Original Research Article

Do Neonatal Iron Stores Depend on Gestational Age?

Abstract

Aims: To establish mean values for serum ferritin at different gestational ages. To determine the relationship between serum ferritin and gestational age.

Methodology: This was a prospective comparative ~~cross sectional~~cross-sectional study carried out at the Neonatal Intensive Care Unit of the University of Nigeria Teaching Hospital (UNTH), Enugu State, Nigeria between June and December 2014. The study included 140 newborns of all birth weights delivered at the UNTH. These comprised gestational ages from 25 weeks to 39 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. Serum ferritin was measured at birth and this was correlated with birth weight and gestational age.

Results: Serum ferritin levels ranged from 20.6 to 296.4µg/l. The mean serum ferritin level was 93.14µg/l ± 57.69. There was a significant difference (F = 11.159, p<0.001) among the mean serum ferritin levels amongst different categories of gestational age. Low serum ferritin was found in 85.7%, 48.1% and 16.7% of extreme preterms, very preterms and moderate to late preterms respectively(χ^2 = 49.777, p < 0.05). Extreme preterms were sixty-four times more likely than term babies to have low serum ferritin (p<0.01, OR = 64.00, 95% C.I for OR = 6.570 – 623.455), while very preterms were ten times more likely than term babies to have low serum ferritin levels (p < 0.001, OR = 9.905 95% C.I = 3.209 -30.570). In addition, moderate to late preterms were two times more likely than term babies to have low serum ferritin levels (p = 0.220, OR = 2.133, 95% C.I for OR = 0.635 – 7.167). There was a significant strong positive correlation between serum ferritin levels and gestational age in the study population (r = 0.656, p < 0.001).

Conclusion: There is a wide range of serum ferritin amongst newborn babies. There is also a significant strong positive correlation between serum ferritin levels and gestational age.

Keywords: Gestational age, Ferritin, Iron stores, preterm and term babies, prospective comparative study, Nigeria. ~~Assessment~~

Introduction

Nutrients play an important role in the growth and development of the growing foetus [1]. The placenta is the organ through which maternal nutrients are transferred via the umbilicus to the foetus [2]. Iron plays a central role in growth and development throughout intrauterine life [3,4].In humans, iron exists as haeme proteins (haemoglobin, myoglobin, cytochrome P450) which are used to transport gases and build enzymes [5,6]. Iron is also a co-factor of many enzymes such as catalase, lipoxygenase, reductase and oxidase, which catalyze many essential body redox reactions [7,8].Thus, iron is very essential in almost every body function[1] and its deficiency has serious consequences [7,9].

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Deficiencies of iron have been linked with early onset of post-natal anaemia [14],defects in growth and function of organ systems [15], altered immune function, temperature instability [12], and neurodevelopmental impairment [5,7,13,14]. It has also been found that between 25% and 85% of preterm neonates worldwide develop evidence of iron deficiency during infancy [12]. As a result of this requirement at every stage during gestation, iron is actively transported across the placenta independent of maternal iron stores[11,13,15-18]. Only in the presence of severe maternal iron deficiency are foetal iron stores reduced [5,7,19,20].Iron accretion starts at the 24th week of gestation and increase gradually until the third trimester, when accretion is at the rate of 1.35mg/kg/day giving iron stores of 75mg/kg [13]. In the foetus, this iron is stored as ferritin in the liver, bone marrow and spleen [7]. This constitutes 10-15% of total body iron at term [7,11,21]. Of the remainder, approximately 70-80% is contained in haemoglobin and 10% is in regulatory proteins such as myoglobin and cytochromes[7,11,21].

Assessment of these stores can be done using parameters such as serum iron [10],haemoglobin [22],mean corpuscular volume [22], and red cell distribution width [22]. Others include zinc protoporphyrin (ZnPP) [23,24], zinc protoporphyrin/haeme ratio (ZnPP/H) and serum transferrin receptor (STfR) [24]. Serum ferritin has been established as the standard for the measurement of total body storage iron in neonates [21,25-28]. Several studies have been carried out on neonatal serum ferritin [29-37]. Some have shown its relationship with gestational age[29-34], while others have shown its dependence on weight [35-37]. However, few studies have documented gestational age-specific mean serum values. The paucity of normative values for serum ferritin in preterm neonates, and values for specific gestational ages, has led to difficulty in establishing the prevalence of abnormal iron stores in preterm ~~newborn~~new born infants [21].In most neonatal intensive care units, assessment of iron status is restricted to the estimation of haemoglobin concentration. Iron supplementation is also rarely practiced before 28 days of life, by which time significant depletion of iron stores may have already occurred. We hypothesized that serum ferritin levels increase with gestational age. This study thus aimed to establish mean values for serum ferritin at different gestational ages and to determine its relationship with gestational age.

