.1 [4.0] weeks) to 38.4% at delivery. Mean (SD) Hb concentrations increased from 103.7 (12.3) at first ANC visit to 112.4 (14.1) at delivery. We observed a significant negative quadratic relationship between infant gross motor (GM) function and Hb concentration at first and second ANC visits. Thus, infant GM scores increased sharply with increasing maternal Hb concentration until 90 g/L where increasing GM was mild, and began to decline after 110 g/L.

CONCLUSIONS: There appears to be an Hb concentration range that may be optimal for GM function of 1-year-old children. This may reflect the importance of physiologic hemodilution, which occurs after the second trimester until 34 weeks of gestation.

WHAT'S KNOWN ON THIS SUBJECT: Studies on the consequences of abnormal prenatal hemoglobin (Hb) concentration have focused on maternal morbidities and adverse birth outcomes. To date, very little is known about the association between prenatal Hb concentration and infant cognitive and motor functions.

WHAT THIS STUDY ADDS: There is an inverted U-shaped relationship between maternal Hb concentration and infant gross motor function. Hb concentration between 90 and 110 g/L appears to be optimal for early gross motor function of children.

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Early childhood, defined as the period from the prenatal phase until 8 years,[1] is the most critical developmental chapter of an individual's life trajectory. During the prenatal phase, the fetus undergoes extensive series of events involving neural migration, synaptogenesis, hippocampal development, and myelination,[2] which provide the structural foundation for brain development and function. This later becomes evident in the early developmental domains (social-emotional, fine-gross motor [GM], and language-cognition) of the growing infant. Due to the sensitivity of the fetal brain, its development could be altered by exposure to prenatal insults such as infections, stress, toxins, nutrient deficiencies and ischemia.[3,4] Children with restricted prenatal development may potentially be mentally and socially impaired later in life.

A recent study in Benin suggests that maternal malnutrition, malaria infection, iron deficiency, helminth infection, and folate deficiency are the major risk factors for anemia in pregnant women at their first antenatal care (ANC) visits before treatments and micronutrient supplementation.[5] Although access to iron and folic acid (IFA) supplements, intermittent preventive treatment of malaria in pregnancy (IPTp), and the use of anthelminthics during pregnancy are being achieved, the burden of anemia in least developed countries remain unacceptably high.[6] In Africa, anemia in pregnancy (hemoglobin [Hb] concentration <110 g/L) is a severe public health problem estimated to be affecting over 17 million pregnant women.[7]

Significant increase, as well as decrease, in Hb concentration in pregnancy may imply deprivation of iron, oxygen, and other essential micronutrients to fetus for development. A study by Gonzales et al[8] revealed a U-shaped relationship between prenatal Hb and the risk of adverse birth outcomes. They observed that low prenatal Hb (<90 g/L) is associated with increased odds of stillbirths and preterm births and small-for-gestational age likewise Hb concentrations greater than 150 g/L.[8] However, to date, little is known about the impact of prenatal Hb levels on early child psychomotor development.

Considering the evidence of adverse effects of low and high Hb levels during pregnancy, we hypothesized an inverted U-shaped relationship between infant cognitive and motor scores and maternal Hb during pregnancy. We therefore explored whether there was a nonlinear relationship between prenatal Hb at different periods of pregnancy and cognitive and GM development of 1-year-old children in Benin. We also compared the cognitive and motor functions of children of anemic and nonanemic women.

METHODS

Population

This prospective study (called TOVI) included 636 1-year-old surviving singletons born to women enrolled in the Malaria in Pregnancy Preventive Alternative Drugs (MiPPAD) study (NCT00811421). MiPPAD was a clinical trial comparing the efficacy of sulfadoxine pyrimethamine and mefloquine as IPTp. Inclusion and exclusion criteria for the clinical trial are fully explained elsewhere.[9] Briefly, HIV-negative women who were at most 28 weeks pregnant and had not taken IPTp, IFA supplements, anthelmintics, or vitamin B12 since conception were recruited in maternity clinics in 3 subdistricts of Allada, Benin, during their first ANC visit.

