ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20230967

Maternal malnutrition during pregnancy among women with sickle cell disease

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SUMMARY

OBJECTIVE: The objective of this study was to compare the nutritional status and dietary intake of pregnant women with sickle cell disease (SS hemoglobinopathy and SC hemoglobinopathy) to healthy controls and report the maternal and perinatal outcomes.

METHODS: This is a prospective, longitudinal cohort study. Pregnant women with a diagnosis of sickle cell disease and control group were recruited in an outpatient clinic of a tertiary care hospital in São Paulo, Brazil. Maternal anthropometric data and dietary intake data were collected at the second and third trimesters.

RESULTS: A total of 49 pregnancies complicated by sickle cell disease were included. Prepregnancy body mass index was significantly lower in the SS hemoglobinopathy group (n=26, median 20.3 kg/m^2) than the SC hemoglobinopathy group (n=23, 22.7 kg/m^2) or control group (n=33, 23.2 kg/m^2, p<0.05). The prepregnancy nutritional status revealed significantly more women classified as underweight in the SS hemoglobinopathy group (15.4%) than in the SC hemoglobinopathy group (4.4%) and control group (1.6%, p=0.009). In the second trimester, maternal protein intake was significantly lower in SS hemoglobinopathy (73.2 g/day) and SC hemoglobinopathy (68.8 g/day) than in the control group (95.7 g/day, p=0.004). In the third trimester, only SS hemoglobinopathy mothers showed dietary intake of protein significantly lower than that of the controls (67.5 g/day vs. 92.8 g/day, p=0.02). Vitamin A and E consumption was also reduced in the third trimester in the SS hemoglobinopathy group (p<0.05).

CONCLUSION: The nutritional status of pregnant women with SS hemoglobinopathy is characterized by a state of undernutrition. The lower protein intake in the second and third trimesters of pregnant women with SS hemoglobinopathy may contribute to this condition. Undernourishment is a serious complication of sickle cell disease, primarily during pregnancy, and it should be addressed during the prenatal period.

KEYWORDS: Nutrition disorders. Sickle cell disease. Pregnancy complication. Anemia.

INTRODUCTION

Sickle cell disease (SCD) refers to a group of hemoglobinopathies caused by inherited single-gene autosomal recessive disorders, which affect the structure of hemoglobin (Hb). Sickle cell anemia, or SS hemoglobinopathy (HbSS), is the result of sickle cell gene homozygosis. Of the other SCD variants, the most common is SC hemoglobinopathy (HbSC). Several studies have reported maternal and fetal complications in pregnant women with SCD: perinatal mortality, preterm labor, fetal growth restriction, preeclampsia, acute painful crises, and urinary and pulmonary infections[1-4].

Medical improvements have allowed women with SCD to reach childbearing age. As this is a multiorgan disease, patients should be monitored for chronic complications and preconceptional counseling has a role in letting them know about the effects of pregnancy[5,6]. Since the late 1980s, undernutrition has been identified as a critical feature of SCD[7]. Growth in children with HbSS is impaired[8], and suboptimal nutritional status has been reported in children and adolescents with SCD[9,10]. Some studies suggest that malnutrition is probably a consequence of increased requirements rather than poor dietary intake[11].

In pregnancy, less is known about the dietary intake of pregnant women with SCD and nutritional adjustments that should be made[12,13]. The aim of this study was to compare the nutritional status and dietary intake of pregnant women with SCD (HbSS and HbSC) to healthy controls and report the maternal and perinatal outcomes.

METHODS

This is a prospective, longitudinal cohort study performed in São Paulo, Brazil. Pregnant participants were recruited from the specialized prenatal care unit in the university hospital from 2010 to 2016. All patients who came to the clinic and met the inclusion criteria were invited to participate in the study. Data were collected from 46 women with a total of 49

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: The Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) funded this study with a research scholarship awarded to LVP (No. 2012/03547-8).
Received on July 28, 2023. Accepted on August 22, 2023.

pregnancies complicated by SCD (HbSS and HbSC). A total of 30 healthy pregnant women in the second trimester and 33 in the third trimester were enrolled as controls. They were singleton pregnant women without any obstetrical or clinical complication, and they were matched for gestational age at nutritional interview. This study was approved by the local Human Research Ethics Committee, and informed consent was signed by all participants.

Pregnant women with a diagnosis of SCD (HbSS and HbSC) were invited to participate in the study at their first prenatal appointment at the specialized prenatal care unit. The inclusion criteria were fetus alive at recruitment and diagnosis of HbSS or HbSC.