Materials and Methods

This prospective comparative ~~cross sectional~~cross-sectional study was carried out at the Neonatal Intensive Care Unit of the University of Nigeria Teaching Hospital (UNTH), Enugu State, Nigeria between June and December, 2014. The study included 140 neonates with gestational ages from 25-39 weeks. These were categorized as follows: extremely preterm (<28 weeks), very preterm (28 to <32 weeks), moderate to late preterm (32 to <37 weeks) and term ≥37 weeks. Babies with C-reactive protein levels > 10mg/dl, 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 [38]); had 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~~*p* < .05.

Blood Sample Collection

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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 [21].

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 [39]:

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

Where:
P1 = Proportion of preterm babies from a previous study(10%) [32]
P2 = Proportion of term babies from a previous study (18%) [32]
Cp power = 13 when p value is 0.05 and power is 95%
Therefore:

$$n = \frac{[(0.1)(0.9) + (0.18)(0.82)]}{(-0.08)^2} \times 13 = 483$$

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 [40].

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

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 sociodemographic variables of the study population are shown in Table I. The male to female ratio was 0.9:1. A majority of the study population was of the Igbo tribe. There was an essentially normal distribution of the study population across all socioeconomic classes.

Table 1: Sociodemographic variables

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Characteristics	**Preterm n = 70 (50%)**	**Term n = 70 (50%)**	**Total n = 140 (100%)**
~~Gender~~Sex			
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 Table 2.

Table 2: Anthropometric indices of the study population (preterms)

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)
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	**140**	**2630 (1045)**	**44.99 (6.90)**	**33.03 (5.81)**	**32.02 (4.23)**

Ferritin levels in the study population

The range of serum ferritin level in the study population was 20.6µg/l - 296µg/l. The distribution of mean serum ferritin levels according to gestational age is shown in figure 1. The mean serum ferritin level in the

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study population was 93.14µg/l± 57.69 with means of 63.13µg/l ± 23.93 and 133.67µg/l ± 50.14 amongst the preterm and term babies respectively (t = 10.623, p < 0.001). There was a significant difference (F = 11.159, p<0.001) among the mean serum ferritin levels amongst different categories of gestational age as shown in Table 3.

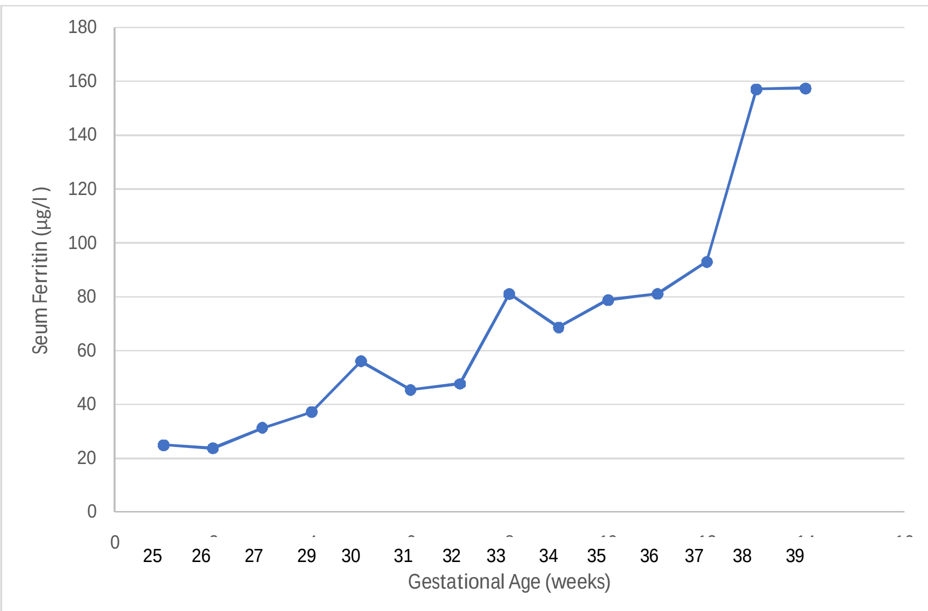

Figure 1: Distribution of mean serum ferritin by gestational age

Table3: Mean serum ferritin levels amongst categories of gestational age

Gestational age (weeks)	**N (70)**	**Mean Serum Ferritin (µg/l)**	**(SD)**	**Range**	**F**	**p-value**
<28	7	29.39	6.33	20.60 – 37.60	11.159	< 0.001
28 - <32	27	48.94	27.60	25.40 – 168.50		
32 – 36	36	71.08	27.49	28.00 – 149.60		
37 - 39	70	128.99	57.81	29.00 – 296.40		

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The prevalence of low serum ferritin was higher in preterm than term babies - 25 (35.7%) vs six (8.6%): (OR – 5.926, 95% C.I OR = 2.248 – 15.619)(p <0.001). 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)			