Data and Hb Assessment During Pregnancy and at Birth

Maternal education, gravidity, gestational age, weight, and height were determined at first ANC. Maternal prepregnancy BMI was calculated by using a method detailed in a previous publication.[5]

At 2 ANC visits, of at least 1-month interval, and at delivery, venous blood was obtained for analyses. Ten microliters of each blood sample was placed into a cuvette of the Hemo-Control photometer (EFK Diagnostics, Magdeburg , Germany) to measure the Hb concentration. Quality control was ensured by daily calibration of the Hemo-Control device by laboratory technicians and by crosschecking the Hb of 1 in 10 consecutive samples at the Allada Central Hospital laboratory by using a hematology analyzer (Erma Laboratory, Tokyo, Japan). Alkaline electrophoresis on cellulose acetate (Helena Laboratories, Beaumont, TX) was used to determine Hb genotypes.

Anemia was defined as Hb <110 g/L. After each assessment, pregnant women with Hb between 70 g/L and 110 g/L were treated with 400 mg of oral ferrous sulfate (200 mg twice daily) in accordance with the national guidelines. Those with Hb below 70 g/L were referred to a district tertiary hospital for blood transfusion. Per the guidelines of Beninese Ministry of Health, oral ferrous sulfate (200 mg daily) and folic acid (5 mg daily) supplements were provided for all pregnant women after the first ANC visit until 3 months after delivery. Additionally, 600 mg of mebendazole were given to pregnant woman in the second trimester. During the study period, drugs and nutrient supplements were given to women without charge.

Assessments at Age 1 Year

Research nurses were trained specifically to administer and score the cognitive and motor tests. Cognitive and motor functions of 636 1-year-old children were assessed by using the Mullen Scales of Early Learning (MSEL),[10] which was translated and adapted for this

setting.[11] The MSEL encompasses the developmental domains of childhood and consists of 5 scales: GM, fine motor, language reception, language expression, and visual reception. After scoring each item, crude scores obtained from each of the 5 scales were transformed into normalized age-specific scores called *T* scores. Three children who obtained crude scores lower than 5 were given the least *T* score in the corresponding scale. *T* scores of all but GM scale were summed and converted to obtain the Early Learning Composite (ELC) scores.[12]

The quality of the home environment (using the Home Observatory Measurement of the Environment [HOME] inventory),[13] postnatal depression (using the Edinburgh Postnatal Depression Scale),[14] maternal nonverbal intelligent quotient (using the Raven's Progressive Matrices test),[15] and infant anthropometric measurements were also assessed at 1 year of age.

Statistical Analyses

Summary statistics and distributional analyses were performed for all variables independently. The 2 dependent variables used in the analyses were the ELC and GM scores. The main independent variables were Hb concentrations (g/L) measured at first and second ANC visits and at delivery. The Hb concentrations were also categorized to reflect the anemia status of pregnant women.

We performed crude linear regression analyses between ELC and GM scores, and Hb concentration and anemia at each ANC visit and at delivery, separately. Bivariate analyses were performed to determine the correlation between covariates maternal and infant characteristics and ELC and GM scores. Direct acyclic graph was used to justify potential confounding.[16] Covariates that were associated with the ELC and crude GM scores at $P <$ .20 were selected for multiple

regression analyses. Stepwise removal of covariates was performed until all covariates in the models remained significant.[17] Because Hb physiologically varies with gestational age, gestational age (trimesters) at time of Hb assessment was kept in the adjusted models even if it was not significant. Because of the physiologic increase in Hb toward the end of pregnancy,[18] preterm births were excluded only when establishing the association between Hb concentration at delivery and infant ELC and GM scores (model II).

