Seasonal and gender differences in hemoglobin value in infants at 5-7 months of age

S. Songül Yalçın, Raziye Dut, Kadriye Yurdakök, Elif Özmert

Unit of Social Pediatrics, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

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Our aims were to analyze the changes in hemoglobin (Hb) value according to gestational age, birth weight, sex, birth season, and weight gain and to detect distribution of Hb values among healthy infants, breastfed for at least four months and receiving routine health care. We conducted a descriptive study using the data of 469 healthy infants at 5-7 months of age in Hacettepe University İhsan Doğramacı Children's Hospital Well-Baby Clinic between 2001-2004. Infants with acute or chronic illness, exchange transfusion and those who had taken or were currently taking iron supplementation were not included into the study. Information regarding the child was obtained from hospital files. Infants with Hb value <10.5 g/dl and <9.5 g/dl were considered to have mild and moderate anemia, respectively. The mean Hb value was 10.7 g/dl (SD = 0.90). The prevalence of anemia was 41.4%. Boys had significantly lower Hb, hematocrit and mean corpuscular volume values and higher red cell distribution width values than girls. Infants born before 37 weeks of gestational age had moderate anemia more frequently. Anemia at 5-7 months of age was more frequent in infants born in spring and summer than in those born in fall and winter (49.2%, 26.8%, p<0.001). Birth weight was positively correlated with Hb value at 5-7 months of age (r=0.14, p=0.003). In the present study, female gender, at-term birth, birth in winter and fall, weight appropriate for gestational age, and regular weight gain showed the lowest risk for anemia development in infants aged 5-7 months with a breast-feeding period of more than four months.

***Key words:** hemoglobin, anemia, season, gender, infant.*

Iron deficiency anemia, the most prevalent nutritional problem in the world, adversely affects physical growth, cognitive and behavioral performance, the immune status, and morbidity from infections in infants. Therefore, early identification of the risk factors for iron deficiency anemia is essential for the prevention not only of anemia but also the numerous and long-term consequences caused by iron deficiency[1,2]. To detect anemia, age-appropriate cut-offs of hemoglobin (Hb) values are necessary and, if present, any physiological changes should be defined[3,4]. However, there have been a limited number of studies addressing the difference in Hb status between male and female infants[5]. There have been some studies about Hb changes by season in adults; however, no published study was found in infants[6-8]. This study was conducted to analyze the changes in Hb value by gestational age, birth weight, sex, and birth season and to detect the distribution of Hb values among healthy breastfed infants (exclusive breast-feeding period of more than four months) with no previous or current iron supplementation at 5-7 months of age who received routine health care at Hacettepe University İhsan Doğramacı Children's Hospital Well-Baby Clinic in Ankara, Turkey.

Material and Methods

Infants who had data available on Hb values at 5-7 months of age, who had received no iron supplementation previously or currently, and who were exclusively breastfed for at least four months were enrolled in the study between 2001-2004 at Hacettepe University İhsan Doğramacı Children's Hospital Well-Baby Clinic in Ankara. Infants with acute or chronic illness and history of exchange transfusion or with a family history of thalassemia were not included. This study was done with the permission of Hacettepe University Institute of Child Health, Department of Social Pediatrics.

Gestational age, birth weight, season of birth, gender, breast-feeding status, and Hb values at 5-7 months were obtained from the files. Anthropometry of infants, measured at birth, and at 5-7 and 9 months of age, were taken from the hospital files. Monthly weight gain rate was calculated by the difference between the weight (g) recorded at the 5-7th and 9th months and birth weight, divided by the decimal age of the infant (months).

Blood samples had been analyzed for complete blood counts [Hb, hematocrit (Htc), mean corpuscular volume (MCV), red cell distribution width (RDW)] by a Coulter Counter-S model (Coulter ®; STKS, Coulter Corp., Hialeah, FL, USA).

Infants were divided into three groups according to their Hb values at 5-7 months of age. Hb values at 5-7 months of age of ≥10.5 g/dl were accepted as normal[2,9,10]; between 9.5 and 10.4 g/dl as mild anemic; and <9.5 g/dl as moderate anemic.

Data were analyzed using SPSS for Windows (SPSS Inc., Chicago, IL, USA). The association between Hb values and the different variables was evaluated through bivariate analysis [chi-square test, Student t test and one way ANOVA (Dunnett t-test treats cases with normal Hb as a control and compares all groups against it), where appropriate] followed by multiple logistic regression analysis.

