Original Research Article

Can Serum Ferritin Concentrations Diagnose Neonatal Anaemia?

Abstract

Aims: To determine the prevalence of low haemoglobin and ferritin levels amongst term and preterm newborn babies. To determine the value of serum ferritin in the diagnosis of low iron stores amongst term and preterm newborns.

Methodology: This was a prospective cross sectional study carried out at the Neonatal Intensive Care Unit of the University of Nigeria Teaching Hospital (UNTH), Enugu, Nigeria between June and December 2014. The study included 140 newborns of all birth weights delivered at the UNTH. These were categorized into preterm (gestational age <37 completed weeks) and term (gestational age ≥37 completed weeks. Babies with C-reactive protein levels > 10mg/dl, who were intra-uterine growth restricted, and whose mothers had conditions associated with low iron stores were excluded from the study. Anthropometric measurements were done for all subjects. Haemoglobin estimation and ferritin assay were carried out and the prevalence of neonatal anaemia was determined using each of these.

Results: The range of haemoglobin concentration in the study population was 12.22g/gl – 22.80g/dl. The mean serum haemoglobin concentrations were 15.69mg/dl ± 1.58 and 16.45 ± 1.92 in the preterm and term babies respectively (t = 2.557, *P* = .0116). The prevalence of low haemoglobin concentrations amongst both preterm and term babies was zero= .024). The range of serum ferritin level in the study population was 20.6µg/l - 296µg/l. The mean serum ferritin levels were 63.13µg/l ± 23.93 and 133.67µg/l ± 50.14 in the preterm and term babies respectively (t = 10.623, *P* < .001). The prevalence of low serum ferritin in the study population was 22.14%, but was higher in preterm than term babies 35.7% vs 8.6%: (OR – 5.926, 95% C.I OR = 2.248 – 15.619)(*P*<.001).

Conclusion: Serum ferritin assay is more useful than haemoglobin estimation in the determination of anaemia during the neonatal period.

Keywords

Anaemia, Ferritin, Iron, Prevalence, Diagnose

Introduction

Anaemia is characterized by a reduction in red cells mass or haemoglobin concentration to levels that are insufficient to meet the metabolic needs of the body [1,2]. It is usually defined as a haemoglobin or haematocrit > 2 standard deviations below the mean for age [2]. Globally, the commonest cause of this reduction is iron deficiency [1] Anaemia and polycythaemia have been documented as the commonest haematological disorders diagnosed at birth [2]. Despite this, there is a dearth of literature on this subject [3]. Studies have shown a prevalence of neonatal anaemia of 17.5 – 21% [3]. Risk factors include premature birth, low birth weight, low maternal blood levels, bleeding in pregnancy (placenta previa and abruption placenta and unsafe delivery practices [2]. Anaemia during the neonatal period has been linked to late neurological deficits, and is a leading risk of perinatal mortality [3]. Newborn babies are however often not routinely screened for anaemia, but are usually only screened following hospitalization.

Accurate determination of iron status is crucial for diagnostic and screening purposes [4] Several markers are available to assess total body iron and iron stores [5]. Some of these include serum iron, haemoglobin (Hb) concentrations, ferritin concentrations, mean corpuscular volume (MCV), total iron binding capacity (TIBC), transferrin saturation, red cell distribution width, zinc protoporphyrin (ZnPP), and serum transferrin receptor (sTfR) [5]. However, each of these has major limitations, some of which include a lack of association with gestational age, and a lack of specificity for iron deficiency [5]. There is thus no agreement on the specific laboratory criteria for iron deficiency [6]. There is also no consensus concerning whether to use single or multiple criteria, and on which iron status variables to use [6]. The usual requirement is either a low serum ferritin or a combination of multiple criteria, e.g., abnormal values for any two of three iron status variables [7].

In clinical settings however, haemoglobin estimation alone is usually used for decision making [3]. This is as a result of its ease in estimation and in interpretation of results [8]. For decades, defining cut-off values for low haemoglobin in infants and children has been a source of debate [9]. In addition, cut-offs for neonates are not included in most guidelines and recommendations [9]. Among both term and preterms, haemoglobin concentrations of 15mg/dl have been reported as optimal [10]. However, minimal acceptable levels are much lower than this (12 g/dl for preterm infants and 11 g/dl for full-term neonates [10]. That notwithstanding, haemoglobin concentration alone cannot be used to diagnose iron deficiency [1]. This is due to the hierarchical loss of tissue iron [11-13]. This means that in the presence of iron deficiency, there is a preference to maintain red blood cell (RBC) iron for the synthesis of haemoglobin, at the expense of brain, heart and skeletal muscle iron stores [11-13]. Thus, by the time measured serum iron deficiency is obtained, iron stores have already been depleted [11].