Afterward, we explored possible nonlinearity of the association between the ELC and GM scores and Hb at each ANC visit and at delivery by using Box-Cox right-hand-side only transformation with a maximum iteration of 10. We fixed the Box-Cox regression such that only Hb was transformable as specified in the equation:

$$y_j = \beta_0 + \beta_1 x_{1j}^{(\lambda)} + \gamma_1 z_{1j} + \gamma_2 z_{2j} \ldots \gamma_k z_{kj} + \varepsilon_j$$

where y is the ELC or GM score, x_1 is the Hb concentration (the only variable transformed by a Box-Cox transform parameter λ), and z_1, z_2… z_k are the covariates selected into the model and they were untransformed.[19]

The Box-Cox regression analyses were run for the association between GM and ELC scores and Hb concentrations at each ANC visit and at delivery. When nonlinearity was confirmed, a quadratic transformation of the Hb variable was used in the multiple regression models as we had hypothesized a plausible inverted U-shaped relationship (model III). Selected confounders were not in the causal pathway of prenatal Hb concentration and infant GM scores.

In a subsequent sensitivity analysis, we further adjusted model III for other known causes of anemia during pregnancy such as iron deficiency,

malaria, and helminth infection at the time of assessment while retaining the previous covariates in the model (model IV).

All statistical analyses were conducted by using Stata IC/12.1 (Stata Corp, College Station, TX).

Ethical Considerations

The study was approved by the institutional review boards of the University of Abomey-Calavi (Benin), New York University, Michigan State University, and the Research Institute for Development's Consultative Ethics Committee (France). At recruitment, we obtained informed consent from all pregnant women and guardians of children who participated in this study.

RESULTS

A total of 636 children (76.8% of 828 eligible) were followed until age 1 year. A flowchart of the follow-up of pregnant women and children has been published elsewhere.[20] Maternal baseline characteristics were similar between children not assessed and those assessed at age 1 year.[20] Mean maternal age (SD) at first ANC visit was 26.8 (5.6) years. The prevalence of malaria was 16.0% at first ANC visit, declined to 3.7% at second ANC visit, and then increased to 10.6% at delivery. Seven percent of children were born preterm, and 9.6% weighed <2500 g at birth (Supplemental Table 5). Mean (SD) Hb at first ANC visit was 103.7 (12.3), 105.4 (10.6) at second ANC visit, and 112.4 (14.1) at delivery. Anemia during pregnancy declined from 67.0% at first ANC visit to 38.4% at delivery (Table 1).

Table 2 shows the associations between maternal and infant characteristics and mean ELC and GM scores. Women who had at least primary education had children with significantly better cognitive and motor function than those who had never schooled ($P < .001$). Underweight women had children with the least GM scores. Family

TABLE 1 Gestational Age and Hb Distribution Among Women Whose Children Were Assessed for Cognitive and Motor Function at Age 1 y

	First ANC Visit, N = 636	Second ANC Visit, N = 627	Delivery, N = 609
Gestational age, wk			
Mean	22.0	28.8	38.3[a]
SD	3.9	3.8	3.2
Range	10–28	18–40	23–55
Hb, g/L			
Mean	103.7	105.4[b]	112.4
SD	12.3	10.6	14.1
Range	41–143	55–138	40–168
Anemia, Hb < 110 g/L			
n (%)	426 (67.0)	403 (64.4)	234 (38.4)

[a] N = 596.
[b] N = 626.

possession scores, Raven's Progressive Matrices, and HOME scores and infant weight at age 1 year were positively correlated with both ELC and GM scores.

As shown in Table 3, prenatal anemia at both ANC visits and at delivery were not associated to ELC scores even after adjusting for confounders. However, in the adjusted model, children of anemic mothers had better GM scores 2.3 (95% confidence interval [CI]: 0.1 to 4.6) than those of nonanemic mothers.

The HOME score, maternal education, and infant weight-for-age covariates that were strongly related to both GM and ELC scores were selected for the Box-Cox regression. The coefficients of the transformed Hb at all 3 assessments (β_1) were not significant for the models for ELC score and Hb concentrations. For the adjusted models involving GM score and Hb, we found that β_1 were significant for Hb at first and second ANC visits and in addition, the model rejected the hypothesis that the model is linear;

indicating that quadratic transformation of Hb at the first and second ANC could be used as hypothesized.