Results

The mean age was 6.3±0.3 months, and 48.2% were male (Table I). Mean ± standard deviation (SD) values were as follows: Hb 10.7±0.9 g/dl, Htc 31.8±2.5%, MCV 73.7±4.6 fl, and RDW 13.7±1.6%. Overall, 41.4% were found to have Hb levels <10.5 g/dl. We found 9.2 g/dl as the cut-off (-2 z score) value of Hb in cases with gestational age ≥37 weeks and birth weight ≥2500 g (Table II).

Boys had significantly lower Hb, Htc, MCV and higher RDW values than girls [10.5±0.9 g/dl, 10.8±0.9 g/dl for Hb (p=0.003); 31.3±2.6%, 32.2±2.4% for Htc (p=0.001); 72.5±4.5 fl, 74.9±4.3 fl for MCV (p<0.001); 13.9±1.6%, 13.4±1.5% for RDW (p=0.001); respectively]. Boys and girls had similar birth weight; however, postnatal growth gain from birth to 5-7 months of age was higher in boys than girls (799±133, 740±125 g/month; p<0.001).

Table I. General Characteristics of Infants

Characteristics	Mean ± SD
Age, months	6.25 ± 0.26
Male, n (%)	226 (48.2%)
Birth characteristics	
Gestational age, week	37.9 ± 1.2
Premature (<37 wk), n (%)	32 (6.9%)
Birth weight, kg	3.22 ± 0.49 kg
Low birth weight (<2.5 kg), n (%)	25 (5.4%)
Length, cm	(n=200) 49.5 ± 2.6
Head circumference, cm	(n=140) 34.3 ± 1.5
Growth at the 6th month	
Weight, kg	8.02 ± 0.90
Height, cm	69.9 ± 2.7
Head circumference, cm	43.4 ± 1.2
Complete blood count	
Hemoglobin, g/dl	10.7 ± 0.9
Hematocrit, %	31.8 ± 2.5
Mean corpuscular volume, fl	73.7 ± 4.6
Red cell distribution width, %	13.7 ± 1.6

Table II. Distribution (z score values) of Hemoglobin (Hb), Hematocrit (Htc), Mean Corpuscular Volume (MCV) and Red Cell Distribution Width (RDW) in Infants Aged 5-7 Months with Gestational Age ≥37 Weeks and Birth Weight ≥2500 Grams

Z score	Hb, g/dl	Htc, %	MCV, fl	RDW, %
n	422	348	395	354
-2	9.2	27.2	65.4	17.2
-1	10.0	29.7	69.9	14.9
0	10.8	32.0	74.6	13.2
1	11.6	34.4	78.0	12.2
2	12.5	36.6	80.3	11.6

Birth weight was associated with Hb value at 5-7 months (r=0.14, p=0.003). A negative correlation was detected between monthly weight gain rate from birth to 5-7 months and Hb value at 5-7 months (r=-0.12, p=0.019, respectively). However, monthly weight gain from 5-7 months to 9 months was positively correlated with Hb value at 5-7 months (r=0.10, p=0.041). Similarly, infants with Hb value <9.5 g/dl had lower monthly weight gain from 5-7 months to 9 months than infants with Hb value ≥10.5 g/dl (313±159, 402±154, g/month respectively; p=0.013).

The effect of birth season on Hb, MCV and RDW values in cases according to gestational age is displayed in Figure 1. Infants born in spring had the significantly lowest mean Hb value (10.5±0.9 g/dl) and those born in autumn had the significantly highest mean Hb value (11.0±0.9 g/dl) (p=0.01). Infants born in autumn had the significantly highest MCV value compared to those born in winter, spring and summer (75.0±4.3 fl, 73.6±4.0 fl, 73.2±4.8 fl, and 73.6±4.6 fl, respectively; p=0.045). RDW values did not change significantly with birth season.

When the factors that affect mild anemia were analyzed, univariate analysis detected birth season (spring and summer vs fall and winter) (odds ratio [OR]: 2.79, 95% confidence interval [CI]: 1.79-4.34) as the only risk factor for the cases with mild anemia (Hb=9.5-10.4 g/dl) (Table III). The birth season in mild anemia had remained significant after controlling for age, prematurity, birth weight, and sex (OR: 2.70, 95% CI: 1.71-4.26). Both univariate and multivariate analysis identified prematurity or/and low birth weight (OR: 5.156, 95% CI: 1.987-13.378) and male gender (OR: 2.644, 95% CI: 1.181-5.920) as the significant risk factors for moderate anemia (Hb <9.5 g/dl). No difference in birth season was detected in cases with moderate anemia (Table III).