Ferritin is the major storage form of iron [4,11]. In the body, small amounts of ferritin are secreted into the plasma [14]. The concentration of this is positively correlated with the size of the total body iron stores in the absence of inflammation [14]. Serum ferritin levels are reduced only in iron deficiency [4,11]. In addition, body ferritin levels, in contrast to haemoglobin, are not affected by residential elevation above sea level or smoking behavior [14]. Different cut-offs have been described for defining low ferritin [15-17]. However, levels below 35µg/l have been found to been associated with depletion of brain stores and with consequent effects on brain function [18]. Serum ferritin estimation has been recommended as the standard for the assessment of body iron stores in both term and preterm babies [4,11]. Serum ferritin being an acute phase reactant, can however be increased in the presence of inflammation [11,14]. Thus its interpretation requires exclusion of other causes of inflammation [19]. The author thus hypothesizes that, amongst preterm and term babies, serum ferritin may be a better marker for the diagnosis of low iron stores than haemoglobin. This study thus aims to determine the prevalence of low haemoglobin and ferritin levels amongst term and

preterm newborn babies. It also aims to determine the value of serum ferritin in the diagnosis of low iron stores amongst term and preterm newborns.

Materials and Methods

This prospective cross sectional study was carried out at the Neonatal Intensive Care Unit of the University of Nigeria Teaching Hospital (UNTH), Enugu, Nigeria between June and December, 2014. The study included 140 neonates. These were categorized as follows: 70 preterm babies (gestational age < 37 completed weeks) and 70 term babies (gestational age ≥ 37 completed weeks). Babies with C-reactive protein levels > 10mg/dl (to exclude other causes of inflammation), who were intra-uterine growth restricted, and whose mothers: had ante partum haemorrhage or other bleeding episodes during pregnancy; had severe anaemia (haemoglobin cut-off point of less than 11g/dl defines maternal anaemia in the later stages of pregnancy [20]); diabetes mellitus or hypertension; and who smoked were excluded from the study. Subjects were enrolled consecutively until the calculated sample size was reached. The study was approved by the University of Nigeria Teaching Hospital Health Research Ethics Committee. Written informed consent was obtained from the parents of the study participants.

Data was collated and analysed using Statistical Package for Social Sciences (SPSS) Version 20. Relationships between continuous variables were determined using correlation and linear regression analysis. Means of continuous variables were compared using Student's t-test, while associations between categorical variables were determined using chi-square and logistic regression analysis as applicable. All tests were considered significant at $P < .05$.

Blood Sample Collection

Umbilical venous blood was collected from a double clamped segment of the umbilical cord during delivery. This was then placed into a small study designated storage box at room temperature designated. Subsequently, the Howard Kelly forceps on one end of the section of the cord was removed. The umbilical vein was identified and depending on its size, a 5,6 or 8 Fr gauge nasogastric tube attached to a 10ml syringe was inserted and at least 6ml of blood was withdrawn. Where this did not work, the blood was obtained by venopuncture of the side of the cord corresponding to the identified umbilical vein. A drop (approximately 0.2 ml) of the blood obtained was first immediately dropped onto a microcuvette which was inserted into the Hemocue® Hb 201^{+} for estimation of haemoglobin concentration. Serum was then obtained from the remaining blood for both CRP and ferritin estimation at the Haematology laboratory of UNTH using the Diagnostic Automation 800 ELISA machine®. Low ferritin was regarded as a measured serum level of less than 35µg/l [11].

Sample Size Determination

The sample size (n) for an infinite population of more than 10,000 was first obtained using the formula for the comparison of proportions [21]:

$$n = \frac{[P1(1 - P1) + P2(1 - P2)]}{(P1 - P2)^2} \times \text{Cp power}$$

Where:
P1 = Proportion of preterm babies from a previous study(10%) [22]
P2 = Proportion of term babies from a previous study (18%) [22]
Cp power = 13 when p value is 0.05 and power is 95%
Therefore:

$$n = \frac{[(0.1)(0.9) + (0.18)(0.82)]}{} \times 13 = 483$$

$(-0.08)^2$

Since this study was done on a finite population (less than 10,000), the sample size for a finite population was then derived using the formula below [23].

$$nf = \frac{no}{(1+ no/N)}$$

Where :

nf = final (or minimum) sample size

no = initial sample size (derived above)

N = population of preterm births over a 12 month period in UNTH i.e. 70.

$$nf = \frac{483}{(1 + 483/70)} = 61$$

An attrition rate of 10% was used in the study to account for possible sample loss. Thus, the total minimum sample size was calculated to be 67 preterm babies, which was rounded off to 70 each.