As shown in Table 4, the regression coefficient of the quadratic terms was negative and significant for the associations between Hb at first and second ANC visits and GM function at age 1 year. Diagrammatic representation of the nature of the association between prenatal Hb at first and second ANC visit and GM score are shown in Figs 1 and 2, respectively. In both figures, the GM for 1-year-old children increased sharply with increasing prenatal Hb until 90 g/L where the increase was steady then declined sharply over Hb level of 110 g/L. The peak for the quadratic curves was 98 g/L and 97 g/L at first and second ANC visits, respectively.

DISCUSSION

To our knowledge, this study is the first to investigate the relationship between Hb levels at different periods during pregnancy and infant cognitive development. This study reveals that there is an inverted U-shaped relationship between prenatal Hb at first and second ANC visits and infant GM function indicating that low and high Hb concentrations during pregnancy may be detrimental to the early motor functions of 1-year-old children. Peak infant GM scores were observed at prenatal Hb of 98 g/L and 97 g/L at first and second ANC visits, respectively. However, prenatal anemia was associated with high GM scores at second ANC visit.

An important strength of our study is that we assessed Hb at different times during pregnancy. Also, the follow-up of 76.4% of eligible children recorded in this study is appreciable because it compares well to other mother–child cohorts in Africa.[21] Additionally, the MSEL used is a comprehensive tool for cognitive and motor assessment of children. Further, the consideration of several potential confounders in our

TABLE 2 Associations Between Characteristics of Pregnant Women and Children and ELC and GM Scores

Characteristics	ELC Score		GM Score	
N = 636	Mean	P	Mean	P
Gender				
Girl	99.2	.21	50.2	.14
Boy	97.8		51.8	
Weight-for-age z score[a]	0.2[c]	<.001	0.3[c]	<.001
Gravidity				
Primigravida	99.8	.28	48.2	.02
Multigravida	98.2		51.6	
Maternal education				
Never schooled	96.2	<.001	49.4	<.001
Primary or more	102.9		54.1	
Maternal occupation				
Housewives	96.1	<.001	49.2	.002
Employed	100.8		52.8	
Prepregnancy BMI				
Underweight	96.4	.07	48.9	.03
Normal	98.6		50.9	
Overweight/obese	101.5		54.8	
Family possession score[b]	0.1[c]	.005	0.2[c]	<.001
HOME score[b]	0.2[c]	<.0001	0.2[c]	<.001
RPM score[b]	0.1[c]	.03	0.1[c]	.002
EPDS score[b]	−0.0[c]	.98	−0.0[c]	.67

EPDS, Edinburgh Postnatal Depression Scale; RPM, Raven's Progressive Matrices.
[a] N = 629.
[b] N = 631.
[c] Represented as correlation coefficients not means.

TABLE 3 Relationship Between Prenatal Anemia and ELC and GM Scores

Anemia	ELC Score		GM Score	
	Crude Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)[a]	Crude Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)[b]
First ANC visit				
No anemia	Reference	Reference	Reference	Reference
Anemia	−1.0 (−3.4 to 1.4)	−0.4 (−2.7 to 1.9)	0.4 (−2.0 to 2.7)	1.6 (−0.7 to 3.9)
Second ANC visit				
No anemia	Reference	Reference	Reference	Reference
Anemia	0.5 (−1.8 to 2.8)	0.6 (−1.6 to 2.9)	2.2 (−0.2 to 4.5)	2.3 (0.1 to 4.6)*
Delivery				
No anemia	Reference	Reference	Reference	Reference
Anemia	−0.7 (−3.1 to 1.7)	−0.6 (−2.9 to 1.8)	−1.1 (−3.5 to 1.4)	−0.6 (−3.0 to 1.8)

*$P < .05$
[a] Adjusted for maternal education, infant weight-for-age z score, HOME score, and gestational age at blood assessment.
[b] Adjusted for maternal education, gravidity, family possession, infant weight-for-age z score, HOME score, and gestational age at Hb assessment.

study such as socioeconomic factors, mother–child interaction, maternal postnatal depression, and maternal IQ based on statistical significance and direct acyclic graphs contributes to the strength of this study.

