Original Research Article

Neonatal Iron Stores Depend on Gestational Age: A Prospective Comparative Cross-sectional study at Neonatal Intensive Care Unit, University of Nigeria Teaching Hospital, Enugu State, Nigeria

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 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 with gestational ages of 25 weeks to 39 weeks, delivered at the UNTH. 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 recorded for all subjects. Serum ferritin was measured at birth and this was correlated with 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 among the mean serum ferritin levels amongst different categories of gestational age (F = 11.159, *P* <.001). 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* < .05). Extreme preterms were sixty-four times more likely than term babies to have low serum ferritin (*P* <.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* < .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* < .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

Ferritin, Iron stores, preterm and term babies

Introduction

Nutrients play important roles in the growth and development of the growing foetus [1]. The transfer of maternal nutrients occurs across the placenta to the foetus [2]. Iron is an important nutrient and 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 for gaseous exchange and to build enzymes" [5]. "Iron is also a co-factor of many enzymes, such as catalase, lipoxygenase, reductase and oxidase, which catalyze many essential body redox reactions" [5,6]. "Thus, iron is very essential in almost every body function and its deficiency has serious consequences" [5,7,8].

Iron is actively transported across the placenta to the foetus, starting at the 24th week of gestation and increasing gradually until the third trimester, when accretion occurs at the rate of 1.35mg/kg/day [9]. This results in foetal iron concentrations of 75mg/kg during the third trimester, when 80% of foetal iron is acquired [12]. "This increasing iron accretion is reflected by the increasing maternal iron requirements as pregnancy progresses, from approximately 0.8mg/day during the first trimester to approximately 3.0-7.5mg/day in the third trimester" [2]. There is also an increase in maternal absorption of both haeme and non haeme iron as gestation progresses, thereby increasing iron availability for transfer across the placenta [2]. However, as a result of this requirement at every stage during gestation, iron transport across the placenta is independent of maternal iron levels, except in the presence of severe maternal iron deficiency [3,10,11].

The most widely accepted mechanism for iron accretion in utero is through the active transport of maternal iron across the placenta [12-14]. "In this mechanism, the maternal serum iron binds two binding sites in the transferrin protein" [13,14]. "The diferric transferrin then binds the Transferrin Receptor-1 (TfR) located in the placental microvillous membrane surface" [13,14]. The new complex is moved into the cell endosome with a subsequent dissociation of the TfR and release of the iron [8,15,16]. "The divalent-metal-transporter-1 (DMT1) then transports the iron from the endosome to the cell cytoplasm" [8,15]. "Iron is consequently transferred outside the cell through the fetal side by Ferroportin (FPN) and it is immediately oxidized to Fe^{3+} by the copper ferroxidase Zyklopen (Zp)" [8,17]. "The oxidized iron can then be stored as ferritin in the placental stroma, or can bind to transferrin and be transported to the fetal circulation through the endothelium of fetal capillaries" [8,17].

"In the foetus, iron is stored as ferritin in the liver, bone marrow and spleen, where it constitutes 10-15% of total body iron at term" [11,18,19]. "Of the remaining iron, approximately 70-80% is contained in haemoglobin and 10% is in regulatory proteins such as myoglobin and cytochromes" [11,18,19]. "By virtue of truncated gestation, between 25% and 85% of preterm neonates develop evidence of iron deficiency during infancy" [7,13,20]. "Such deficiencies have been linked with early onset of post-natal anaemia, defects in growth and function of organ systems, altered immune function, temperature instability, and decreases in cognitive, motor, and social emotional development" [8,18,21].

"Neonatal iron stores can be assessed using parameters such as serum iron, haemoglobin, mean corpuscular volume, and red cell distribution width" [7]. "Other parameters include: zinc protoporphyrin (ZnPP); zinc protoporphyrin/haeme ratio (ZnPP/H); and serum transferrin receptor (STfR)" [7,18]. "Serum ferritin has been established as the standard for the measurement of total body storage iron in neonates" [19,22]. The World Health Organization guideline on the use of ferritin to assess the iron status of populations recommends a cut-off value of <30µg/l to define iron deficiency amongst apparently healthy children from 0-23 months [23]. However, Sidappa *et al* reported impaired auditory recognition memory processing at birth amongst infants born with serum ferritin <35µg/l compared with those with serum ferritin ≥ 35µg/l [19]. Several studies have been carried out on neonatal serum ferritin [19,24-29]. Some have shown ferritin's relationship with gestational age [24,28,29], while others have shown its dependence on weight [26-28]. However, few studies have documented gestational age specific mean serum values [19]. "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 amongst preterm new born infants" [22]. 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 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 [30,31]; had diabetes mellitus or hypertension; and who smoked were excluded from the study [32]. Subjects were enrolled consecutively until the calculated sample size was reached. Socioeconominc class was determined using the classification system proposed by Olusanya et al [33]. Anthropometric measurements (weight, occipito-frontal circumference, chest circumference and length) were recorded for all subjects. 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 analyzed 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" [19].

