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Ferritin concentrations in low-birth babies in South-west Nigeria

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Abstract: *Background*: In the absence of acute phase reaction, ferritin concentration has been used as a standard measurement of iron stores. Low birth weight babies are at risk of developing iron lack because ferritin concentration at birth is influenced by duration of gestation, maternal iron status and conditions altering maternal–foetal iron exchange.
Aim: The aim of this study was to determine the ferritin concentrations of low birth weight babies in comparison with that of normal birth weight babies.
Materials and methods: Forty-four normal birth weight (NBW) babies and 40 low birth weight (LBW) babies were recruited for the study. About 1.0ml of venous blood was drawn aseptically from each subject into a micro EDTA tube, centrifuged at 5000rpm for 5 minutes, the plasma separated into cryotubes and stored at-20^{o}C until ready for quantitative determination of ferritin concentrations using direct immunoenzymatic colorimetric method.
Data obtained was analysed statistically using the Statistical Package for Social Sciences (SPSS, version 23, Chicago, IL, USA).
Results: Gestational age correlated positively with ferritin concentrations in LBW neonates ($p<0.05$) while APGAR score correlated positively with ferritin concentrations in normal birth weight babies ($r=0.398$; $p<0.05$). Though not *statistically significant* ($p=0.214$), median values for ferritin concentrations were 188.5µg/dl and 373µg/dl for LBW and NBW neonates respectively.
Conclusion: Gestational age correlated positively with ferritin concentrations in LBW neonates.

Keywords: Low birth weight, ferritin, APGAR score, gestational age.

Introduction

Iron is an essential micronutrient for almost all living organisms. It plays an important role in DNA, RNA, and protein synthesis and takes part in electron transport, cellular respiration, and regulation of gene expression[1]. Iron is also essential in early brain growth and function because it supports neuronal and glial energy metabolism, neurotransmitter synthesis and myelination[2].
Full-term infants begin life with approximately 75 mg/kg body weight of iron[3]. These stores are rapidly depleted over the first few months of life and most children are in rather tenuous iron balance, as their intake must keep pace with rapid growth[4].

Foetal iron stores are primarily acquired from the mother during the third trimester but this is limited in the presence of maternal iron deficiency[3] which is the most common cause of anaemia among pregnant women, especially in developing countries[5]. Babies of iron-deficient anaemic mothers are often associated with lower levels of serum ferritin than non-anaemic non-iron -deficient mothers[6].

Iron deficiency is associated with inferior maternal and foetal outcomes[6]. The sequelae of maternal iron deficiency anaemia on mothers include, preterm delivery, post partum haemorrhage and depression while intrauterine growth restriction, delivery of premature and low birth weight babies are parts of adverse foetal outcome[7].
Most foetal iron is transferred from the mother during the third trimester of gestation and ferritin concentration at birth is influenced by duration of gestation, foetal sex, maternal iron status and conditions altering maternal–foetal iron exchange such as adolescent pregnancy and reduced inter-pregnancies interval[8]. However, this transfer is interrupted by preterm delivery, resulting in iron stores at birth being proportional to birth weight[8] Newborns with low birth weight defined by World Health Organisation (WHO) as weight less than 2500g at birth[9] are therefore at risk of developing iron lack[8].

Globally, WHO estimates that about 30 million LBW babies are born annually accounting for 23.4% of all births[10] and LBW levels in sub-Saharan Africa are estimated at 15 percent[11]. In Nigeria, prevalence of LBW babies varies across the various geopolitical zones.

Dahlui et al[12] in a demographic survey reported a prevalence of 7.5% in North-Central, 13% in North-East, 27.2% in North-West, 4.7% in South-East,11.5% in South-South and 3.4% in South-West. As expected, the proportion of LBW children in the rural areas was higher than that of the urban areas in their study.
The care of LBW neonates may impose an enormous burden on caregivers especially in developing countries where resources are limited. Though it is estimated to be very high, there are no documented estimates of costs of care for LBW/VLBW (very low birth weight) in sub-Saharan Africa where the costs are majorly direct out of pocket by the families[13].

In neonates, there is a progressive decline in haemoglobin level in the first week of life. This persists for 6-8 weeks and the resulting anaemia is known as the physiologic anaemia of infancy[14]. With the onset of respiration at birth, considerably more oxygen becomes available for binding to haemoglobin, and, as a consequence, the haemoglobin-oxygen saturation increases from 50% to 95% or more; this increase in blood oxygen content and delivery results in the down regulation of erythropoietin (EPO) production, leading to suppression of erythropoiesis[14]. Furthermore, aged RBCs that are removed from the circulation are not replaced making oxygen needs to become greater than oxygen delivery[14].
The anaemia of prematurity commonly occurs 3-6 weeks of life and is caused by untimely birth occurring before placental iron transport and foetal erythropoiesis are complete; repeated phlebotomy for laboratory testing; low plasma levels of erythropoietin due to both diminished production and accelerated catabolism; rapid body growth and need for commensurate increase in red cell volume/mass and disorders causing RBC losses due to bleeding and/or haemolysis[15].

