Iron deficiency anemia in late-preterm infants

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Iron deficiency anemia is a common problem in newborn infants. The American Academy of Pediatrics recommends iron prophylaxis at 4 months of age for term infants. There is no specific recommendation for iron prophylaxis in late-preterm infants. We aimed to establish the optimum time for iron prophylaxis in late-preterm infants. Thirty-eight late-preterm (Group 1) and 38 term (Group 2) infants born on the same day were enrolled in the study. Hemoglobin, ferritin and reticulocyte values at birth, 2nd month and 4th month were assessed. The cord ferritin, hemoglobin and reticulocyte levels did not differ significantly between groups. However, at the 2nd month, median ferritin and hemoglobin values were lower in late-preterm infants than term infants (145 mg/dl vs. 195 mg/dl, p=0.001 and 10.1 g/dl vs. 11.6 g/dl, p<0.001, respectively). Median ferritin levels were lower at the 4th month in late-preterm infants than term infants, but this difference was not significant after exclusion of three late- preterm infants who required iron therapy (49 mg/dl vs. 62 mg/dl, p=0.2). There was a tendency of higher frequency of anemia in late-preterm infants at 4 months (42.8% vs. 21.1%), but this was statistically insignificant (p=0.07). At the 2nd month of age, the median ferritin and hemoglobin levels of late-preterm infants were lower than those of term infants. Further studies with larger sample sizes are required to determine the need for earlier supplementation of iron in late-preterm infants.

***Key words:** late-preterm, iron, ferritin, hemoglobin, iron supplementation, anemia.*

The rate of late-preterm birth has been increasing over the last 15 years, from 7.3% to 9.1% in the United States, due to increasing numbers of multiple gestations[1,2]. Late-preterm infants are less mature -both physiologically and metabolically- than term infants[3]. Compared to term birth, late-preterm birth is associated not only with increased mortality but also with higher risk for several diseases and complications such as transient tachypnea of the newborn, respiratory distress syndrome, persistent pulmonary hypertension of the newborn, temperature instability, neonatal jaundice, hypoglycemia, feeding problems, and prolonged hospital stay[3,4]. Additionally, late-preterm infants have higher rates of hospital readmissions during the neonatal period[5]. Despite their increasing number and vulnerable nature, late-preterm infants are often treated by their health care providers and parents as though they are term infants[6].

Iron is an essential element for the function of rapidly growing and differentiating cells[7]. It is incorporated in the structure of heme-proteins such as hemoglobin (Hb), myoglobin and electron transfer proteins of the mitochondria. Its pivotal role in early brain growth and metabolism is well documented[8]. Iron deficiency anemia (IDA) and iron deficiency (ID) without anemia can have long-lasting detrimental effects on neurodevelopment[9]. Eighty percent of iron present in a healthy term neonate is accumulated during the third trimester. Since preterm infants miss out on this crucial period of iron deposition, they are at increased risk for ID, the damaging effects of which may not be rehabilitated despite intensive iron supplementation[10]. Other etiologic factors leading to ID in the preterm population are maternal ID, poorly controlled maternal diabetes, maternal smoking, intrauterine growth retardation, multiple gestations, preterm birth, acute and chronic fetal hemorrhage, uncompensated phlebotomy losses, and

Table I. Demographic and Clinical Features

	Term (n=38)	Late-Preterm (n=38)	p
Birth weight (g) (median/min-max)	3325(2550-4350)	2465(1520-3390)	<0.001
Gestational age (median/min-max)	38.3(37-41.2)	35.5(34-36.6)	<0.001
Gender n (%)	Female: 14 (36.8) Male: 24 (63.2)	Female: 20 (52.6) Male: 18 (47.4)	0.2
Route of birth n (%)	SVD: 5 (13.2) C/S: 33 (86.8)	SVD: 3 (7.9) C/S: 35 (92.1)	0.7
Maternal age (median/min-max)	31 (18-39)	30 (20-47)	
Multiple gestations n (%)	1 (2.7)	8 (26.6)	<0.001
NICU admission n (%)	-	10 (26.3)	0.002
Duration of hospitalization (median/min-max)	2 (2-7)	4 (2-14)	<0.001
Maternal Hb (g/dl) (median/min-max)	12 (9.4-14.6)	11.9 (9.2-14.3)	0.6
Maternal anemia (Hb <11 g/dl) n (%)	9 (24)	7 (23)	1

C/S: Cesarean section. SVD: Spontaneous vaginal delivery. NICU: Neonatal intensive care unit. Hb: Hemoglobin.

inadequate and delayed iron supplementation[11].