Discussion

In the present study, low birth weight and high postnatal weight gain were found to be predictive of low Hb levels at the sixth month of age. The fact that lower birth weight increases the risk of anemia among infants could indicate a limited iron store and show the importance of the intervention measures

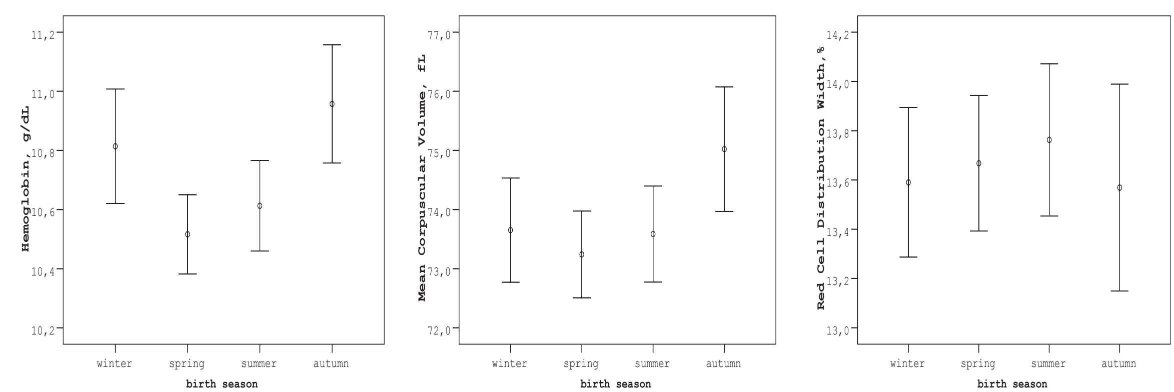

Fig 1. The mean values and 95% confidence interval of hemoglobin (a), mean corpuscular volume (b), and red cell distribution width (c) according to birth season.

Table III. Hemoglobin Value (g/dl) at 5-7 Months of Age by Birth Characteristics

	Hemoglobin value, n (%)			Univariate analysis*		Multivariate analysis*	
	≥ 10.5 (a)	9.5-10.4 (b)	< 9.5 (c)	b vs a	c vs a	b vs a	c vs a
n	275	161	33				
Birth season							
Spring and summer	155 (50.8)	126 (41.3)	24 (7.9)	2.79 (1.79-4.34)	2.07 (0.93-4.61)	2.70 (1.71-4.26)	1.89 (0.82-4.35)
Fall and autumn	120 (73.2)	35 (21.3)	9 (5.5)				
Sex							
Male	125 (55.3)	78 (34.5)	23 (10.2)	1.13 (0.76-1.67)	2.76 (1.27-6.02)	1.01 (0.67-1.53)	2.64 (1.18-5.92)
Female	150 (61.7)	83 (34.2)	10 (4.1)				
Gestational age, birth weight							
<37 wk and/or <2500 g	22 (50.0)	13 (29.5)	9 (20.5)	1.01 (0.49-2.06)	4.28 (1.77-10.33)	1.07 (0.50-2.30)	5.16 (1.99-13.38)
≥37 wk and ≥2500 g	251 (59.5)	147 (34.8)	24 (5.7)				
Gestational age							
<37 wk	18 (56.3)	7 (21.9)	7 (21.9)	0.65 (0.27-1.59)	3.81 (1.46-9.98)		
≥37 wk	255 (58.8)	153 (35.3)	26 (6.0)				
Birth weight							
<2500 g	11 (44.0)	8 (32.0)	6 (24.0)	1.25 (0.49-3.19)	5.29 (1.81-15.44)		
≥2500 g	262 (59.4)	152 (34.5)	27 (6.1)				

*Odds ratio (95%confidence interval).

(iron supplementation) in prenatal and infant health programs[2]. The observation that higher growth reduces iron reserves confirms results reported in other studies[2,9,11-13]. Similar to our study, Abshire[14] reported that infants with high growth rates should be assessed for anemia at six months of age.

In the present study, male infants at 5 to 7 months of age had a 2.8-fold higher risk of having Hb value <9.5 g/dl. These sex differences in iron status might be caused by a "true" iron deficiency. The observed sex differences at 5 to 7 months of age can be attributed simply to growth-related factors, as postnatal weight gain was higher in boys ($p<0.001$). Similarly, the gender difference in iron indicators as found in the Swedish, Icelandic and Norwegian studies has been suggested to be due to faster growth velocity in boys with higher iron requirement than in girls[5,15,16]. Domellöf et al.[5] reported that boys (compared with girls) had 0.2 g/dl lower mean Hb, 2.7 fl lower MCV, 40% lower ferritin, and 1.1 mg/L higher transferrin receptor (TfR) at four months, all of these seemingly suggesting greater iron deficiency in boys. Choi et al.[17] recently reported significantly higher TfR in male than in female infants at 4 to 6 months of age. These results also seem to indicate that erythropoietic activity and the iron requirement in male infants is greater than in female infants at this age.