Maternal dietary intake data were collected by a single research nutritionist. Face-to-face interviews were conducted in the second and third trimesters of pregnancy by using a validated semiquantitative food-frequency questionnaire (FFQ) for the Brazilian population. The FFQ comprises questions about food and beverages, but not about vitamin or mineral supplement use. The tool is composed of 57 food items, including consumption frequency, portion size, preparation method (raw, boiled, or fried), and additions (sugar or salt). For each food item, subjects report serving sizes (i.e., small, medium, or large) and consumption frequencies (nine options). The dietary intake reference period was the previous 6 months. Nutrients were analyzed using the nutrition software Nutrilife©. The reported foods were converted into means of estimated daily intake of total energy, carbohydrates, proteins, total fat, and fibers. All macronutrients were energy-adjusted. The micronutrients analyzed were calcium, iron, zinc, vitamin A, vitamin E, vitamin C, and folates, which included the daily intake. The Brazilian Standard Food Composition Table[14] was used to calculate average daily intakes of total energy, carbohydrates, fat, and fibers. Food intake was reported in grams/day, and micronutrient intakes were reported using the most appropriate unit for each nutrient.

Maternal anthropometric data were measured by trained nurses. Demographic data were collected during the first prenatal visit. Body mass index (BMI) was calculated using weight and height (kg/m^2) and was obtained at baseline using prepregnancy weight and maternal weight at the end of pregnancy (immediately before birth). In late pregnancy, the maternal nutritional status was defined according to the expected BMI for gestational age[15].

Pregnant women with SCD were scheduled for prenatal care every 1-4 weeks, according to the severity of the disease. All patients were known to have SCD at their first appointment; nevertheless, the hemoglobin phenotype of some patients was confirmed by electrophoresis. Hematological data were collected during pregnancy for clinical purposes, and the last evaluation was used for analysis. Data were obtained from the patient's charts and the electronic records of the laboratory. Blood transfusion was performed for symptomatic anemia or worsening anemia with concurrent pain crisis. Prophylactic antenatal transfusions to maintain a certain hemoglobin or hematocrit level during pregnancy were not performed as this is not included in our management protocol. The sickle cell crises mentioned in this study were defined as acute pain episodes requiring hospitalization for analgesia and intravenous hydration. Hypertensive disorders encompassed chronic hypertension and preeclampsia. Pulmonary complications included pneumonia, acute chest syndrome, and pulmonary thromboembolism. Diagnosis of urinary tract infection was based on a positive urine culture routinely screened in each trimester of pregnancy. Other SCD events included persistent proteinuria, aseptic femoral necrosis, and splenic sequestration.

Statistical analysis

Data were analyzed using the Medcalc program, version 11.5.1.0 (Medcalc Software, Belgium). Descriptive statistics were reported as frequency and percentage for categorical data and as means and standard deviation or median and range for continuous variables. The Kruskal-Wallis test was used to compare the medians between the groups. Categorical data were compared using the chi-square test or the Fisher's exact test when appropriate. Statistical significance was set at $p<0.05$.

RESULTS

Table 1 shows the maternal characteristics of the pregnant women enrolled in this study. Prepregnancy BMI was significantly ($p<0.001$) lower in the HbSS group than in the HbSC group or the control group. The prepregnancy nutritional status revealed more women classified as underweight in the HbSS group. Furthermore, the gestational weight gain was significantly lower in HbSS pregnancies. As expected and given the SCD features, when compared with the control group, hemoglobin and hematocrit levels were significantly lower, and white blood cell count was significantly higher. The HbSS group presented a significantly higher platelet count than the HbSC and the control groups.

Maternal dietary intake evaluated by FFQ in the second and third trimesters is presented in Table 2. In the second trimester, the dietary intake of protein was significantly lower in the HbSS and HbSC groups than in the control group. In the third trimester, maternal dietary intake of protein was significantly lower in the HbSS group when compared with the

Table 1. Maternal characteristics of pregnant women complicated by sickle cell disease.

