

The Assessment of Newborn Iron Stores at Birth: A Review of the Literature and Standards for Ferritin Concentrations

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Key Words

Ferritin · Diabetic mother, infant · Iron · Iron deficiency

Abstract

Background: Serum ferritin measurements are used in clinical populations to estimate total body iron stores and the risk of subsequent iron deficiency or overload. The lack of normative newborn serum ferritin concentration data between 23 and 41 weeks has led to difficulty in establishing the incidence and degree of abnormal iron status in the neonatal period. **Objectives:** The primary objective of this review was to summarize the maternal and gestational factors that determine ferritin concentrations in full-term and pre-term newborn infants and to generate comprehensive reference values. The secondary objective was to assess serum ferritin concentrations in newborn infants at risk for abnormal fetal iron metabolism, including maternal diabetes mellitus, intrauterine growth restriction and maternal smoking during pregnancy. **Methods:** Serum ferritin and gestational age data at birth from 457 low-risk pre-term and term infants of 23–41 weeks gestation obtained from 35 published studies reviewed from a period of 25 years and from recently collected data from our centers were assessed by regression

analysis. Slopes and intercepts of the high-risk groups were compared with the standard curve. **Results:** Umbilical cord serum ferritin concentrations increased with advancing gestational age, from a mean of 63 $\mu\text{g/l}$ at 23 weeks to 171 $\mu\text{g/l}$ at 41 weeks gestation ($p < 0.001$). The infants of diabetic mothers had a lower intercept than the control infants ($p < 0.001$). **Conclusions:** Iron deficiency and overload have been implicated in neurodevelopmental impairments. Normative cord serum ferritin data may permit a more precise assessment of infants who are at risk for abnormal iron status at birth.

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Background

Iron is an essential micronutrient that plays a significant role in critical cellular functions in all organ systems in all species. Iron is particularly vital for early brain growth and function in humans since it supports neuronal and glial energy metabolism, neurotransmitter synthesis and myelination [1–5]. The need to establish standard curves for cord serum ferritin concentrations throughout the third trimester of pregnancy is based on

the risk of developing brain iron deficiency as storage iron pools become depleted in certain gestational conditions [6–8]. Iron deficiency during the fetal or postnatal periods can alter brain structure, neurochemistry and cognitive functioning, and lead to long-term cognitive and motor impairment that cannot be corrected by iron supplementation [9–11]. Newborn infants with the lowest quartile of cord ferritin concentrations ($<76 \mu\text{g/l}$) have impaired mental and psychomotor function at school age [12]. Iron-deficient infants of diabetic mothers (IDM) with low neonatal ferritin concentrations ($<35 \mu\text{g/l}$) have impaired auditory recognition memory processing at birth compared with iron-sufficient IDM (ferritin $>35 \mu\text{g/l}$) [13]. Pre-term infants with low serum ferritin concentrations ($<75 \mu\text{g/l}$) at 37 weeks post-conception have abnormal neurologic reflexes [14].

Direct measurement of brain iron in newborn infants is not currently feasible. Total body iron and iron storage estimates are based on measurements of serum markers, such as hemoglobin (Hgb) and ferritin concentrations [15]. Measurement of fetal and neonatal iron stores as a proxy for non-heme tissue iron deficiency is based on the principle that there is a hierarchical loss of tissue iron after the iron stores are depleted [1, 6]. Under conditions of negative iron balance, the red blood cell (RBC) iron is preserved at the expense of brain iron, which, in turn, is spared at the expense of heart and skeletal muscle iron [1, 6].

A wide spectrum of measures are used to diagnose iron deficiency. Hgb, mean corpuscular volume, and red cell distribution width are late markers of iron deficiency and may not reflect tissue iron status in newborn infants. Zinc protoporphyrin (ZnPP) and ZnPP to heme ratio (ZnPP/H) are elevated during iron-deficient erythropoiesis, but in neonates it is not clear whether elevated ZnPP/H ratios reflect enhanced rates of erythropoiesis during rapid growth or true total body iron deficiency [16]. Moreover, ZnPP/H ratio is affected by maternal chorioamnionitis [17]. Elevated serum transferrin receptor (sTfR) and sTfR to log of ferritin ratio reflect tissue iron deficiency and are seen in neonates following maternal iron deficiency and smoking. The data on sTfR are relatively limited in newborn term and pre-term infants, and additional studies are needed to establish normal standards for newborn infants [15].