Association between low serum ferritin levels and categories of gestational ages

Low serum ferritin was found in six (85.7%) out of seven extreme preterms, thirteen (48.1%) out of 27 very preterms, and six (16.7%) out of 36 moderate to late preterms (Tables 5a, b, c). The differences among these proportions were significant (χ^2 = 49.777, p < 0.05). Extreme preterms were sixty-four times more likely than term babies to have low serum ferritin (p<0.01, OR = 64.00, 95% C.I for OR = 6.570 – 623.455), while very preterms were ten times more likely than term babies to have low serum ferritin levels (p < 0.001, OR = 9.905 95% C.I = 3.209 -30.570). (Table 5b, c). In addition, moderate to late preterms were two times more likely than term babies to have low serum ferritin levels. This however was not significant (p = 0.220, OR = 2.133, 95% C.I for OR = 0.635 – 7.167). (Table 5c)

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Table 5a: Association between low serum ferritin levels and extreme preterm and term babies

	Ferritin levels				
Gestational age category (weeks)	**Normal n (%)**	**Low n (%)**	**p-value**	**OR**	**95% C.I for OR**
Extremely preterm (< 28)	1 (14.3)	6 (85.7)	< 0.001	64.000	6.570 – 623.455
Term	64 (91.4)	6 (8.6)			

Table 5b: Association between low serum ferritin levels and very preterm and term babies

	Ferritin levels				
Gestational age category (weeks)	**Normal n (%)**	**Low n (%)**	**p-value**	**OR**	**95% C.I for OR**
Very preterm (28 - <32)	14 (51.9)	13 (48.1)	< 0.001	9.905	3.209 – 30.570
Term	64 (91.4)	6 (8.6)			

Table 5c: Association between low serum ferritin levels and moderate to late preterm and term babies

	Ferritin levels				
	Normal	**Low**	**p-value**	**OR**	**95% C.I for**

Gestational age category (weeks)	n (%)	n (%)			OR
Moderate to late preterm (32 - <37)	30 (83.3)	6 (16.7)	0.220	2.133	0.635 – 7.167
Term	64 (91.4)	6 (8.6)			

Relationship between serum ferritin and gestational age

There was a significant strong positive correlation between serum ferritin levels and gestational age in the study population (r = 0.656, $p < 0.001$). A coefficient of determination (R^2) of 0.432 indicates that about 43% of the variation that exists in serum ferritin levels can be attributed to gestational age (Figure 2).

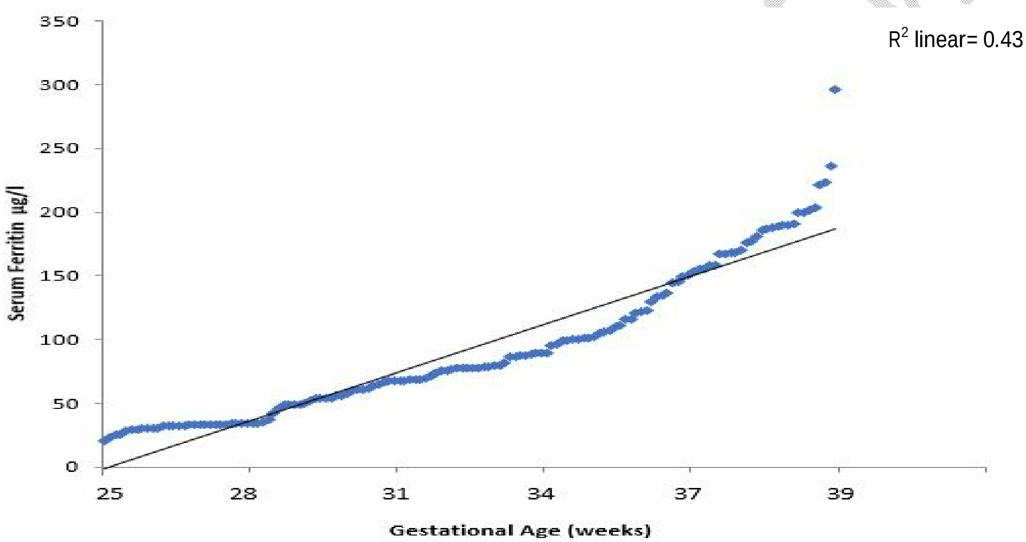

Fig 2: Scatter diagram showing relationship between serum ferritin and gestational age

Discussion

In this study, iron stores were assessed using serum ferritin. The assessment of iron stores using other parameters has several drawbacks [10,22,24].Parameters such as serum iron,haemoglobin,mean corpuscular volume,and red cell distribution widthare non-specific, are late markers of iron deficiency and may not reflect tissue iron status in newborns [10,22].Others such as zinc protoporphyrin (ZnPP) and zinc protoporphyrin/haeme ratio (ZnPP/H). are inversely related to gestational ageand are also elevated in conditions such as maternal chorio-amnionitis [22-24]. Serum transferrin receptor (STfR) levels in umbilical cord blood are not directly influenced by gestational age [41]. Thus, STfR levels are not a good indicator of foetal iron stores [41]. Serum ferritin as a standard for the measurement of total body storage iron has been established by several authors, and its relationship with total body iron stores has been established in neonates [21,25-28].Serum ferritin values correlate positively with the size of the total body iron stores in the absence of concurrent infection 10,22,23,25,23].