During pregnancy, there is a ~50% physiologic increase in plasma volume, peaking between 28 to 34 weeks of gestation, and a disproportionate 20% to 30% increase in red cell mass, which results in a decrease Hb concentration.[22] This hemodilution during the second and third trimesters may be essential for fetal growth as the reduced thickness of the blood enhances effective flow of oxygen and other nutrients to the fetus.[22] This could explain 2 observations in our results. Firstly, the observed high motor function

among children of anemic women at second ANC visit when more than 50% of women were between 28 and 34 weeks of gestation. Secondly, the optimum GM function observed among children of pregnant women with Hb levels between 90 and 110 g/L at first and second ANC visits even after adjusting for other known risk factors for low maternal Hb. This Hb range (90–100 g/L) for optimum GM function, considered anemic, raises questions about the cutoff for anemia.

Low GM function was observed at low Hb levels on the left end of the inverted U-shaped curve. The observed low levels of Hb among pregnant women at first ANC visit could be a result of pathologic anemia due to malaria, helminths, and iron deficiency among other unmeasured

micronutrient deficiencies that are risk factors. Low Hb levels at second ANC visit could be due to a combination of the aforementioned etiologies and physiologic increase in plasma volume.[23] Extremely low Hb concentration implies deficient oxygen transport to the fetus.[24] Although the fetus has mechanisms to adapt to decreased maternal oxygen delivery, the costs of such adaptation could be expensive, possibly leading to impaired fetal growth.[22]

Low Hb levels during pregnancy could diminish the amount of accessible iron for the fetus. Iron availability is essential for effective fetal growth and function of several organ systems including the brain and skeletal muscle.[25] Prenatal iron deficiency is associated with decreased apical dendrite length and

TABLE 4 Linear and Quadratic Models for the Association Between Maternal Hb Concentration and Infant ELC and GM Scores

	Model I, β (95% CI)	Model II, β (95% CI)	Model III, β (95% CI)[a]	Model IV, β (95% CI)[a]
ELC score				
First ANC visit	0.05 (−0.04 to 0.14)	0.03 (−0.06 to 0.11)	NA	NA
Second ANC visit	0.02 (−0.09 to 0.12)	−0.00 (−0.10 to 0.10)	NA	NA
Delivery	0.03 (−0.06 to 0.12)	0.02 (−0.07 to 0.10)	NA	NA
GM score				
First ANC visit	0.02 (−0.07 to 0.11)	−0.04 (−0.13 to 0.05)	-5.5×10^{-3} (-9.5×10^{-3} to -1.4×10^{-3})**	-5.6×10^{-3} (-9.6×10^{-3} to -1.6×10^{-3})**
Second ANC visit	−0.06 (−0.17 to 0.04)	−0.09 (−0.19 to 0.01)	-6.6×10^{-3} (-1.2×10^{-2} to -9.2×10^{-4})**	-7.0×10^{-3} (-1.3×10^{-2} to -1.2×10^{-3})*
Delivery	−0.02 (−0.11 to 0.07)	−0.04 (−0.13 to 0.05)	NA	NA