Sample Size Determination

The sample size determination for this study was based on a previous study carried out by the author [26].

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 approximately equal distribution of the study population across all socioeconomic classes.

Table 1: Sociodemographic variables of the study population

Characteristics	Preterm n = 70 (50%)	Term n = 70 (50%)	Total n = 140 (100%)
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

Gestational age (weeks)	N (140)	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 levels 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 study population was 93.14µg/l ± 57.69 with mean values of 63.13µg/l ± 23.93 and 133.67µg/l ± 50.14 amongst the preterm and term babies respectively (t = 10.623, P < .001). There was a significant difference (F = 11.159, P <.001) among the mean serum ferritin levels amongst different categories of gestational age as shown in Table 3.

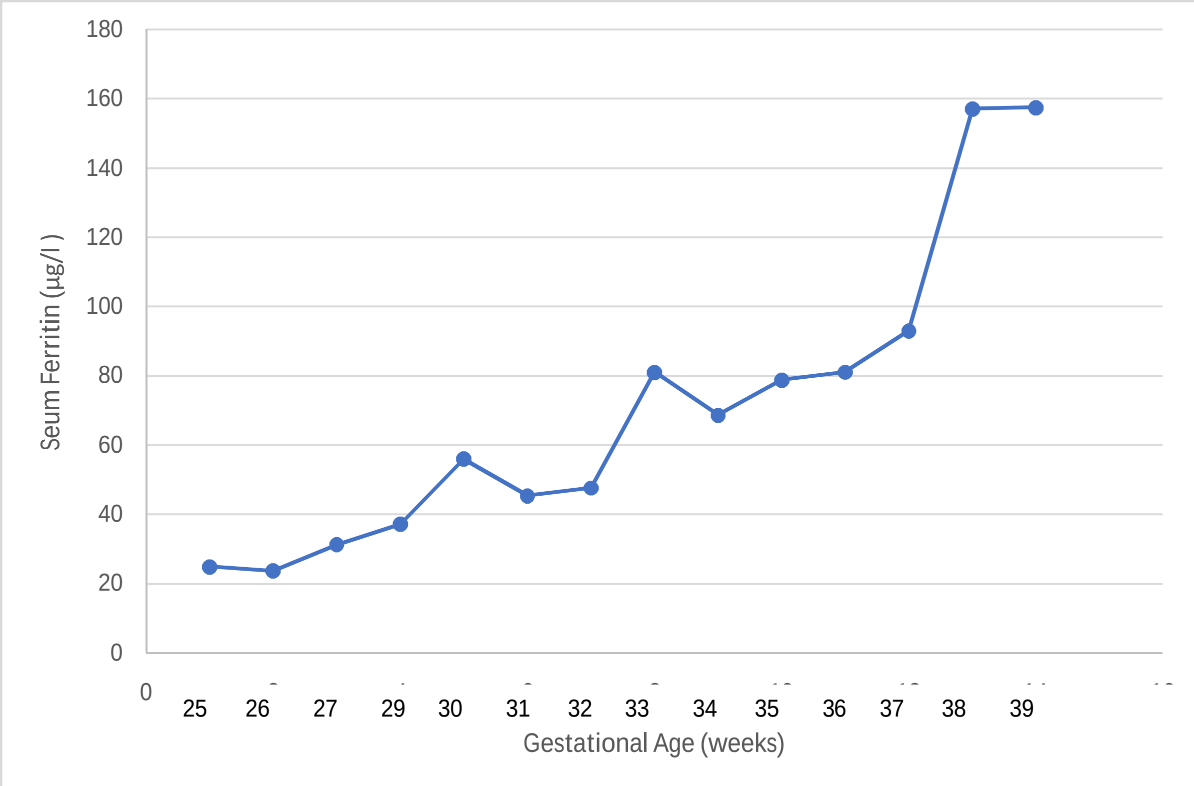

Figure 1: Distribution of mean serum ferritin by gestational age

Table 3: Mean serum ferritin levels amongst categories of gestational age

Gestational age (weeks)	**N (140)**	**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		