Characteristics	HbSS (n=26)	HbSC (n=23)	Control (n=63)	p
Maternal age, years	25.5 (17–34)	25.0 (19–44)	28.0 (18–39)	0.367
Nulliparous women	16 (61.5)	13 (56.5)	38 (60.3)	0.626
Education				
Elementary school	14 (53.8)	8 (34.8)	26 (41.3)	0.376
High school/college	12 (46.2)	15 (65.2)	37 (58.7)	
Prepregnancy BMI (kg/m^2)	20.3 (16.4–26.3)	22.7 (17.4–27.6)	23.2 (18.0–37.2)	<0.001[a]
Prepregnancy nutritional status				
Underweight	4 (15.4)	1 (4.4)	1 (1.6)	
Eutrophic	20 (76.9)	15 (65.2)	38 (60.3)	0.009
Overweight/obese	2 (7.7)	7 (30.4)	24 (38.1)	
BMI in late pregnancy (kg/m^2)[b]	23.1 (19.1–31.1)	26.1 (22.1–34.8)	28.5 (22.2–41.5)	<0.001[a]
Nutritional status in late pregnancy[b]				
Underweight	15 (60.0)	4 (18.2)	7 (11.1)	
Eutrophic	8 (32.0)	10 (45.5)	26 (41.3)	<0.001
Overweight/obese	2 (8.0)	8 (36.4)	30 (47.6)	
Weight gain during pregnancy, kg[b]	8.0 (–1 to 17.7)	11.9 (3.1–18.5)	13.7 (0.2–28)	<0.001[a]
Hemoglobin electrophoresis				
A2	2.8 (0–5)	0 (0–4.1)	–	
Fetal	11.4 (1–24)	1.3 (0–8.3)	–	
S	83.5 (67.2–96)	50.2 (38.7–83)	–	–
C	0 (0)	46.7 (27.8–53.3)	–	
Hemoglobin, g/dL	7.7 (5.8–9.5)	9.8 (6.5–11.5)	12.2 (11.2–14.7)	<0.001[c]
Hematocrit, %	22.5 (16.7–28.6)	28.2 (19.2–36.4)	36.3 (32.7–41.3)	<0.001[c]
White blood cell count, n.10^3/mL	16.9 (3.5–31.9)	12.4 (4.9–24.2)	9.3 (5.5–14.5)	<0.001[c]
Platelets, n.10^3/mL	322 (36–896)	176 (59–561)	225 (158–357)	0.010[a]

Data are expressed as n (%), mean (SD), or median (min–max). [a]HbSS *vs.* control: p<0.05; HbSS *vs.* HbSC: p<0.05; HbSC *vs.* control: p=NS. [b]25 cases of HbSS and 22 cases of HbSC (one case of miscarriage was excluded in each group). [c]HbSS *vs.* control: p<0.05; HbSS *vs.* HbSC: p<0.05; HbSC *vs.* control: p<0.05.

HbSC group and controls. The maternal micronutrient dietary intake showed no significant differences in the second trimester; however, in the third trimester, the HbSS group presented a significantly lower intake of vitamins A and E than the HbSC and the control groups.

Table 3 shows the maternal complications and perinatal results in the groups. No significant differences were found between the HbSS and the HbSC groups, except for the need of blood transfusions during the prenatal period.

DISCUSSION

This study has demonstrated that the nutritional status of pregnant women with HbSS is characterized by a state of malnutrition associated with adverse maternal and perinatal outcomes. We found few studies addressing the nutritional status of pregnant women with SCD[16] and none investigating maternal dietary intake. In the literature, there were only studies of the nutritional status of children and adults with SCD. Many of the articles reported an association of this disease with malnutrition and growth failure[17].

In children with SCD, accelerated metabolism is triggered by chronic hemolysis, anemia, and vaso-occlusive crises. Even in periods without crises or complications, the demand for protein, energy, minerals, and vitamins increases to fulfill the body's metabolic functions. The same takes place during pregnancy; however, specific dietary recommendations are not clear for women with SCD-complicated pregnancies.

Table 2. Data from nutritional assessment questionnaire applied during the second and third trimesters of pregnant women complicated by sickle cell disease.