Serum ferritin concentration has been used as a standard measurement of iron stores in infants, children and adults [18–21]. The relationships between ferritin concentrations and total body storage iron in these populations are well established. In adults, $1 \mu\text{g/l}$ of serum ferritin is equivalent to 8–10 mg of storage iron [22]. In new-

born infants, the ratio of serum ferritin to liver non-heme iron concentration is closer to 1:2.7 [23]. In spite of the wide availability of serum ferritin as a screening test, normative data at birth, as a function of specific gestational ages from 23 to 41 weeks, are limited.

Ferritin: Biology and Clinical Significance

The major form of iron storage is ferritin. Tissue ferritin exists as a 24-unit polymer consisting of two subunits, the heavier (H) acidic subunits and the lighter (L) basic subunits. The standard serum ferritin assay only detects the L-rich ferritin, which is a small fraction of total body ferritin [24].

Low serum ferritin concentrations are seen only in iron deficiency. Elevated ferritin concentrations in the newborn can be a consequence of neonatal hemochromatosis, excessive iron administration or RBC transfusions. Serum ferritin concentrations are also elevated during periods of infection, inflammation and neoplasia. Under these conditions, serum ferritin behaves as an acute-phase reactant that can mask the diagnosis of iron deficiency [25].

Maternal Iron Requirements and Fetal Endowment

Iron requirements in women are significantly higher in the pregnant state than in the non-pregnant state. The total iron requirement of a full-term pregnancy is approximately 1,000 mg [26]. Iron requirements for pregnant women increase significantly in the second and third trimesters, with the expansion of maternal blood volume and fetal red cell mass [26]. The fetus accumulates iron at a rate of 1.35 mg/kg of fetal weight in the third trimester, maintaining an average iron content of 75 mg/kg of body weight during the last trimester [27, 28]. At term, 70–80% of fetal iron is present in RBCs as Hgb, 10% in tissues as myoglobin and cytochromes, and the remaining 10–15% stored in reticuloendothelial and parenchymal tissues as ferritin and hemosiderin [27].

The placenta serves as the regulatable conduit for maternal–fetal iron transport. The amount of iron passing through the placenta increases with gestation. Iron is transferred against a concentration gradient from the placenta to the fetus, especially during the later stages of pregnancy. The placenta can also serve as a storage organ for iron during pregnancy.

Factors That Determine Neonatal Ferritin Concentration

Factors that influence neonatal ferritin concentration at birth include duration of gestation, fetal sex, maternal iron status and conditions altering maternal–fetal iron

exchange. The influence of gestational age has been reported in a large number of studies, many of which contain small numbers of subjects or relatively large gestational age groupings (e.g., term vs. pre-term). In one of the larger studies, normal full-term newborn infants had cord serum concentrations between 100 and 260 $\mu\text{g/l}$ [29]. At- or near-term female newborn infants have higher cord serum ferritin concentrations than male infants, potentially due to differences in sex hormones, blood volume and iron utilization [12]. When term and pre-term infants are combined, sex differences in cord serum ferritin levels are not as prominent [30].

The influence of gestational age on cord blood ferritin concentration has been assessed primarily through studies comparing pre-term with term infants. Pre-term infants have lower cord serum ferritin concentrations than term infants [19, 30–32]. The lower ferritin levels in pre-term infants are accompanied by lower serum iron and total iron binding capacity, and by higher reticulocyte counts and cord sTfR levels, implying increased iron utilization for fetal erythropoiesis [32].