The prevalence of low serum ferritin was higher amongst preterms compared with term babies - 25 (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)			

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 (Table 5). The differences among these proportions were significant (χ^2 = 49.777, *P* < .05). Extreme preterms were sixty-four times more likely than term babies to have low serum ferritin (*P* < .01, OR = 64.00, 95% C.I for OR = 6.570 – 623.455), while very preterm babies were ten times more likely than term babies to have low serum ferritin levels (*P* < .001, OR = 9.905 95% C.I = 3.209 -30.570). (Table 5). 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* = .220, OR = 2.133, 95% C.I for OR = 0.635 – 7.167). (Table 5)

Table 5: Association between low serum ferritin levels and categories of gestational age

	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)	< .001	64.000	6.570 – 623.455
Term	64 (91.4)	6 (8.6)			
Very preterm (28 - <32)	14 (51.9)	13 (48.1)	< .001	9.905	3.209 – 30.570
Term	64 (91.4)	6 (8.6)			

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* < .001). A coefficient of determination (R^2) of 0.432 indicates that approximately 43% of the variation that exists in serum ferritin levels can be attributed to gestational age (Figure 2).

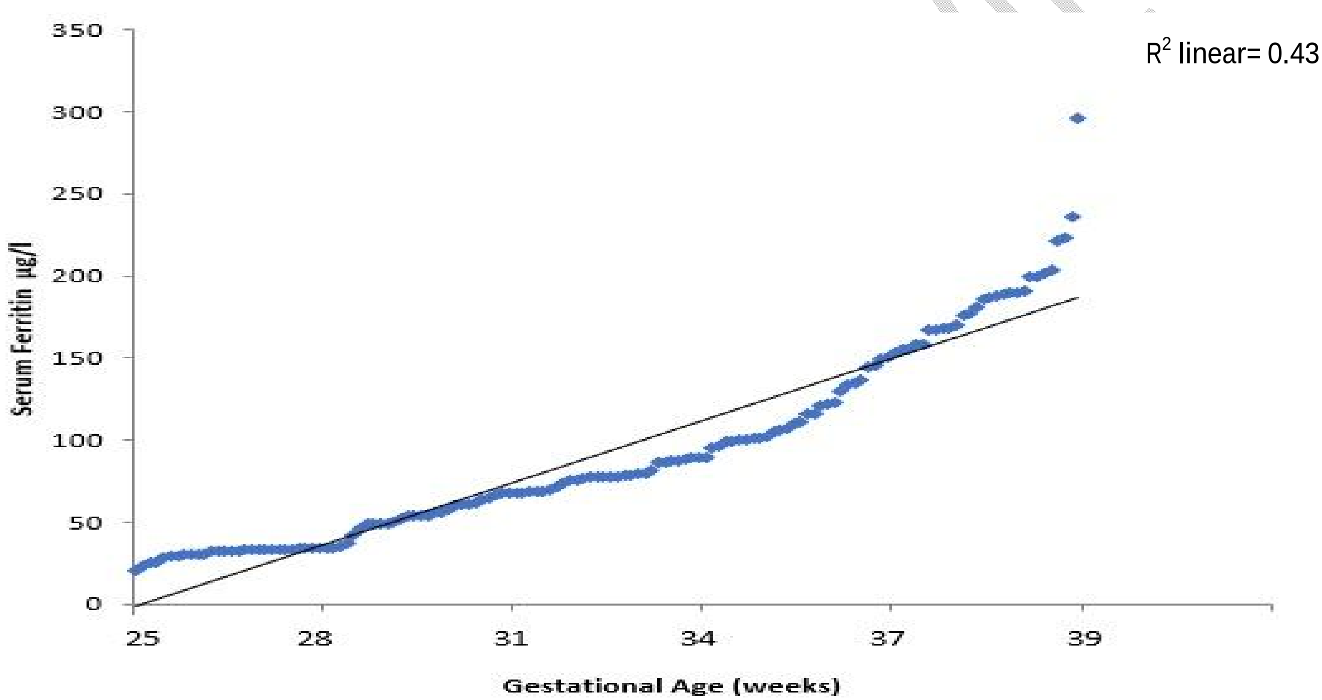

Fig 2**:** Scatter diagram showing relationship between serum ferritin and gestational age