Model I, crude (unadjusted); Model II, linear model adjusted for maternal education, infant weight-for-age z score, HOME score, and gestational age at blood assessment (for ELC score) and in addition, gravidity, family possession (for GM score); Model III, quadratic model adjusted for maternal education, gravidity, family possession, infant weight-for-age z score, HOME score, and gestational age at Hb assessment; Model IV, Model III + adjusting for iron deficiency, helminth, and malaria at respective ANC visit; NA, not applicable. *$P < .05$; **$P < .01$.
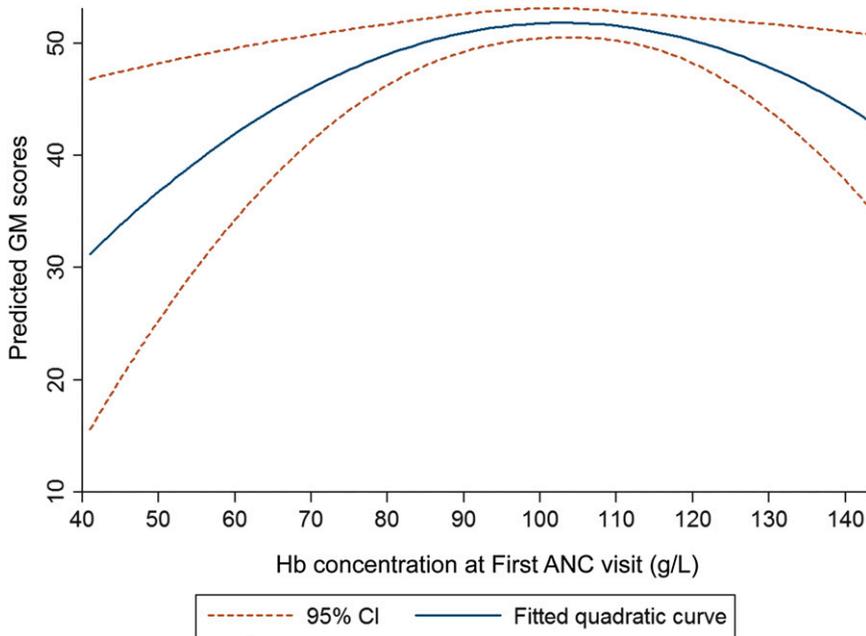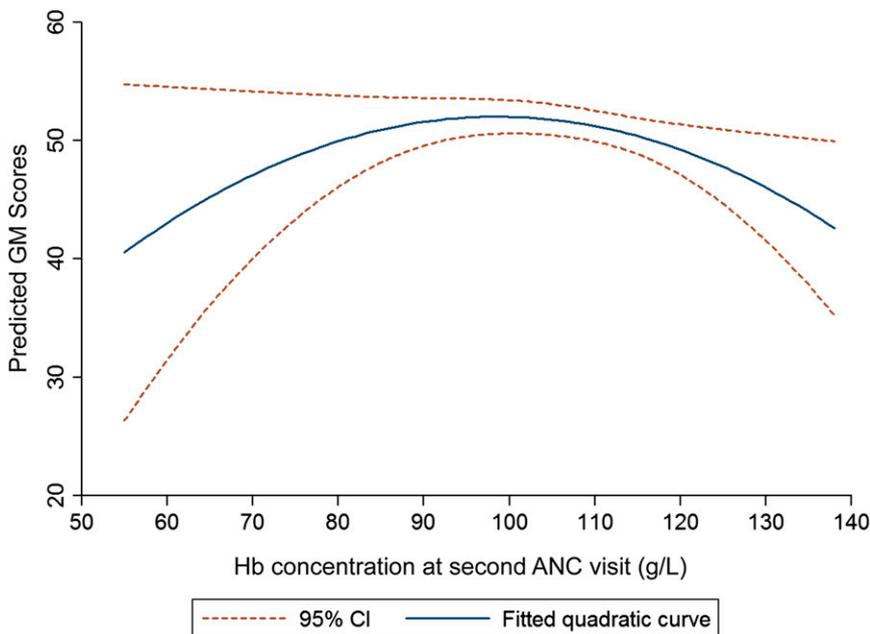[a] β (95% CI) for the quadratic term for Hb.