Few studies provide ferritin concentration data for specific gestational ages. Siimes and Siimes [29] demonstrated a median ferritin level of 45 $\mu\text{g/l}$ at 14–16 weeks gestation and 200 $\mu\text{g/l}$ at 39 weeks gestation. Fetuses undergoing percutaneous umbilical blood sampling, but who were not affected by any pathologic maternal-fetal conditions, had mean plasma ferritin increased from 17.7 $\mu\text{g/l}$ at 18–20 weeks gestation to 56.8 $\mu\text{g/l}$ at 32–35 weeks gestation [33]. A similar trend in pre-term appropriate-for-gestational-age infants with birth weights from 600 to 2,000 g has been noted [34]. Jansson et al. [31] showed that serum ferritin concentration measured in pre-term infants at 24–48 h of age were significantly lower in infants <34 weeks gestation (range 26–270 $\mu\text{g/l}$), compared with infants >34 weeks gestation (range 20–600 $\mu\text{g/l}$).

The influence of maternal iron status on cord serum ferritin concentration has been assessed in iron-sufficient and iron-deficient mothers. In pregnancies characterized by maternal iron sufficiency, a relationship between maternal iron status and cord serum ferritin concentrations has been difficult to demonstrate [19, 29, 30, 35, 36]. All iron indices are higher in the cord blood than in the mother [36], emphasizing that fetal iron stores are independent of maternal iron status [30]. These studies demonstrate that iron is accreted by the fetus against a concentration gradient and that transplacental iron transport increases in response to the rapidly growing fetus in late third trimester.

Thirty percent of pregnant women have low serum ferritin concentrations at the end of pregnancy, despite prophylactic iron therapy [37]. Studies of maternal-fetal iron metabolism in pregnancies complicated by iron deficiency can be divided into those in which the mother is frankly anemic [38–40] and those in which she only has low ferritin concentrations [37, 41–44]. Term infants of frankly anemic mothers have low cord serum ferritin, iron and transferrin saturation at birth [38, 40]. Anemic mothers (mean Hgb: 87.2 g/l) with increased erythropoietin levels have infants with low cord serum ferritin concentrations [39]. In addition, the cord serum erythropoietin at birth is inversely related to maternal Hgb, suggesting more active erythropoietic effort secondary to hypoxemia in fetuses of anemic mothers.

Full-term infants born to iron-deficient, non-anemic mothers with low serum ferritin concentrations have lower cord serum ferritin concentrations compared with infants born to mothers who have normal ferritin concentrations [37, 41–43]. For example, the serum ferritin concentration of infants born to mothers with ferritin concentrations <10 $\mu\text{g/l}$ is $98.5 \pm 50.6 \mu\text{g/l}$ when compared with a value of $147.2 \pm 66.0 \mu\text{g/l}$ seen in infants born to mothers with normal ferritin concentrations [42].

In addition to maternal iron deficiency, impaired placental function and increased fetal iron demand in excess of placental transport capacity are significant risk factors for fetal/neonatal iron deficiency. Clinical conditions that result in these abnormalities of fetal iron metabolism include maternal hypertension resulting in placental vascular insufficiency and chronic fetal hypoxia with augmented fetal erythropoiesis [8].

Infants with intrauterine growth restriction (IUGR) are at risk for iron deficiency primarily because of impaired iron transport and chronic intrauterine hypoxia due to poor placental function. IUGR is seen in pregnancies complicated by severe maternal hypertension or pre-eclampsia, due to genetic disorders or severe maternal malnutrition. Serum ferritin concentrations are decreased and transferrin levels are increased in IUGR infants at birth [8, 29, 34]. In a postmortem study, Georgieff et al. [45] demonstrated infants with IUGR secondary to Potter's syndrome to have significantly reduced liver and brain iron concentrations compared with control infants.

Chronic fetal hypoxia increases fetal iron requirements for secondary erythropoiesis and is also characteristic of pregnancies complicated by maternal diabetes mellitus [46] and maternal smoking [47]. In these condi-

tions the iron delivery to fetal organs such as liver, heart and brain are often reduced to maintain iron supply to the expanded red cell mass [6, 7, 48, 49].