With regards to the relation between birth season and anemia, differences in birth season in the present study were only significant in cases having Hb between 9.5-10.4 g/dl, and not in cases having Hb value <9.5 g/dl. Similar to Hb values, MCV values differed by season. Black et al.[7] reported seasonal variation in the iron status of adults in Mexico and significantly higher Hb concentrations in the post-harvest season in all sex and physiological status groups. They supposed that the post-harvest season was a time when more meat was eaten and there was an improvement in hemoglobin and iron status. Similarly, Backstrand et al.[6] found on the basis of their cross-sectional data that hematocrit values were lowest among the nonpregnant women whose measurements were made during early summer or late spring. Previous studies showed a seasonal pattern in Hb in pregnant women in Nepal, in which the prevalence of anemia was highest during and after the monsoon period[8,18]. In our study, Hb values in infants 5-7 months of age changed with birth season. Seasonality in iron variables might be due to the complexity of iron absorption, iron mobilization, erythropoiesis, and variation in diet. Interestingly, García-Casal et al.[19] reported that iron concentrations in algae were high and varied widely, depending on the species and time of year.

The World Health Organization (WHO) estimates that 39% of children younger than 5 years and 52% of pregnant women in developing countries are anemic, with half having iron deficiency anemia[2,20]. Anemia is regarded as a public health problem when the frequency of low Hb value is more than 5% in the population[2]. Anemia (Hb <10.5 g/dl) was detected in nearly half of the infants at 6 months of age in the present study. Diagnostic criteria for anemia in young infants are poorly defined in infants aged 6 months, and the high proportion of anemic children indicates the need to reevaluate the definition of anemia. In clinical practice, commonly used cut-off values for identifying iron deficiency and iron deficiency anemia at 6-12 months of age are Hb <11 g/dl, but these values are extrapolated from older age groups and may not be appropriate for infants[11,21]. Furthermore, no reference values based on breastfed infants have been published for any iron status variables, even though exclusive breast-feeding is recommended for the first 6 month of life[22]. Interpretation of the anemia is highly dependent on the reference data used and may be erroneous if the reference used does not adequately represent iron status. Moreover, reference data is based on a sample of predominantly formula-fed infants whose pattern of growth has been demonstrated to deviate substantially from that of healthy breastfed infants[23]. With age- and nutrition-appropriate references, relevant control of iron deficiency anemia could be done[4,24].

A cut-off value of Hb was reported to be <10.5 g/dl in iron-replete infants at 4-6 months[4,5,9]. We found a cut-off value (-2 z score) of 9.2 g/dl in breastfed infants (exclusive breast-feeding period ≥4 months) at 5-7 months of age. Our results are supported by a study of 1175 unselected British 8-month-old infants whose mean ± SD Hb was 11.7±1.1 g/dl, giving a cut-off value (-2SD) of 9.5 g/dl[11]. Better defined cut-off values for the indicators used are needed and, in particular, how they are correlated to functional outcomes including growth and development[3]. Domellöf et al.[4] found that growth variables were useful predictors of iron deficiency anemia at 6 months, as defined by the Hb response to iron. Because weight measurements are much less expensive than laboratory analyses, this information may be useful for targeting interventions. In the present study, only moderately anemic (Hb <9.5 g/dl) infants aged 5-7 months had a significantly low weight gain between 5-7 months and 9 months. One of the limitations of our study is that serum iron and ferritin parameters were not studied. However, we only aimed to detect seasonal and gender differences in Hb in breastfed infants whose exclusive breast-feeding period was more than four months. For MCV, –2 SD cut-off values were reported to be 68–70 fl at 6–9 months in a study of Finnish infants fed iron-fortified formula[25] and 73–71 fl for iron-replete, breastfed Swedish infants[4]. Our –2 SD cut-off value was 65.4 fl at 5-7 months of age, suggesting that some of these infants may have been iron deficient. However, we might overdiagnose some cases as iron deficiency anemia and give unnecessary treatment. Therefore, further studies are necessary to detect a cut-off value for iron deficiency anemia in infants 6 months of age.

In the present study, the prevalence of anemia observed is of severe public health significance, justifying the use of broad spectrum interventions to improve iron nutritional status, as recommended by WHO. Female gender, at-term birth, birth in winter and fall, weight appropriate for gestational age, and regular weight gain were shown to have the lowest risk for developing anemia in our population.