Intakes/day	Second trimester				3rd trimester			
	HbSS (n=22)	HbSC (n=21)	Control (n=30)	p	HbSS (n=22)	HbSC (n=20)	Control (n=33)	p
GA at FFQ, weeks	11.1 (2.9)	21.8 (2.8)	21.9 (3.2)	0.202	33.1 (2.3)	33.6 (2.1)	35.0 (3.0)	0.031[a]
Energy, kcal	1,518 (653–2,828)	1,562 (841–2,440)	1,694 (955–3,577)	0.165	1,648 (853–2,721)	1,530 (835–2,357)	1,829 (1,304–3,823)	0.037[b]
Macronutrients								
Carbohydrates								
g	200 (95–440)	223 (102–361)	220 (115–643)	0.403	210 (126–410)	191 (88–350)	228.1 (129.3–464.5)	0.125
% of energy	51.7 (41.1– 73.5)	53.4 (36.9–69.3)	51.3 (40.3–72.0)	0.491	55.8 (40.9–72.5)	50.9 (31.9–61.3)	48.9 (38.4–73.4)	0.097
Proteins								
g	73.2 (36.3–111.3)	68.8 (38.2–113.3)	95.7 (53.7–143)	0.004[c]	67.5 (37.9–127.8)	81.7 (42.6–149.6)	92.8 (51.6–253.3)	0.020[a]
% of energy	18.8 (10.4–31.5)	16.6 (12.6–26.1)	20.0 (11.6–33.4)	0.066	18.4 (10.5–30.9)	23.4 (10.4–29.3)	22.0 (9.3–31.9)	0.010[d]
Fat								
g	40.0 (14.3–133.7)	47.9 (25.9–105.3)	54.9 (26.4–117.5)	0.235	50.4 (17.6–103.2)	51.6 (21.8–71.2)	58.3 (38.4–121.0)	0.090
% of energy	28.0 (15.6–42.6)	27.1 (17.1–41.6)	27.6 (16.4–39.1)	0.861	28.0 (14.8–40.0)	27.8 (20.2–38.9)	28.9 (15.1–36.7)	0.626
Fiber, g	18.0 (9.9–42.3)	23.0 (10.7–33.0)	21.0 (13.0–37.8)	0.094	16.4 (8.4–32.9)	23.3 (10.4–50.6)	18.4 (6.7–36.0)	0.036[e]
Micronutrients								
Calcium, mg	409.9 (91.0–1,247.5)	575.3 (88.1–1,086.9)	747.6 (166–1,208)	0.021[a]	607.2 (91.9–1,974.1)	590.6 (112.0–1,558.4)	734.4 (244–1,726)	0.117
Iron, mg	13.1 (6.7–17.9)	10.1 (6.0–18.4)	12.2 (7.2–25.0)	0.177	10.5 (6.0–25.3)	14.3 (6.2–21.5)	12.7 (6.0–42.2)	0.468
Zinc, mg	10.3 (4.5–25.5)	9.2 (0.8–17.2)	13.0 (4.5–22.0)	0.103	9.4 (3.3–21.6)	13.6 (3.4–25.9)	13.0 (4.0–55.7)	0.063
Vitamin A, µg	538 (58–2,224)	575 (171–1,926)	897 (243–6,330)	0.075	447 (64–3,093)	730 (250–2,441)	940 (232–5,150)	0.005[a]
Vitamin E, mg	5.3 (2.5–17.9)	5.3 (2.1–11.5)	6.7 (2.5–24.7)	0.102	5.6 (1.9–10.9)	9.5 (3.4–14.1)	6.7 (3.0–20.2)	0.007[d]
Vitamin C, mg	96.6 (19.2–936.9)	85.1 (13.5–315.3)	150.6 (32.0–656.6)	0.078	145.2 (40.6–696.7)	108.6 (14.2–291.0)	128.8 (49.6–548.7)	0.417
Folate, µg	93.9 (56.7–162.3)	99.3 (28.8–169.2)	125.6 (51.7–316.8)	0.072	97.6 (35.5–205.0)	130.6 (76.2–213.8)	136.6 (69.9–400.1)	0.053

Data are expressed as mean (SD) or median (min–max). [a]HbSS *vs.* control: p<0.05; HbSS *vs.* HbSC: p=NS; HbSC *vs.* control: p=NS. [b]HbSS *vs.* control: p=NS; HbSS *vs.* HbSC: p=NS; HbSC *vs.* control: p<0.05. [c]HbSS *vs.* control: p<0.05; HbSS *vs.* HbSC: p=NS; HbSC *vs.* control: p<0.05. [d]HbSS *vs.* control: p<0.05; HbSS *vs.* HbSC: p<0.05; HbSC *vs.* control: p=NS. [e]HbSS *vs.* control: p=NS; HbSS *vs.* HbSC: p<0.05; HbSC *vs.* control: p=NS.

Table 3. Maternal complications and perinatal results by a group of pregnant women complicated by sickle cell disease.