The wide range of 20.6µg/l - 296µg/l in serum ferritin for the entire study population is similar to the wide range of 40µg/l - 224µg/l obtained from the meta-analysis by Sidappa [21] and co-workers in the USA. It is also similar to the values obtained by Carpani et al[32].These similarities corroborate observations that there is a wide range in serum ferritin levels in newborn babies, posing a problem to its interpretation. Thus, despite the fact that being delivered at lower gestational ages deprives the neonate of maximal iron accretion, an interplay of several other factors may also determine the amount of iron that finally gets to the fetus. The wider range of serum ferritin observed in this study could also be attributed to the different assay technique used in this study (ELISA), as compared to other studies (chemiluminescent, immunoassay and radioimmunoassay) However, since various assay methods correlate well and inter-laboratory differences are similar to batch-to-batch variability within a laboratory [21], no attempt was made to control for the methodology.

Mean serum ferritin levels were also shown to increase with advancing gestational age. This replicates the findings of Carpani,*etal.,* [32] in Italy in 2009, and has been the observation of several other authors [12,20]. At the beginning of the 21st century, Sweet and co-workers [20]assayedcord blood transferrin receptors to assess fetal iron status at birth. They observed mean ferritin values of 75µg/l (range 44-117) at 26 to 28 weeks GA, increasing through 90µg/l (range 45-142) at GA 32 to 36 weeks, to 131µg/l (range 90-238) at GA 37 to 41 weeks [20]. Few years later, Rao, *et al.*, ~~and colleagues~~[11] studied iron in fetal and neonatal nutrition. The authors showed that preterm birth deprives the fetus of the significant iron accretion that occurs beyond 32 weeks gestation [11]. The findings of the study also revealed that 25-85% of preterm infants with a birth weight less than 1500g were at risk of iron deficiency during infancy [11].In the same year, Sidappa, *et al.*,~~and colleagues~~ [21]carried out a meta-analysis of 35 published studies over a period of 25 years. They documented a steady increase in ferritin level from a mean of 63µg/l at 23 weeks to 171µg/l at 41weeks gestation [21]. Most of these studies however, contained small numbers of subjects or relatively large gestational age groupings (term vs preterm), with few providing gestational age specific ferritin concentration data.

Increasing iron stores with increasing gestational age is most likely a reflection of improved iron availability and growing iron stores during late gestation. Furthermore, it was evident in this study that the prevalence, and possibility of having low serum ferritin increases with lower gestation. This finding also complements the findings of other authors [32,34], and shows that iron stores increase with advancing gestational age. One of such findings was that shown in the meta-analysis carried out by Siddappa, *et al.*, ~~and colleagues~~ [21] in 2007, where umbilical cord serum ferritin reduced with reducing gestational age. Only few other studies, however, considered ferritin levels at different categories of prematurity. Most only reviewed preterm versus term serum ferritin values.

In this study, though there was a strong positive relationship between serum ferritin and gestational age, there was a low coefficient of determination. This means that only 43% of the variation existing in ferritin levels can be attributed to gestational age. Thus, there is a large interplay of other factors determining iron stores, some of which could be the factors that lead to preterm delivery. Nigeria ranks third on the WHO list of countries with the highest preterm delivery rate [43]. This has been attributed, among other reasons, to maternal malnutrition and infections [43]. These may reduce fetal iron stores. Furthermore, the enzymes and co-factors involved in the uptake and absorption of iron in the fetus may also be affected by the same factors that predispose to preterm birth. The three outliers (with much higher serum ferritn levels than other subjects) in the scatter plot showing the relationship between serum ferritin and gestational age, also weakened the strong relationship and reduced the coefficient of determination. These three isolated subjects further support the large variability of other factors that could affect iron stores in preterms. Looking at this from a different perspective, the absence of these three outliers, would have increased the coefficient of determination. This would have strengthened the positive relationship between ferritin

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levels and gestational age, enabling one make a stronger statement regarding serum ferritin values at different gestational ages.

Conclusion

There is a wide range of serum ferritin amongst newborn babies. There is also a significant strong positive correlation between serum ferritin levels and gestational age.

Consent

Written informed consent was obtained from the parents of the study participants.

Ethical Approval

The study was approved by the University of Nigeria Teaching Hospital Health Research Ethics Committee.

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