IDM born to gestational, insulin-dependent and non-insulin-dependent diabetic mothers are at risk for low iron stores [8, 46, 50]. Sixty-five percent have ferritin concentrations $<60 \mu\text{g/l}$, with a mean value of $26 \mu\text{g/l}$ [8]. Fetal hyperglycemia and hyperinsulinemia during gestations complicated by maternal diabetes mellitus increases fetal metabolic rate and oxygen consumption and result in fetal hypoxemia [51, 52]. The abnormal iron indices in IDM are due to increased fetal iron utilization for erythropoiesis [46, 50]. The degree of iron abnormality at birth correlates with elevated fetal erythropoietin and fetal glycosylated Hgb concentrations [46]. RBC iron content increases proportionately with the decrease in serum ferritin concentration. The lower ferritin concentrations in IDM could also have been secondary to placental dysfunction preventing adequate transfer of maternal iron to the fetus [54].

Maternal smoking is another risk factor for fetal and neonatal iron deficiency. Healthy term infants born to iron-sufficient mothers who smoked during pregnancy have elevated fetal erythropoietin, cord Hgb, sTfR concentrations and decreased cord ferritin concentrations consistent with intrauterine hypoxemia [47, 54, 55]. Fetal hypoxemia was likely induced by elevated carboxyhemoglobin levels, decreased uteroplacental blood flow and increased placental vasoconstriction caused by nicotine and catecholamines [55]. Increased cord hematocrit values positively correlate with maternal thiocyanate levels [54]. There is a significant inverse relationship between cord serum ferritin and the hematocrit, suggesting iron stores are mobilized for Hgb synthesis [54].

Iron Stores in Healthy Term and Pre-Term Infants at Birth: Generation of Standards from the Literature and the Current Data Set

Although the neonatal literature is robust in ferritin studies, most suffer from small sample sizes and a lack of ferritin concentrations reported at specific gestational ages. Generating normal values for serum ferritin concentration in umbilical cord blood based on a greater number of subjects assessed at specific gestational ages would help to identify infants at risk for perinatal iron deficiency. The primary objective of the study was to determine the mean and the 5th and 95th percentile confidence limits of the relationship of ferritin to gestational age between 23 and 41 weeks. The secondary objective was to assess neonatal serum ferritin concentrations in infants at risk for fetal and neonatal iron deficiency.

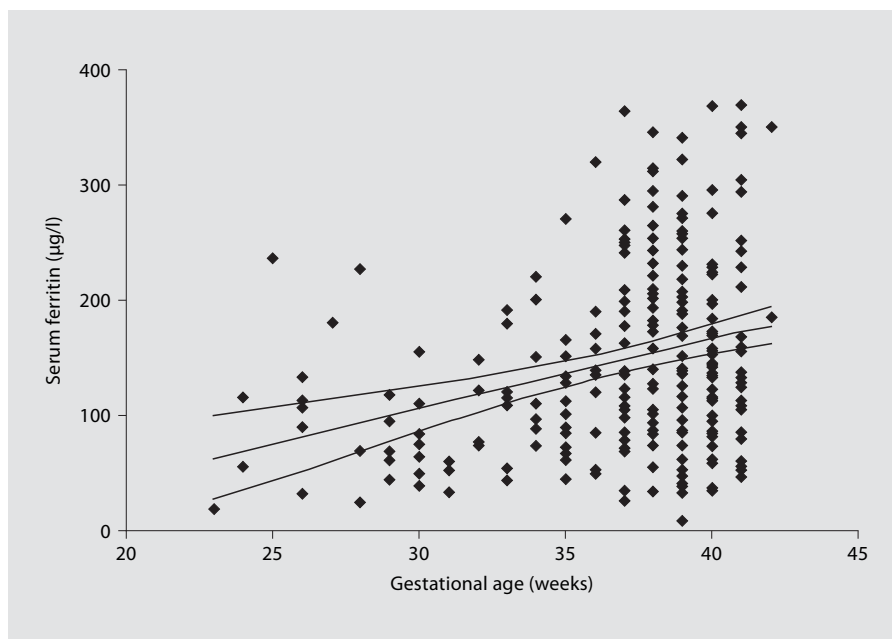
Analysis Based on Data from the Literature