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FIGURE 1
Relationship between Hb concentration at first ANC visit and infant GM scores. The solid line indicates the fitted model, whereas the dash lines represent 95% CIs.

could alter the hippocampal development even in the early stages of pregnancy.[25,26] The apical dendrites in the hippocampus play a substantial role in memory and sensory functions. Studies in pregnant mice have also revealed that

there is a direct relationship between maternal iron levels and fetal brain iron.[27] Low fetal brain iron could be responsible for the poor neuromotor skills in infants as a study revealed that 1-year-old children with brain iron deficiency (≤34 μg/L) had

FIGURE 2
Relationship between Hb concentration at second ANC visit and infant GM scores. The solid line indicates the fitted model, whereas the dash lines represent 95% CIs.

slower motor development compared with those with adequate brain iron.[27,28] However, the inverted U-shaped association persisted at second ANC visit after women were given IFA supplements and even after adjusting for iron deficiency, helminth, and malaria suggesting that we really measured the effect of Hb on motor function.

Conversely, higher than normal prenatal Hb could be due to nonexpansion of plasma and as a result, increased blood viscosity. Increased viscosity implies reduced blood flow to the intervillous space.[22] This could lead to fetal stress due to placental-fetal perfusion and consequently impair the development of essential fetal organs.[22] This condition of hemoconcentration could explain the right-hand-side of the quadratic curves where increasing Hb concentrations during pregnancy were associated with decreasing infant GM scores and may reflect the disadvantage of hemoconcentration during pregnancy.

The curvilinear nature of the observed relationship in our study is analogous to that between prenatal Hb and low birth weight.[29,30] Maternal Hb concentration is a predictor of pregnancy complications and several adverse birth outcomes such as low birth weight, stillbirth, and preterm birth , which could mediate the pathway between prenatal Hb and infant GM function.[31] These adverse birth outcomes have been identified to be risk factors for poor cognitive and motor development.[32,33] A study of ~223 000 singleton pregnancies also revealed a U–shaped relationship between maternal Hb concentration and early neonatal mortality with the lowest perinatal mortality in the 90 to 110 g/L Hb range.[34]

Chang et al[35] suggested that children born to women who were anemic at the third trimester performed significantly lower than those of nonanemic women in cognitive assessment tests, but the authors did not assess the relationship between

Hb concentration, as a continuous variable, and the cognitive scores. Contrary to the findings of Chang et al,[35] we observed no significant association between maternal anemia and infant cognitive function of our study. In the aforementioned study, the authors only assessed Hb in the third trimester with anemia prevalence of 45.2%. They also stated that anemia in the study population was mainly due to iron deficiency, which could explain the difference in findings. In our study population, prenatal anemia was multifactorial.[5]

Pregnant women were enrolled in a clinical trial and as a result received several interventions that are likely to improve maternal health, birth outcomes, and neonatal health and potentially influence the cognitive function of children. Hence, our study is likely to underestimate the real magnitude of the effect of low and high maternal Hb on offspring cognitive development in the population who may seek fewer than 2 ANC visits during pregnancy. Also, caution should be taken in interpreting our results especially in the extreme ends of the curve as the CIs are wider due to the small number of observations.

CONCLUSIONS

This study reveals that there is an inverted U-shaped relationship between maternal Hb concentration during pregnancy and motor function of 1-year-old children. There appears to be an optimal range maternal Hb (90–110 g/L) that may be beneficial to infant GM function. It is the first study to report a quadratic relationship between prenatal Hb concentration and GM development of infants. Further studies are required to corroborate this curvilinear association. A follow-up study to investigate if this association persists even in the later life of the children is also necessary.

ABBREVIATIONS

ANC: antenatal care visit
CI: confidence interval
ELC: Early Learning Composite
GM: gross motor
Hb: hemoglobin
HOME: Home Observatory Measurement of the Environment
IFA: iron and folic acid
IPTp: intermittent preventive treatment of malaria in pregnancy
MiPPAD: Malaria in Pregnancy Preventive Alternative Drugs
MSEL: Mullen Scales of Early Learning

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