Iron supplementation is recommended at the 1st postnatal month for preterm infants and at the 4th-6th postnatal month for otherwise healthy term infants[12]. In our country, late-preterm infants are treated generally like term infants, and iron supplementation is begun at the 4th-6th postnatal month in these infants. We hypothesized that IDA is more common in late-preterm infants, and aimed to establish the optimum time for iron prophylaxis in this population.

Material and Methods

In this prospective study, 38 late-preterm (Group 1) and 38 term (Group 2) babies were enrolled in the study between April 2009 and April 2010. The control group infant was enrolled in the study if he/she was born on the same day as a late-preterm baby. If there was more than one term infant on the day of birth of the late-preterm infant, we randomly assigned a patient to the control group after selecting the name from among unlabelled envelopes. All mothers received routine iron supplementation during their pregnancy. Infants with a gestational age <34 weeks, cord Hb <13 g/dl (normal cord Hb 16.5±1.5 g/dl)[13], major congenital malformations, or a family history of hemoglobinopathy or other hemolytic anemias were excluded from the study. Informed consent of the parents was obtained before blood sampling.

Blood samples were obtained from the cord blood of each infant at birth. Blood samplings were repeated at the 2nd and 4th postnatal months. Hb concentrations were measured by spectrophotometric method, and ferritin levels were determined by using the electrochemiluminescence immunoassay method and Modular Analytics E170 analyzer. An EDTA sample was sent immediately for measurement of Hb and mean cell volume (Beckman Coulter LH-780, United States).

Three late-preterm infants whose Hb values were <8.5 g/dl with accompanying reticulocytosis at the 2nd postnatal month were started on iron supplementation. These infants were excluded from analyses at the 4th month.

Hemoglobin (Hb), ferritin and reticulocyte values were analyzed at birth and at the 2nd and 4th postnatal months. Late-preterm infants were further divided into subgroups with respect to neonatal intensive care unit (NICU) admission, having a mother with gestational diabetes mellitus (GDM) and multiple gestations. A subgroup analysis was performed by using nonparametric tests.

The Statistical Package for the Social Sciences (SPSS) 13.0 program was used for statistical analysis. Student's t-test was used when continuous variables were distributed normally. Mann-Whitney U test was the statistical test

Table II. Anthropometric Measurements at Birth and 2nd and 4th Months of Age

	Term (n=38)	Late- Preterm (n=38)	P
Birth weight (g)	3325(2550-4350)	2465(1520-3390)	<0.001
Height at birth (cm)	50(48-52)	45(42-51)	<0.001
Head circumference at birth (cm)	35(34-36)	33(31-36)	<0.001
Weight at the 2nd month (g)	5400(4450-6500)	4700(3800-6780)	<0.001
Height at the 2nd month (cm)	56(53-59)	55(32-62)	0.7
Head circumference at the 2nd month (cm)	39(37-41.5)	38(36-41)	0.02
Weight at the 4th month (g)	7280(6350-9100)	6280(4050-8510)	<0.001
Height at the 4th month (cm)	65(61-68)	64(58-68)	0.1
Head circumference at the 4th month (cm)	41(40-44)	41(39-44)	0.3

of choice when the distribution of continuous variables was non-normal. Categorical data were analyzed by using X^2 test.

Results

The median gestational age and birth weight of infants in Groups 1 and 2 were 35.5 vs. 38.3 weeks and 2465 vs. 3325 g, respectively (p<0.001) (Table I). Multiple births were more common in the late-preterm group (26.6% vs. 2.7%, p<0.001) (Table I). Median duration of hospitalization was longer in late-preterm infants (4 days vs. 2 days, p<0.001). Although none of the term babies was admitted to the NICU, 26.3% of late-preterm infants were admitted to NICU (Table I). Anthropometric measurements of the patients are given in Table II.

Cord ferritin, Hb and reticulocyte levels did not differ significantly between groups (Table III). However, at the 2nd month, median ferritin and Hb values were significantly lower in late-preterm infants (145 mg/dl vs. 195 mg/dl, p=0.001 and 10.1 g/dl vs. 11.6 g/dl, p<0.001, respectively) (Table III). Three infants with a Hb of <8.5 g/dl and reticulocytosis at the 2nd month were started on therapeutic doses of iron supplementation. These infants were excluded from the analysis of the data of the 4th month, but their Hb values had increased to normal at 4 months of age. Median ferritin and Hb levels were not statistically significantly lower in late-preterm infants at the 4th month (Table IV). The frequency of anemia was not significantly different at the 4th month between late-preterm and term infants (42.8% vs. 21.1%, p=0.07) (Table V). If the three infants who were excluded had been included in the analysis of the 4th month, the frequency of anemia at the 4th month would have been 47.3%, and this would have been significantly higher than that of the term group (p=0.04).