We assessed 35 papers [12, 14, 19, 20, 23, 29–42, 44, 47, 50, 54, 56–67] describing neonatal ferritin concentrations in newborn infants identified through the PubMed search engine (<http://www.ncbi.nlm.nih.gov/entrez/>). Articles were included for generating the gestation-specific standard curve only if: (1) ferritin concentrations of individual infants were available; (2) gestational ages of the subjects were specified within 2 weeks, and (3) the data came from infants not at risk for abnormal fetal/neonatal iron metabolism (e.g., maternal iron deficiency, diabetes mellitus, IUGR, smoking and inflammatory conditions). The individual serum ferritin concentrations of the subjects and their respective gestational ages were analyzed to determine the mean and the 5th and 95th percentile confidence limits of the relationship of ferritin to gestational age. Additional articles that provided individual subject cord serum ferritin concentration grouped by either term or pre-term birth (but not specific gestational age) were included only to analyze the 5th, 25th, 50th, 75th and 95th percentiles for the term (≥ 37 weeks estimated gestational age) vs. pre-term (< 37 weeks estimated gestational age) infants. The data from these articles was not utilized for the gestation specific regression analysis.

Analysis Based on Two Contemporary Data Sets

In the contemporary data set, cord serum ferritin concentrations at birth at specific gestational ages were obtained from infants born between 23 and 41 weeks gestation enrolled in ongoing studies at the University of Minnesota and the University of Iowa [16]. Institutional Review Boards at both institutions approved the study, and informed consent was obtained from the mothers. Two groups of infants were enrolled. The low-risk control group consisted of infants born to mothers whose pregnancies were uncomplicated by conditions known to alter fetal/neonatal iron status, including anemia, diabetes mellitus, IUGR and smoking. The second group consisted of infants with one of three gestational risk factors for altered fetal/neonatal iron status: maternal diabetes mellitus, IUGR and maternal smoking [8, 46, 47]. Infants with more than one risk factor were excluded from analysis. Infants with umbilical cord serum ferritin values $>370 \mu\text{g/l}$ were excluded because such values were rarely found in the literature analysis and likely reflected infants with documented or undocumented inflammatory or iron-overloaded states. Infants with chromosomal anomalies, congenital syndromes or infections were also excluded from both groups.

Fig. 1. Ferritin concentrations as a function of gestational age in infants from the combined control data sets. The regression line and its 5th and 95th percentile confidence limits for the mean regression are shown ($n = 245$, $r = 0.30$, $r^2 = 0.09$, $Y = 6.01X - 74.56$; $p < 0.001$).



Analytical Methods

Serum ferritin was measured by chemiluminescent immunoassay (Beckman Access Immunoassay System; Beckman-Coulter Inc.; Brea, Calif., USA) at the University of Minnesota and by radioimmunoassay at the University of Iowa. Inter-assay variability was 5.2 and 6.9% for ferritin concentrations assayed at the two institutions, respectively. Studies included from the review of literature had used different assay techniques as well. Since various assay methods correlate well and inter-laboratory differences are similar to batch-to-batch variability within a laboratory [22, 68], no attempt was made to control for the methodology.

Data Management and Statistical Analysis

Linear regression analysis was used to assess the relationship between gestational age and serum ferritin concentration in the remainder of the infants from the historical data set and the low-risk control infants from the current enrollment. The a priori intention was to combine the data sets if no statistical difference existed between the two. The 95% confidence interval of the slope and intercept for each curve was calculated. Given the relatively low number of subjects at gestational age < 30 weeks, the relatively low trajectory of the slope for ferritin across gestational age and the pronounced tendency for the historical literature to group subjects into term and pre-term infants, we calculated the 5th, 25th, 50th, 75th

and 95th centiles for term and pre-term control infants, instead of gestation-specific centiles.

To address our second objective, linear regression was used to compare the relationship between ferritin concentration and gestational age in each of the three risk groups. The slopes and intercepts of the regression lines for the three high-risk groups were compared with the low-risk control group. The fraction of the variation r^2 , shared between X and Y, was analyzed for all the regression models. Statistical significance was set at a p value < 0.05 .