The relationships between ferritin concentrations and total body storage iron in neonatal populations are well established[9] and ferritin concentration is most commonly used as an indicator for iron deficiency[1]. While low ferritin concentrations are seen only in iron deficiency[3], elevated levels are seen during periods of infection, inflammation and neoplasia and under these conditions, ferritin behaves as an acute-phase reactant that can mask the diagnosis of iron deficiency[17]. However, if acute phase reaction has been excluded, ferritin concentration remains the best index of iron store[18].
The aim of this study was to determine the ferritin concentrations in LBW babies and compare with that of NBW babies in South-West, Nigeria.

Materials and methods

The subjects who participated in this study comprised low birth weight and normal birth weight babies at the Neonatal Unit (NNU) of the Lagos University Teaching Hospital, Idi-Araba, Lagos Nigeria.

Data Collection

The instrument used for data collection in this study included questionnaires which were administered to the babies' care-givers/mothers after birth; other relevant clinical information such as gestational age, sex, APGAR score at 5 minutes was obtained from the babies' case notes. Maternal information was also obtained from mothers' case files.

Inclusion criteria

Inclusion criteria for the study group included babies with birth weight less than 2500g, who had no evidence of sepsis or other inflammatory conditions. The control group included normal birth weight babies (birth weight ≥ 2500g) without any chronic conditions or sepsis.

Exclusion criteria

Babies whose mothers were less than eighteen years of age and those with HIV, diabetes mellitus, non-pregnancy induced hypertension, tuberculosis and other chronic health conditions.

Ethical approval and consent from mother

Ethical approval was obtained from the Research and Ethical Committee of Lagos University Teaching Hospital. Consent of the parents/guardians was obtained before any sample was taken from the babies.

Sample size determination

The minimum sample size for this study was determined using OpenEpi version 2.20, a web-based epidemiologic and statistical calculator at a statistical power and alpha level set at 95% and 0.05 respectively. A final sample size of 40 participants per group was obtained for the study. A 10% allowance was made to accommodate incomplete/missing data (but 40 LBW and 44 NBW babies completed the study).

Selection of subjects/Blood sampling

Non-random sampling technique was adopted. Babies had their blood samples taken within 7 days of birth. About 1.0ml of venous blood was drawn aseptically into a micro EDTA tube and centrifuged at 5000rpm for 5 minutes and the plasma separated into cryotubes and stored at-20^{o}C.

Determination of ferritin concentration

Direct immunoenzymatic colorimetric method for quantitative determination of ferritin concentration in the sera (Rapid Lab Immunodiagnostics®, United Kingdom) was employed. The absorbance was read with the microplate reader (STAT-FAX 2100® by Awareness Technologies Inc. Palm City Fl, USA).

Data analysis

Data entry and analysis was performed using the Statistical Package for Social Sciences (SPSS, version 23, Chicago, IL, USA). The descriptive data were given in percentages and as mean ± standard deviation (SD). For the homogeneous variables, mean values were compared in the LBW and NBW groups using the Student's t-test. Heterogeneous data were analyzed using the Mann–Whitney U-test. Chi-squared test was used for the analytic assessment of possible associations of discreet variables. The differences were considered statistically significant when the *P* value obtained was less than 0.05.

Results

Forty-four samples and 40 samples of LBW babies were analysed. The demographic characteristics of the subjects are shown in Table 1. Mean gestational age for the neonates was 26 weeks. About 54.5% of the NBW neonates were born below 26 weeks of gestation while 57.5% of the LBW neonates were born below 26 weeks of gestation. Male to female ratio in both groups was 1:1. Majority of the neonates were of singleton deliveries, 90.9% for NBW and 92.5% for LBW neonates. APGAR score (5 minutes) was significantly lower for LBW neonates compared with NBW neonates (p=0.000); About 86.4% of the NBW babies had APGAR score less than 7 while 92.5% of LBW babies had APGAR score less than 7. Maternal age was not significantly different for both groups.

Table 2 shows the comparison of the differences in the predictor variables between LBW and NBW babies. Gestational age, maternal age, birth weight, APGAR score and ferritin concentrations were not normally distributed as Kolmogorov–Smirnov test statistics for data normality was at p<0.05. Median gestational age, birth weight, and APGAR score for LBW neonates were 28 weeks, 1.5kg, and 5.0 respectively while Median gestational age, birth weight, and APGAR score for NBW neonates were 38 weeks, 3.8kg and 7.0 respectively. Significant variations were observed for median gestational age, birth weight, and APGAR score between LBW neonates and NBW neonates (0.000). Maternal age was identical for both LBW and NBW neonates (32 vs 33; p=0.326).

Median value for ferritin concentration was 188.5 and 373 for LBW and NBW neonates respectively. However median ferritin concentration did not vary significantly in both groups (p=0.214).
When the association between ferritin concentration and predictor variables were considered separately for LBW and NBW neonates, gestational age correlated positively with ferritin concentration in LBW neonates (r= 0.258 and 0.359; p<0.05 respectively). For NBW neonates, APGAR score correlated positively with ferritin concentrations (r=0.398; p<0.05) Table 3

The linear regression model was a good fit (F=2.385; p=0.046) as shown in Table 4. Regression analysis of predictor variables which included APGAR score, gestational age and birth weight of both LBW and NBW neonates contributed 21% of the observed variation in ferritin concentrations (r^2= 0.21). However, only gestational age and birth weight associated significantly with variations in ferritin concentrations with a beta score of 0.846 and 0.638 respectively.