Of 67 mothers in the study population, 23% had anemia (Hb <11 g/dl); 24% of mothers with term infants and 23% of mothers with preterm infants had anemia (p=1). Hb and ferritin values of cord blood were not significantly different between groups. No correlation

Table III. Comparison of Ferritin, Hb and Reticulocyte Values of Cord Blood at 2nd Postnatal Month

	Term (n=38)	Late-preterm (n=38)	p
Cord ferritin (mg/dl) (median/min-max)	223(49-565)	242(46-767)	0.4
Cord Hb (g/dl) (median/min-max)	16.5(13.6-21)	17.6(14-21)	0.1
Cord reticulocyte (%, median/min-max)	3.5(0.6-5.4)	4.4(0.5-8.8)	0.1
Ferritin (mg/dl) (at the 2nd month) (median/min-max)	195(109-304)	145(33.6-368)	0.001
Hb (g/dl) (at the 2nd month) (median/min-max)	11.6(8.9-16.1)	10.1(8.4-15.8)	<0.001
Reticulocyte (%, at the 2nd month) (median/min-max)	1.7(0.6-3.3)	2.4(1.3-3.5)	<0.001

Hb: Hemoglobin.

Table IV. Comparison of Ferritin, Hb and Reticulocyte Values at 4th Postnatal Month

	Term (n=38)	Late-preterm (n=35)*	p
Ferritin (mg/dl) (at the 4th month) (median/min-max)	68(14-213)	49(6.6-198)	0.2
Hb (g/dl) (at the 4th month) (median/min-max)	11(9-13.4)	10.7(8.2-14.7)	0.3
Reticulocyte (%) (at the 4th month) (median/min-max)	1.2(0.6-2.2)	1.4(0.76-3.9)	0.5

*Three late-preterm infants were excluded from analysis at the 4th month.

was detected between maternal and fetal Hb (p=0.7).

Late-preterm infants (n=38) were further divided into subgroups with respect to NICU admission (n=10), having a mother with GDM (n=5) and multiple gestations (n=8). After the subgroup analysis, it was found that the median ferritin level at the 2nd month was 150 mg/dl in infants having a mother with GDM and 145.1 mg/dl in infants not having a mother with GDM (p=0.7). Similarly, at the 4th month, the median ferritin level was 44.5 mg/dl in infants having a mother with GDM and 49 mg/dl in infants not having a mother with GDM (p=0.9). Median Hb levels did differ significantly at the 2nd or 4th month in this subgroup.

The median ferritin level of late-preterm infants at the 2nd month who were admitted to the NICU was 132 mg/dl and that of infants who were not admitted to the NICU was 148.9 mg/dl (p=0.5). These values were 51 mg/dl and 43 mg/dl at the 4th month, respectively (p=0.1). Median Hb levels did differ significantly at the 2nd or 4th month in this subgroup.

Median ferritin level at the 2nd month in late-preterm infants with multiple gestations was 132 mg/dl and in singleton pregnancies was 147.3 mg/dl (p=0.5). Similarly, median ferritin level at the 4th month was 49 in infants with multiple pregnancies and 47 in singleton pregnancies (p=0.7). Median Hb levels did differ significantly at the 2nd or 4th month in this subgroup.

Discussion

In this study, we found that ferritin and Hb levels of late-preterm infants were lower than those of term infants at 2 months of age despite having similar cord blood values. Three (7.8%) late-preterm infants required iron therapy.

Preterm infants have decreased total body iron. This deficit increases with decreasing gestational age. Rapid postnatal growth, frequent phlebotomies and delayed enteral feeding aggravates ID in preterm infants. Preterm infants (born at <32 weeks' gestational age) who are fed human milk should receive 2-4 mg/kg/day of iron supplementation after 1 month of age[12].