	HbSS	HbSC	Control	p
Maternal complication				
Arterial hypertension	6 (23.1)	6 (26.1)	-	0.930
Pain crisis	15 (57.7)	10 (43.5%)	-	0.480
Alloimmunization	10 (38.5)	5 (21.7)	-	0.300
Pulmonary infection	9 (34.6)	2 (8.7)	-	0.070
Antenatal blood transfusion	8 (30.8)	2 (8.7)	-	0.008
Urinary infection	8 (30.8)	4 (17.4)	-	0.451
Blood transfusion at childbirth/postpartum	5 (19.2)	3 (13.0)	-	0.707
Total of deliveries	**n=25**	**n=22**	**n=63**	**P**
Gestational age at delivery, weeks	37.4 (25.6–39.3)	37.9 (25.7–40.1)	39.9 (36.0–41.3)	<0.001[a]
Prematurity (<37 weeks)	10 (40.0)	5 (22.7)	2 (3.2)	<0.001[a]
Delivery mode				
Cesarean	21 (84.0)	18 (81.8)	37 (58.7)	0.024[b]
Vaginal	4 (16.0)	4 (18.2)	26 (41.3)	
Total of newborns	**n=26[e]**	**n=22**	**n=63**	**P**
Birth weight, g	2,220 (292–3,390)	2,865 (378–3,820)	3,220 (2,450–4,520)	<0.001[c]
Birth weight <2.500 g	18 (69.2)	7 (31.8)	1 (1.6)	<0.001[c]
Small-for-gestational age infant	16 (61.5)	6 (27.3)	3 (4.8)	<0.001[c]
1st min Apgar <7	8 (30.8)	3 (13.6)	2 (3.2)	0.001[b]
5th min Apgar <7	1 (3.8)	2 (9.1)	0 (0)	0.071
Perinatal result				
Fetal death	1 (3.8)	1 (4.5)	0	0.029[b]
Neonatal death	2 (7.7)	1 (4.5)	0	
Alive	23 (88.5)	20 (90.9)	63 (100)	

Data are expressed as median (min–max) or n (%). [a]HbSS *vs.* Control: p<0.05; HbSS *vs.* HbSC: p=NS; HbSC *vs.* control: p<0.05. [b]HbSS *vs.* Control: p<0.05; HbSS *vs.* HbSC: p=NS; HbSC *vs.* control: p=NS. [c]HbSS *vs.* Control: p<0.05; HbSS *vs.* HbSC: p<0.05; HbSC *vs.* control: p<0.05. [e]One twin pregnancy.

On comparing the data on maternal weight gain, this study found that the total weight gain of pregnant women with HbSS was below the minimum recommended by the Institutes of Medicine (2009) as well as below that of the HbSC women and the controls. The study by Thame et al.[16] also noted this outcome in pregnant women with SS SCD. This result supported the fact that most of the women began pregnancy with a lower weight than that of the controls. These findings indicate that the condition is due to the disease itself, which further hinders the total weight gain.

In the literature, there are reports on the dietary intake of macro and micronutrients by children, adolescents, and adults with SCD. However, there are no studies conducted with pregnant women. The first study of dietary intake carried out with children showed that an increase in protein intake with the attendant energy rise can improve the clinical status and the growth of children with SCD[18]. Our study found lower protein intake in the second and third trimesters in pregnant women with HbSS and lower energy consumption detected in pregnant women with HbSC in the third trimester. Undernourishment is considered a serious complication of SCD, primarily during pregnancy, and it should be addressed during prenatal care. There is a need for setting new dietary requirements for proteins and energy, particularly for HbSS pregnant women.

Studies show low serum levels of vitamins A, C, and E in HbSS patients, but these studies are not sufficient to establish that supplementation ensures clinical benefits[19]. Vitamin A is relevant in times of rapid proliferation and cell differentiation. Our study found that pregnant women with the SS type

of SCD consume insufficient amounts of vitamin A in the third trimester of pregnancy, for the amounts are lower than the recommended intake and lower than the control group's consumption. Vitamin E is considered a biological antioxidant that maintains the integrity of cell membranes containing polyunsaturated fatty acids[20]. The hypothesis with respect to the HBSS carriers is that vitamin E can protect RBC by inhibiting hemolysis.

The low nutrient intake among pregnant women with SCD indicates a need for more appropriate nutritional support for this particular condition. Not only dietary intake but also socioeconomic factors and lifestyle should be taken into account. Many factors contribute to poor dietary intake and length of hospital stay during pregnancy. Complications such as fever, painful crises, infection, and poor nutrition counseling are unfavorable conditions that negatively influence the nutritional status of this population.

This study has limitations. First of all, this was a single-center study with a limited sample size. More studies are certainly required to define the nutritional needs of women with SCD-complicated pregnancies. Additionally, regional, socioeconomic, and ethnic differences are also potentially confounding variables. Once aware of the complexity of the disease and of the maternal and perinatal complications, nutritionists should outline new preventive strategies and offer nutrition counseling to pregnant women with SCD.

CONCLUSION

The nutritional status of pregnant women with HbSS is characterized by a state of undernutrition. The lower protein intake in the second and third trimesters of pregnant women with HbSS may contribute to this condition. Undernourishment is a serious complication of SCD, primarily during pregnancy, and it should be addressed during the prenatal period. Nutritional care will help minimize adverse outcomes and ensure improvements in maternal–fetal health.

AUTHORS' CONTRIBUTIONS

LVP: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing. **AMKI:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing. **RMYN:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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