Table 1: Demographic characteristics of the subjects

Demographic Variables Gestational Age (weeks)		Normal BW N(%)	Low BW N(%)	X^2	P-value
Mean=26	<26	24(54.5)	23(57.5)		
	≥26	20(45.5)	17(42.5)	0.07	0.783
Sex					
	Male	22(50)	18(45)		
	Female	22(50)	22(55)	0.21	0.646
Birth weight (median=3.8)					
	<3.8	19(43.1)	40(100)		
	≥ 3.8	25(56.9)	0(0.0)	32.36	0.000
Status					
	Singleton	40(90.9)	37(92.5)		
	Multiple	4(9.1)	3(7.5)	0.07	0.978)
Apgar Score(minutes)					
	<7	6(13.6)	37(92.5)		
	≥7	38(86.4)	3(7.5)	52.15	0.000
Maternal age (years)					
	<32	18(40.9)	20(50)		
	≥32	26 (59.1)	20(50)	0.70	0.403

Table 2: Comparing Differences in Predictor Variables Between Low Birth Weight and Normal Birth Weight Babies

Predictor Variables (Median values)	NBW	LBW	P-values
Gestational age (weeks)	28	38	0.000
Maternal age (years)	32	33	0.326
Birth weight (kg)	1.5	3.8	0.000
APGAR score (minutes)	5.0	7.0	0.000
Venous blood Ferritin (ng/ml	188.5	373	0.214

Table 3: Correlation Between Venous Blood Ferritin in LBW and NBW Neonates and Predictor Variables

Predictor Variables	Correlation coefficient for LBW venous blood ferritin r(p-value)	Correlation coefficient for N Correlation coefficient for LBW venous blood ferritin r(p-value)BW venous blood ferritin r(p-value)
Birth weight (kg)	0.074(0.321)	0.146(0.179)
APGAR score (mins)	0.138(0.192)	0.398(0.004)
Gestational age (weeks)	0.359(0.010)	-0.145(0.181)

Table 4: Linear Regression Statistics for Association Between Venous Blood Ferrittin and Associated Predictor variables

Predictor Variables	Beta score	P-value
Birth weight (kg)	0.638	0.007
APGAR score (mins)	0.059	0.712
Gestational age (weeks)	0.846	0.001

Model statistics (ANOVA ; F=2.385; p=0.046). Adjusted R^2 = 0.211

Discussion

Low birth weight (LBW) is a major public health problem worldwide especially in developing countries. It results in huge economic loss to the health sector[13]. In this study, maternal age was not significantly different for the two groups. Maternal age has no identifiable effects on the pregnancy outcomes except for teenage pregnancy in which poor nutrition and/or infection and low weight gain as a result of inadequate dietary intake during gestation have been identified as determinants of low birth weight[19].

Differences in the birth weight and APGAR score were established in the two groups. This shows a clear distinction between the wellness indices of LBW and NBW neonates as measured by the APGAR scores and it is in line with many reports which indicated increased morbidity and mortality for LBW neonates[20,21].

The median value for ferritin concentration in LBW neonates was not statistically different from that for NBW neonates though the serum ferritin in LBW neonates is lower than that of NBW neonates. The wide reference range (20 - 250µg/dl) of ferritin concentrations could account for this non-significant difference. This finding is in agreement with many previous reports[3,22]. On the contrary, however, Agarwal et al[23], was of the opinion that serum ferritin concentrations at birth increased with increasing birth weight.

A similar direct relationship also exists between ferritin and APGAR score in the NBW neonates from this study. This has been reported by Nalivaeva et al[24] who established a significant relationship between neonatal ferritin levels and APGAR score and recommended that an improvement in nutrition, socioeconomic status and qualitative antenatal care can reduce the incidence of anaemia and improve quality of life in neonates.

It is well established that hypoferittinemia /iron lack can subsequently lead to LBW or prematurity . A high proportion of LBW babies may be preterm and may not have enough surfactant to prevent difficulty in breathing, promote cardiopulmonary transition; they may also have weak respiratory muscles with the ribs are easily becoming curved leading to the development of birth asphyxia[25]. It has been observed that infants in poor clinical condition at birth as indicated by low APGAR score due to perinatal hypoxia that may or not be due to iron deficiency may have increased risk of long-term cognitive impairment[26].

Conclusion

Gestational age correlated positively with ferritin concentrations in LBW neonates while ferritin concentration correlated positively with APGAR score in normal birth weight babies.

Recommendation

It is recommended that LBW neonates with low APGAR score at birth should be routinely screened for iron -lack.

Study limitation

Limitation of this study was the inability to obtain serum C-reactive protein levels or erythrocyte sedimentation rate of the subjects to rule out those with hyperferritinaemia due to acute phase reaction.

Conflict of Interest: None
Funding: None

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