REFERENCES

1. Grantham-McGregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. J Nutr 2001; 131: 649S-666S; discussion 666S-668S.
2. World Health Organization/UNICEF/UNU. Iron Deficiency Anemia Assessment, Prevention, and Control. Geneva: WHO/NHD/01.3, 2001.
3. Hernell O, Lonnerdal B. Is iron deficiency in infants and young children common in Scandinavia and is there a need for enforced primary prevention? Acta Paediatr 2004; 93: 1024-1026.
4. Domellöf M, Dewey KG, Lonnerdal B, Cohen RJ, Hernell O. The diagnostic criteria for iron deficiency in infants should be reevaluated. J Nutr 2002; 132: 3680-3686.

5. Domellöf M, Lonnerdal B, Dewey KG, Cohen RJ, Rivera LL, Hernell O. Sex differences in iron status during infancy. Pediatrics 2002; 110: 545-552.
6. Backstrand JR, Allen LH, Black AK, de Mata M, Pelto GH. Diet and iron status of nonpregnant women in rural Central Mexico. Am J Clin Nutr 2002; 76: 156-164.
7. Black AK, Allen LH, Pelto GH, de Mata MP, Chávez A. Iron, vitamin B-12 and folate status in Mexico: associated factors in men and women and during pregnancy and lactation. J Nutr 1994; 124: 1179-1188.
8. Bondevik GT, Lie RT, Ulstein M, Kvale G. Seasonal variation in risk of anemia among pregnant Nepali women. Int J Gynaecol Obstet 2000; 69: 215-222.
9. Domellöf M, Cohen RJ, Dewey KG, Hernell O, Rivera LL, Lonnerdal B. Iron supplementation of breast-fed Honduran and Swedish infants from 4 to 9 months of age. J Pediatr 2001; 138: 679-687.
10. Michaelsen KF, Milman N, Samuelson G. A longitudinal study of iron status in healthy Danish infants: effects of early iron status, growth, velocity and dietary factors. Acta Pædiatr 1995; 84: 1035-1044.
11. Emond AM, Hawkins N, Pennock C, Golding J. Haemoglobin and ferritin concentrations in infants at 8 months of age. Arch Dis Child 1996; 74: 36-39.
12. Hadler MC, Colugnati FA, Sigulem DM. Risks of anemia in infants according to dietary iron density and weight gain rate. Prev Med 2004; 39: 713-721.
13. Wharf SG, Fox TE, Fairweather-Tait SJ, Cook JD. Factors affecting iron stores in infants 4-18 months of age. Eur J Clin Nutr 1997; 51: 504-509.
14. Abshire TC. The anemia of inflammation. Pediatr Clin North Am 1996; 43: 623-637.
15. Hay G, Sandstad B, Whitelaw A, Borch-Iohnsen B. Iron status in a group of Norwegian children aged 6–24 months. Acta Paediatr 2004; 93: 592-598.
16. Thorsdottir I, Gunnarsson BS, Atlasdottir H, Michaelsen KF, Palsson G. Iron status at 12 months of age - effects of body size, growth and diet in a population with high birth weight. Eur J Clin Nutr 2003; 57: 505-513.
17. Choi JW, Pai SH, Im MW, Kim SK. Change in transferrin receptor concentrations with age. Clin Chem 1999; 45: 1562-1563.
18. Jiang T, Christian P, Khatry SK, Wu L, West KP Jr. Micronutrient deficiencies in early pregnancy are common, concurrent, and vary by season among rural Nepali pregnant women. J Nutr 2005; 135: 1106-1112.
19. García-Casal MN, Pereira AC, Leets I, Ramírez J, Quiroga MF. High iron content and bioavailability in humans from four species of marine algae. J Nutr 2007; 137: 2691-2695.
20. DeMaeyer E, Adiels-Tegman M. The prevalence of anaemia in the world. World Health Stat Q 1985; 38: 303-316.
21. Centers for Disease Control and Prevention (CDC). Recommendations to prevent and control iron deficiency in the United States. Morb Mortal Wkly Rep 1998; 47: 1-29.
22. World Health Assembly (WHA). Infant and Young Child Nutrition. Resolution WHA 54.2. Geneva, Switzerland: WHO; 2001.
23. de Onis M, Onyango AW. The Centers for Disease Control and Prevention 2000 growth charts and the growth of breastfed infants. Acta Paediatr 2003; 92: 413-419.
24. Zetterström R. Iron deficiency and iron deficiency anaemia during infancy and childhood. Acta Paediatr 2004; 93: 436-439.
25. Saarinen UM, Siimes MA. Developmental changes in red blood cell counts and indices of infants after exclusion of iron deficiency by laboratory criteria and continuous iron supplementation. J Pediatr 1978; 92: 412-416.