Results

Study characteristics

The baseline characteristics of the study population is shown in Table I. There were 68 males and 72 females, giving a male to female ratio of 0.9:1. Mothers of 84 (60%) babies reside in urban areas while mothers of 56 (40%) babies reside in rural areas. Majority of the subjects (36.4%) were of the upper socioeconomic class.

Table I: Demographic, maternal and neonatal variables

Characteristics	**Preterm n = 70 (50%)**	**Term n = 70 (50%)**	**Total n = 140 (100%)**
Gender			
Male	34 (24.3)	34 (24.3)	68
Female	36 (25.7)	36 (25.7)	72
	70	**70**	**140**
Tribe			
Ibo	68	64	132
Yoruba	1	3	4
Hausa/Fulani	1	3	4
	70	**70**	**140**
Socioeconomic Class			
Upper	27	24	51
Middle	15	26	41
Lower	28	20	48
	70	**70**	**140**

The gestational age of the study population ranged from 25 weeks to 39 weeks, with birth weight ranging from 0.55kg to 5.2kg. The distribution of other anthropometric parameters amongst the study population is shown in Tables 2 and 3.

Table 2: **Anthropometric indices of the preterm babies**

Gestational age (weeks)	**N (70)**	**Weight (g) Mean (SD)**	**Length (cm) Mean (SD)**	**OFC (cm) Mean (SD)**	**CC (cm) Mean (SD)**
<28	7	680 (0.80)	24.29 (4.82)	23.71 (1.07)	21.14 (1.21)
28 - <32	27	1610 (0.46)	39.59 (4.41)	27.49 (9.73)	29.24 (3.29)
32 – 36	36	2288 (0.51)	45.39 (3.62)	33.64 (1.73)	31.46 (3.58)
TOTAL	**70**	**1861 (0.68)**	**41.06 (7.44)**	**30.27 (7.11)**	**29.55 (4.43)**

Table 3: **Anthropometric indices of the term babies**

Gestational age (weeks)	**N (70)**	**Weight (g) Mean (SD)**	**Length (cm) Mean (SD)**	**OFC (cm) Mean (SD)**	**CC (cm) Mean (SD)**
37	32	2840 (270)	47.27 (2.26)	34.94 (1.38)	33.30 (1.63)
38	28	3750 (610)	49.84 (2.53)	36.25 (0.91)	35.21 (1.93)
39	10	4210 (700)	51.80 (3.49)	37.20 (0.95)	36.10 (1.35)
TOTAL	**70**	**3400 (0.73)**	**48.92 (3.03)**	**35.79 (1.42)**	**34.49 (2.04)**

Haemoglobin concentrations in the study population

The range of haemoglobin concentration in the study population was 12.22g/gl – 22.80g/dl. The mean serum haemoglobin concentrations were 15.69mg/dl ± 1.58 and 16.45 ± 1.92 in the preterm and term babies respectively (t = 2.557, *P* = .0116). The prevalence of low haemoglobin concentrations amongst both preterm and term babies was zero.

Ferritin levels in the study population

The range of serum ferritin level in the study population was 20.6µg/l - 296µg/l. The mean serum ferritin levels were 63.13µg/l ± 23.93 and 133.67µg/l ± 50.14 in the preterm and term babies respectively (t = 10.623, *P* < .001). The prevalence of low serum ferritin in the study population was 22.14%, but was higher in preterm than term babies 35.7% vs six 8.6%: (OR – 5.926, 95% C.I OR = 2.248 – 15.619)(*P* <.001). In

addition, preterms were found to be six times more likely than term babies to have low serum ferritin levels (OR – 5.926, 95% C.I OR = 2.248 – 15.619) (Table 4).

Table 4: **Frequency of low serum ferritin levels in preterm and term subjects**

Ferritin levels (µg/l)	**Preterm**	**Term**	**Significance**	**OR**	**95 % C.I for OR**
Low n (%)	25 (35.7)	6 (8.6)	p <0.001	5.926	2.248 – 15.619
Normal n (%)	45 (64.3)	64 (91.4)			

Discussion

The mean haemoglobin concentration of newborn babies in this study was similar to the values of 12.54 ± 2.54 g/dl and 13.44 ± 2.23 g/dl (*P* = 0.02) obtained by Adediran et al [24] amongst term anaemic and non anaemic respectively in South-West Nigeria. However, higher values were recorded by Tiruneh et al [25] in Ethiopia and Esslami et al [26] in Iran. This difference could be explained by the slightly higher and much higher sample sizes used in the former and latter studies respectively. It should however be noted that there is paucity of literature on mean haemoglobin levels in the entire population of newborns. Most literature concentrate on subsets of newborns such as low birth weight, anaemic, or categories of preterm neonates [27-29].