Results

We included 626 high- and low-risk newborn infants from 23 to 41 weeks gestation from the historic and contemporary data sets. After excluding 23 and 24 infants who met one of the exclusion criteria in the historical cohort and the contemporary cohort, respectively, we qualified 298 infants from the literature and 281 infants from the current data set for the final analysis. The excluded infants included 8 term infants with high serum ferritin concentrations ($> 370 \mu\text{g/l}$) in the current data set and 4 term and 3 pre-term infants in the historic data set. Data from the literature consisted of a single study of 86 term and pre-term infants where gestation-specific cord serum ferritin concentrations were documented [29] and

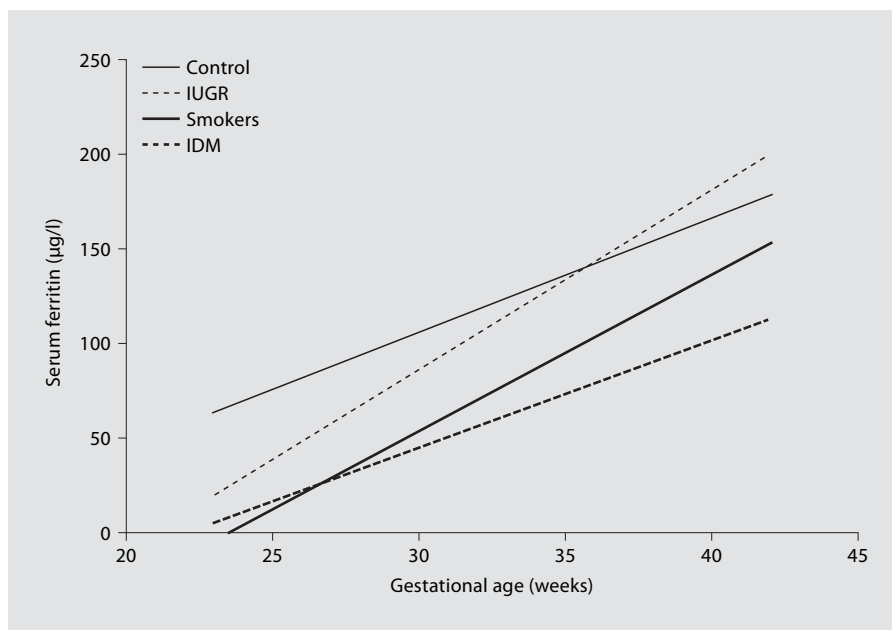


Fig. 2. The regression lines for infants of mothers who smoke ($n = 19$, $r = 0.44$, $r^2 = 0.13$, $Y = 8.26X - 194.02$; $p = \text{NS}$), infants of diabetic mothers (IDM, $n = 70$, $r = 0.22$, $r^2 = 0.05$, $Y = 5.65X - 124.00$; $p = \text{NS}$), and infants with IUGR ($n = 33$, $r = 0.42$, $r^2 = 0.18$, $Y = 9.43X - 195.67$; $p < 0.01$) in comparison with the combined control group.

212 infants from five additional studies that provided specific cord serum ferritin concentration for individual subjects who were categorizable as either term or pre-term infants [19, 20, 31, 34, 42]. The contemporary data set provided gestational age-specific cord serum ferritin concentrations for 159 low-risk control infants between 23 and 41 weeks, as well as 122 high-risk infants comprised of 70 IDM, 33 IUGR and 19 infants born to mothers who smoked during pregnancy.

The regression lines generated from the historical data set and the low-risk control infants from the contemporary data set were not statistically different and thus, the data sets were collapsed to generate a single standard curve (fig. 1). The prediction line and the 95% confidence intervals for the mean demonstrated that cord ferritin concentrations increased with advancing gestational age ($p < 0.001$) from a mean of 63 $\mu\text{g/l}$ at 23 weeks gestation to 171 $\mu\text{g/l}$ at 41 weeks. The 95th confidence band was wider for lower gestational infants in comparison with the term infants reflecting the fewer subjects at these gestational ages.