Discussion

In this study, iron stores were assessed using serum ferritin. The assessment of iron stores using other parameters has several drawbacks [29,32,34]. Parameters such as serum iron, haemoglobin, mean corpuscular volume, and red cell distribution width are non-specific, are late markers of iron deficiency, and may not reflect tissue iron status in newborn babies [19,32,34]. Other parameters such as zinc protoporphyrin (ZnPP) and zinc protoporphyrin/haeme ratio (ZnPP/H). are inversely related to gestational age and are also elevated in conditions such as maternal chorio-amnionitis [35-37]. Serum transferrin receptor (STfR) levels in umbilical cord blood are not directly influenced by gestational age [38]. Thus, STfR levels are not a good indicator of foetal iron stores [38]. On the other hand, 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 [32,39,40]. In addition, serum ferritin values correlate positively with the size of the total body iron stores in the absence of concurrent infection [40].

The wide range of serum ferritin [20.6µg/l - 296µg/l] for the entire study population is similar to the wide range of 40µg/l - 224µg/l obtained from the meta-analysis by Sidappa, *et al.*, [19] in the USA. It is also similar to the values obtained by Carpani., *et al* [41]. 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 [19], 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, *et al*., [41] in Italy in 2009, and has been the observation of several other authors [38,42]. At the beginning of the 21st century, Sweet, *et* al., [38] assayed cord blood transferrin receptors to assess fetal iron status at birth. The researchers observed mean ferritin values of 75µg/l (range 44-117) at 26 to 28 weeks of gestation, increasing through 90µg/l (range 45-142) at gestational age of 32 to 36 weeks, to 131µg/l (range 90-238) at gestational age of 37 to 41 weeks [38]. Few years later, Rao, *et al*., [42] 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 [42]. 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 [42]. In the same year, Sidappa, *et* al., [19] carried out a meta-analysis of 35 published studies over a period of 25 years. They documented a steady increase in ferritin levels, from a mean of 63µg/l at 23 weeks to 171µg/l at 41 weeks gestation [19]. 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 is inversely proportional to gestational age. This finding also complements the findings of other authors [27,41], and shows that iron stores increase with advancing gestational age. One of such findings was observed in the meta-analysis carried out by Siddappa, *et al*., [19] where umbilical cord serum ferritin was found to reduce 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, <35µg/l was used as the cut off to define low serum ferritin. The World Health Organization guideline on the use of ferritin to assess the iron status of populations recommends a cut-off value of <30µg/l to define iron deficiency amongst apparently health children from 0-23 months [23]. However, Sidappa, *et al*., reported impaired auditory recognition memory processing at birth amongst infants born with serum ferritin <35µg/l compared with those with serum ferritin > 35µg/l [19]. The latter value was used in this study in order to reduce the risks of missed cases of iron deficiency which may portend irreversible consequences of iron deficiency later in life. Furthermore, since already existing cutoffs are not based on a systematic appraisal of published work, but rather on qualitative expert opinion, the WHO and CDC are coordinating projects to address this evidence gap [40]. Until the completion of these projects, it has been recommended clinicians are encouraged to rely on laboratory standards and local guidelines [40].

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 same 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 out liers (with much higher serum ferritin 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 out liers, could have increased the coefficient of determination. This would have strengthened the positive relationship between ferritin 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. It is thus recommended that serum ferritin be assayed in preterm neonates to ascertain their iron status. Further studies are also recommended to assess the need for iron supplementation amongst preterm neonates.

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 (+234 42 252-022).

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SOCIO ECONOMIC CLASSIFICATION BY OLUSANYA *ET AL*

A

SCORES	FATHER'S OCCUPATION
1	Professionals, Top Civil Servants, Business Executives and Politicians
2	Middle level bureaucrats, Technicians, Skilled Artisans and Well-to-do Traders
3	Unskilled workers and those in general whose income is at or below the national minimum wage

B

SCORES	MOTHER'S LEVEL OF EDUCATION
0	Education up to University level
1	Secondary or Tertiary below University (e.g. College of Education, School of Nursing)
2	No schooling or up to Primary level only

Adding scores from A and B above gives the social class of the subject.

Social class 1 or Upper class: Score 1 or 2

Social class 2 or Middle class: Score 3

Social class 3 or Lower class: Score 4 or 5