Iron deficiency (ID) is also a common problem for term infants. Hay et al.[14] reported on a cohort of 284 term Norwegian infants, using the definitions provided by Dallman[13], and the prevalence of ID at 6 months of age was 4% and increased to 12% at 12 months of age. Iron content of breast milk is not only insufficient but also varies greatly[15]. Healthy

Table V. Frequencies of Anemia and Hypoferritinemia in Term and Late-Preterm Infants (excluding 2 infants receiving iron supplementation after the 2nd postnatal month)

	Term (n=38)	Late-Preterm (n=38)	p
Cord ferritin <75 mg/dl (n, %)	1 (2.6)	3 (7.9)	0.6
2nd month Hb <9.4 (n, %)	3 (7.9)	7 (18.4)	0.3
2nd month ferritin <50 mg/dl (n, %)	-	2 (5.3)	0.5
4th month Hb <10.5 (n, %) (*Term n=38, late-preterm infant n=35)	8 (21.1)	15 (42.8)	0.07
4th month ferritin <20 mg/dl (n, %)	3 (7.9)	3 (8.6)	1

* If infants started on iron treatment at the 2nd month had been included in the analysis of the 4th month, the rate of anemia would have increased to 44.7%, and the difference would have reached statistical significance (p<0.05).

term infants require relatively little amounts of iron early in life, but the iron demand is significant after 6 months of age.

Karaoğlu et al.[16] aimed to determine the prevalence of anemia in pregnant women in eastern Turkey. Eight hundred and twenty-three pregnant women had completed questionnaires and complete blood counts and serum iron, folate and vitamin B12 values. Prevalence of anemia was 27.1% in pregnant women. Of the anemic women, 50% had ID. The rate of anemia in pregnant women in our study was 23.8%. Hb and ferritin values of cord blood were not significantly different between groups. This fact indicates that a fetus has the capacity to achieve sufficient ferritin and Hb levels despite adverse maternal iron and hematologic status. No correlation was detected between maternal and fetal Hb.

Ziegler et al.[17] reported that 2.8% of breastfed infants develop IDA in first six months of life. The prevalence of ID among toddlers is 6.6-15.2% depending on ethnicity and socioeconomic status, whereas the prevalence of IDA is 0.9-4.4%. Both ID and IDA have long-lasting detrimental effects on neurodevelopment. Appropriate iron intake and methods for screening for ID and IDA are very important[18]. Akarsu et al.[19] reported that the prevalence of ID was 21.9% and that of IDA was 26.2% in children 4 months-2 years of age. Similarly, the prevalence of ID was 7.9% and of IDA was 21% at 4 months of age in term infants in our study. No single measurement is currently available that will characterize the iron status of a child. To identify ID or IDA, Hb concentration must be combined with measurements of iron status such as serum ferritin, reticulocyte Hb concentration, or serum transferring receptor (sTfR) concentrations[18].

Ferritin is the major iron storage protein. Low ferritin levels are seen only in ID states. Siddappa et al.[18] reviewed the literature to generate standard ferritin concentrations. Since most of the studies suffered from a small sample size, they combined these historical data with their contemporary data. They calculated the 5th, 25th, 50th, 75th, and 95 th centiles of serum cord ferritin for term and preterm control infants. In our study, we defined low ferritin if it was below the 5th percentile for age.

Prematurely born infants miss out on the period of active iron deposition in the third trimester. Insufficient iron stores and rapid growth rate render the preterm population vulnerable to ID. Twenty-five to 85% of preterm infants with gestational age <32 weeks or birth weight <1500 g suffer from ID during infancy[11]. Iron stores of infants are adequate for erythropoiesis until the birth weight is doubled. In our study, late-preterm infants doubled their birth weight at 2 months of postnatal age. In order to prevent ID, the American Academy of Pediatrics and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend iron supplementation at a dose of 2 mg/kg/day to all infants born at <32 gestational weeks either at discharge or on the 30th postnatal day. Iron prophylaxis is started at the 4th-6th month in healthy term newborns[5,20]. In most of the studies, term and late-preterm infants are evaluated in the same group. For this reason, data regarding postnatal hematocrit values in late-preterm infants are insufficient. In this study, cord Hb and ferritin values were similar in term and late-preterm infants; however, at the 2nd postnatal month, these parameters were significantly lower in late-preterm infants. This finding may be attributed to the rapid growth rate and phlebotomy losses. Three late-preterm infants with Hb values <8.5 g/dl were started on iron prophylaxis at the 2nd postnatal month. None of our patients received erythrocyte transfusion.

If the three infants with anemia at the 2nd month had been included in the analysis, the frequency of anemia would have been significantly higher in the late-preterm group than the term group at the 4th month. If the same anemic patients were not given iron therapy, their ferritin would have been lower at the 4th month, and it was probable that the median ferritin of late-preterm babies would have been lower than that of term babies at 4 months of age.

Late-preterm infants exhibit rapid postnatal growth and double their birth weight at 2 months of age. Earlier iron supplementation -probably at the 2nd postnatal month- may be indicated for the late-preterm population. A study with a larger sample size is needed to confirm our findings.

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