The calculated 5th, 25th, 50th, 75th and 95th centiles for term and pre-term control infants are shown in table 1. Ferritin concentrations were lower for the pre-term infants compared with term infants, although both groups had similar 5th centile values: $<40 \mu\text{g/l}$ in term infants and $<35 \mu\text{g/l}$ in pre-term infants. Interestingly, 35 $\mu\text{g/l}$ was the concentration predicted to be the level at

Table 1. Cord serum ferritin concentration percentiles for low-risk term and pre-term infants

	Cord serum ferritin concentration, $\mu\text{g/l}$				
	Percentile: 5th	25th	50th	75th	95th
Term (≥ 37 weeks), $n = 308$	40	84	134	200	309
Pre-term (< 37 weeks), $n = 149$	35	80	115	170	267

which liver iron stores are low enough to compromise brain iron content, and below which newborn infants demonstrate abnormalities in recognition memory processing [13].

The three risk groups were compared with the control group using dummy coded variables for the intercept differences and slope differences using the standard practice [69]. The slopes of each of the 3 high-risk groups were not different from the control [$\Delta R^2 = 0.003$, $\Delta F(3, 359) = 0.422$, $p = 0.738$] and were dropped from the equation. In contrast, significant differences were found for the intercept values [$\Delta R^2 = 0.092$, $\Delta F(3, 362) = 13.33$, $p < 0.001$]. The IDM (fig. 2) group had a lower intercept than the control [$-63.5(10.44)$, $p < 0.001$].

Discussion

To date, the majority of studies had evinced the relationship between maternal and fetal iron status and the comparison of iron status between term and pre-term newborn infants. In merging data sets from the literature with data from two contemporary studies, we have been able to generate a standard curve for ferritin concentrations in newborns from 23 to 41 weeks and to define the 5th, 25th, 50th, 75th and 95th percentiles of ferritin concentrations for pre-term and term infants. These curves can be used to identify which infants are at neurodevelopmental risk from iron deficiency or iron overload during gestation.

The cross-sectional data may also be of use to guide postnatal iron therapy in term and pre-term infants. For example, term IDM, IUGR and infants of mothers who smoked during pregnancy and were born with low neonatal iron stores have significantly lower ferritin concentrations between 6 and 9 months of age [70, 71], and thus enter their second postnatal year with a higher risk of becoming iron deficient [70]. The AAP currently recommends screening term infants for iron deficiency anemia between 9 and 12 months of age and high-risk infants including pre-term and low-birth-weight infants at an unspecified time point earlier than 9 months. There are no recommendations for IDM or infants of mothers who smoked during pregnancy either for screening or for early iron therapy [72]. High-risk term infants could be identified more specifically by using the 5th centile cutoffs from the current study and they could be potentially screened earlier.

Pre-term infants have a highly variable iron status at the time of hospital discharge [73]. Factors that predispose pre-term infants to a net negative iron balance at 37 weeks post-conception include a low fetal endowment, excessive phlebotomy, late onset of iron supplementation, low levels of iron supplementation, recombinant human erythropoietin therapy and rapid postnatal growth. It is not unusual for pre-term infants to be discharged with Hgb concentrations as low as 75 g/l. If accompanied by low ferritin concentrations for post-conceptual age as defined by our standards, this would represent a significant reduction in total body iron [27]. Neutral iron balance is more likely in pre-term infants with older gestational ages at birth, early onset of enteral iron therapy, adequate iron supplementation and relatively slow postnatal growth. Finally, some pre-term infants have been documented with very high ferritin concentrations, indicative of iron overload [74, 75]. Factors that may predis-

Table 2. Total body iron content of preterm infants*

Serum ferritin concentration		Hemoglobin concentration, g/l			
$\mu\text{g/l}$	Percentile	75	100	120	140
35	5th	65	79	90	101
80	25th	81	94	105	116
115	50th	88	101	112	123
170	75th	95	109	120	131
267	95th	104	117	128	139

* Total body iron content (TBI) was determined as follows: $\text{TBI} = \text{Hgb iron content (HbI)} + \text{body storage iron (BSI)} + \text{functional iron in tissues}$. $\text{HbI} = \text{Body weight (kg)} \times \text{Hgb (g/dl)} \times 2.74$ [76], $\text{BSI} = 21.99 \log(\text{serum ferritin}) - 29.04$ [76, 77]. Functional iron content in tissues = 7 mg/kg [27, 28].

pose pre-term infants to iron overload include multiple RBC transfusions, early onset of intravenous iron therapy and potentially, extremely aggressive enteral iron therapy. The total body iron status of the discharged pre-term infant may vary by a factor of two, ranging from 65 to 140 mg (table 2).