Haemoglobin levels were significantly lower in preterms when compared with term babies. This is similar to the findings by Eslami et al [26] of a mean hemoglobin value of cord blood in preterm neonates of 14.77g/dl +/- 1.69, and in term neonates of 15.4g/dl +/- 5.07 SD and SD. (*P*=0.036). It has previously been documented that between 22 and 40 weeks gestation, haemoglobin concentrations increase linearly by approximately 0.21g/dl per week of gestation [N]. This reflects the increasing metabolic needs of the growing foetus with a concurrent increase in cell mass and body size [30].

Using the recommended cut-off of 11g/dl and 13g/dl in preterm and term babies yielded a zero prevalence for foetal anaemia. Several other cut-offs have been recommended for both healthy and sick neonates [1,6,30,31]. The World Health Organization (WHO) recommends 11g/dl as the cut-off to define anaemia in infants and children [1]. However, these cut-offs were derived from a few western studies and have not been revised since. Also, this value was applied to infants from six months of age and did not include newborn babies [1]. Domellöf et al [6] conducted a study to re-evaluate the diagnostic criteria for iron deficiency amongst infants. A slightly lower cut-off of 10.5g/dl was obtained [6]. This however was also limited to infants 6-9 months of age [6]. Haemoglobin cut-offs to establish anemia amongst neonates remains a subject of debate. Using higher haemoglobin cut-offs, several other studies have documented a prevalence for foetal anaemia ranging from 5.7-65.6% [24,32,33] Adediran et al [24] in South West Nigeria reported a prevalence of 28.9%, while a prevalence of 65.6% was obtained in Abakaliki, South East Nigeria [32]. Values of 26.4 have been reported in other parts of Nigeria [33] An even lower prevalence have been observed in other parts of Africa [24, 34] and in Western countries [35-37]

In our study, using a serum ferritin concentration of <35µg/L to define low serum ferritin levels, the prevalence of low serum ferritin was 22.14%. Several studies have reported on the prevalence of low ferritin levels amongst newborn babies [9,11,15]. Ferritin measurements and corresponding cut-offs facilitate the monitoring of iron deficiency trends and the assessment of the impact of health and nutrition interventions

[14]. However, the lack of normative values for serum ferritin concentration amongst neonates with gestational age between 23 and 41 weeks has led to difficulty in establishing the prevalence of low iron stores amongst this population [9]. The WHO/CDC in 2005, stated that serum ferritin values of less than 12 µg/l in children <5 years are indicative of a depletion of iron stores [14]. In neonates however, and more especially in preterms, rapid growth and development creates a greater demand for iron, with larger iron stores needed to meet this demand [11,12,38,39]. Thus, at serum ferritin levels of <15µg/l, the neonate already has deficient iron stores with a significant risk for neurodevelopmental problems [18]. Several authors have proposed different values for the definition of low ferritin in neonates [4,11, 18]. Sidappa and co-workers [18] in USA, 2004, were able to estimate from existing nomograms that newborn ferritin concentrations less than 35µg/l represent a risk to the developing brain. This value was thus used as a cut-off in their neurodevelopmental studies [40].

The prevalence of low serum ferritin obtained in this study is much lower than the 59.2% obtained by Adediran et al [41] in an earlier study on term babies in South-West Nigeria. This is despite them using a higher ferritin cut-off of 60µg/l. The use of term babies alone is also expected to have dampened the effect as ferritin levels are known to increase with gestational age. A much lower prevalence of 19.8% was obtained by Zhang et al [15] in a cohort of full term normal birth weight infants in China, using similar cut-offs as ours. However, the authors excluded babies with a C-reactive protein (CRP) of > 5 mg/l, compared with 10mg/l used in this current study. It has been widely agreed that, in addition to ferritin, an independent indicator of the acute phase response, such as C-reactive protein (CRP), α-1 antichymotrypsin (ACT), α-1-acid-glycoprotein (AGP) and serum amyloid A, should be measured [14,42-44]. CRP is the most commonly used as it responds quickly to inflammation [18,19,45-47] with values of greater than 10mg/dl being the cut-off signifying infection [18,19,45-47]. Using lower cut-offs than this can result in the inclusion of subjects whose serum ferritin concentrations may be reflective on an inflammatory process, thereby reducing the number of newborns seen as having low serum ferritin, and thus reduce the prevalence of low serum ferritin.

Conclusion

The assessment of low iron stores in newborn babies is crucial to their subsequent well-being. There is a wide variation of haemoglobin levels amongst newborn babies. The prevalence of anaemia was zero using haemoglobin levels to determine iron stores, and 22.14% using ferritin concentrations. Using serum ferritin in the diagnosis of low iron stores is thus more beneficial.

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