The enteral iron requirements of the discharged pre-term infant during the first year can be estimated from Hgb and ferritin concentrations at discharge. A pre-term infant discharged at approximately 37 weeks post-conception age with a weight of 2 kg, who is expected to reach a weight of 10 kg at 12 months corrected age would require 3.5 mg of elemental iron daily if the infant's iron endowment is adequate at discharge (serum ferritin $\geq 116 \mu\text{g/l}$) but would require 4.3 mg daily if iron stores are low (serum ferritin $< 35 \mu\text{g/l}$). This suggests that the current recommendation of the American Academy of Pediatrics to supplement 2 mg/kg/day of elemental iron for all exclusively breastfed premature infants during the first year of life [72], may be inadequate for the iron-deficient pre-term infant. Future studies are required to determine the likely long-term impact of such supplementation.

It may be prudent to closely monitor the iron status of pre-term infants with low iron stores for development of postnatal iron deficiency while in the hospital. Currently there are no recommendations from the American Academy of Pediatrics or any other organization on monitoring of iron status, as well as adjusting the dose of iron supplementation in response to monitoring in pre-term infants. Depending upon the number of RBC transfusions, the serum ferritin concentration varies widely in these infants. As with other age groups, low

ferritin is seen only in conditions of iron deficiency during the perinatal period. Therefore, infants identified with low ferritin concentrations for their post-conceptual age based on the data in the current study may benefit from either early institution of iron supplementation (e.g., from 2 weeks instead of from 1 month as currently recommended) or higher dose (e.g., 4 mg/kg/day instead of 2 mg/kg/day). On the other hand, it may be prudent to withhold iron supplementation or reduce the dose in pre-term infants with elevated serum ferritin concentrations for post-conceptual age (>90th percentile), since their total body iron status as well as the fate of the supplemented iron in these situations is unknown.

Finally, determining the serum ferritin for gestational age at discharge may also potentially be used as a starting point for monitoring the iron status of pre-term infants after discharge. Serum ferritin decreases during the first year of life [78]. In pre-term infants <1,700 g a serum ferritin <50 µg/l at 2 months portends the risk of subsequent early-onset iron deficiency [79]. Therefore, serum ferritin and Hgb could be measured at 2 months of post-natal age, and every 2 months thereafter until 6 months of age, i.e. during the period when the iron demand is likely to be higher due to rapid growth rate in pre-term infants. Those infants with birth weight <1,500 g, those consuming breast milk exclusively or low iron formula or cow's milk, and those who had received few RBC transfusions during the neonatal period and in whom iron supplementation was delayed are likely to benefit the most from such screening.

Beyond 6 months of age, serum ferritin does not correlate well with measures of erythropoiesis in pre-term

infants [78]. Therefore, serum ferritin may not be a reliable indicator of iron deficiency as a stand-alone lab test. Additional tests of iron deficiency, such as Hgb, mean corpuscular volume, red cell distribution width, ZnPP/H ratio and transferrin saturation are necessary to monitor total body iron status at this age.

Conclusion

We have reviewed the importance of assessing neonatal iron status in the term and pre-term infant. The normative curve of cord serum ferritin concentration may be useful for identifying infants with iron deficiency at birth and thus, at risk of long-term neurodevelopmental impairments. Infants with serum ferritin in the lower quartile may benefit from close monitoring of their iron status. One weakness of the study is relatively few subjects (10% of total) with gestational ages ≤30 weeks. Additional studies are needed to validate the normative ferritin values at lower gestational ages and to evaluate the usefulness of the normative curve for determining the optimal dosage of iron supplementation. Future studies are also needed to compare the usefulness of serum ferritin vis-à-vis other biomarkers of iron status at birth and beyond.

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