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Original Article

Evaluation of iron deficiency anemia in preterm and low birth weight infants

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Abstract

Objective: Anemia affects 571 million women of reproductive age and 269 million children under the age of five, constituting a significant global public health concern. In line with the WHO/UNICEF 2030 Sustainable Development Goals, it is aimed to reduce the prevalence of anemia worldwide, especially in women of reproductive age and children, by 15% in 2025. This study evaluated preterm and low-birth-weight infants for iron deficiency anemia.

Methods: This study included preterm and low-birth-weight infants followed in our clinic between 2020 and 2022 (24 months). It was a retrospective cohort study. Complete blood count results obtained at the time of birth and/or during hospitalization in the neonatal intensive care unit were evaluated. Complete blood count, ferritin, and iron values routinely measured in the outpatient clinic at 12-month control appointments were also evaluated.

Results: We followed 203 cases between 1 January 2020 and 1 January 2022. While 50.2% (n=102) of the patients were male, 49.8% (n=101) were female and the cases included 12 twins (5.9%). Data analysis revealed that 6.4% of the infants were extremely early preterm (n=13), 19.7% were very early preterm (n=40), 18.7% were moderately preterm (n=38), and 55.1% were late preterm (n=112). Furthermore, 69.4% had low birth weight (n=141), 63% had very low birth weight (n=128), and 6.4% had extremely low birth weight (n=13). When hemoglobin values were compared between infants given and not given iron prophylaxis, statistical significance was found in terms of anemia (p=0.04).

Conclusion: To prevent anemia in preterm and low-birth-weight children, iron prophylaxis should be started in the early period. Families should be informed about immunization, nutrition, and follow-up. It is important to intervene when anemia develops with close cooperation among neonatologists, pediatricians, and family physicians.

Keywords: Anemia, exclusive breastfeeding, infant, iron deficiency, low birth weight, preterm.

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INTRODUCTION

Postoperative peritoneal adhesions that occur after abdominal surgery are one of the current problems Anemia is defined as values of hemoglobin or erythrocytes of two standard deviations below the normal mean for age and sex. The World Health Organization (WHO) has urged countries to intensify their efforts to reduce the prevalence of anemia in women of reproductive age, with the objective of halving the prevalence by 2025. Despite some progress, however, the global community has not yet reached the desired level of achievement in reducing anemia. Anemia affects 571 million women of reproductive age and 269 million children under the age of five, constituting a significant global public health concern. The most common type of anemia is nutritional anemia. Nutritional anemia is a condition in which the hemoglobin concentration in the blood is abnormally low with a deficiency of one or more nutrients. Although nutritional anemia is most commonly due to iron deficiency, it may also be due to deficiencies of vitamins and minerals such as vitamin B12, folate, zinc, or copper. In the last 20 years, iron deficiency has become an important public health problem. It was estimated that 30% of the world's population was anemic in 2012, mostly due to iron deficiency. In line with the WHO/UNICEF 2030 Sustainable Development Goals, it is aimed to reduce the prevalence of anemia worldwide, especially in women of reproductive age and children, by 15% in 2025 (1-5).

Iron is widely used in the human body. All body systems are affected by its deficiency and many related systemic signs and symptoms may occur. Iron myelination is necessary in the synthesis of neurotransmitters such as dopamine, norepinephrine, and serotonin. Iron deficiency anemia (IDA) negatively affects cognitive and behavioral test results in children and adolescents (6-8).

According to the WHO, infants with a gestational age of ≤37 weeks are considered to be preterm births. These infants are further categorized as extremely early preterm (less than 28 weeks), very early preterm (28 to 32 weeks), moderately preterm (32 to 34 weeks), and late preterm (34 to 37 weeks). The term "low birth weight" (LBW) is used to describe infants for whom the first recorded weight within hours of birth is<2500 g. Infants of very low birth weight (VLBW) weigh<1500 g and infants of extremely low birth weight (ELBW) weigh<1000 g (9).

IDA is common in both preterm and low-birth-weight infants. Premature and low-birth-weight infants have higher iron requirements due to increased postnatal growth compared to term infants. Therefore, they are at higher risk of developing iron deficiency or IDA (10).

In addition, physiological factors such as short erythrocyte lifespans in preterm infants, higher fetal hemoglobin levels compared to term infants, endogenous erythropoietin (EPO) deficiency, low iron stores, and pathological factors such as iatrogenic phlebotomy or oxidative hemolysis due to sepsis influence the development of anemia in these infants (11-13).

Our study aimed to evaluate preterm and low-birth-weight infants followed in our unit for IDA.

MATERIALS AND METHODS

Ethics approval was received from the ethics committee of our hospital (Number: E-46059653-020; Date: 06-15-2022). The study was conducted in accordance with the Declaration of Helsinki.

Preterm and low-birth-weight infants followed in our clinic between 1 January 2020 and 1 January 2022 were included in this study, which was planned as a retrospective cohort study. Complete blood count (CBC) results obtained at the time of birth and/or during hospitalization in the neonatal intensive care unit were evaluated. CBC, ferritin, and iron values routinely measured in the outpatient clinic at 12-month control appointments were also evaluated. By interviewing the mothers and examining hospital records, the status of infants receiving or not receiving anemia prophylaxis between the ages of 0 and 12 months, breastfeeding durations, and transitions to complementary foods were evaluated. Data were also collected regarding whether formula support was given to the infants or a breast milk-enriching protein supplement (euprotin) was used and whether blood transfusions were administered. Based on these findings, the preterm and low-birth-weight infants born in our region were evaluated in terms of iron deficiency.

Statistical analysis

IBM SPSS Statistics 21.0 (IBM Corp., Armonk, NY, USA) software was used. The normal distribution of the parameters was analyzed using the Shapiro Wilk test. In addition to using descriptive statistics (mean, standard deviation, frequency), for the comparison of the quantitative data of parameters with a normal distribution, One Way Anova test was used in intergroup comparisons as well as Tukey's HSD test and Tamhane's T2 test in determining the group that causes the change. For non-normally distributed parameters, Kruskal Wallis test was used in intergroup comparisons and Mann Whitney U test in determining the group that causes the difference. Student-t test was utilized in comparing normally distributed parameters between two groups, and Mann Whitney U test in comparing the non-normally distributed parameters between two groups. Pearson correlation analysis was applied to analyze the correlations between normally distributed parameters. The level of significance was accepted as $p<0.05$

RESULTS

We followed 203 cases between 1 January 2020 and 1 January 2022. While 50.2% (n=102) of the patients were male, 49.8% (n=101) were female and the cases included 12 twins (5.9%). Data analysis revealed that 6.4% of the infants were extremely early preterm (n=13), 19.7% were very early preterm (n=40), 18.7% were moderately preterm (n=38), and 55.1% were late preterm (n=112). Furthermore, 69.4% had LBW (n=141), 63% had VLBW (n=128), and 6.4% had ELBW (n=13). The average birth weight was 1967.7±0.24 g and average gestational age was 33 weeks. Among all analyzed infants, the lowest weight was 585 g, the highest weight was 3130 g, the lowest gestational age was 22 weeks, and the highest gestational age was 37 weeks. Eight infants (3.9%) died after delivery or during neonatal intensive care. Respiratory support (i.e., noninvasive or mechanical ventilation) was used in 73.3% (n=149) cases due to respiratory distress. Formula support was given to 71.4% (n=145) of the infants due to insufficient breast milk, to ensure harmony between the mother and infant, or for other reasons. A breast milk-enriching protein supplement (euprotin) was used in 15.7% (n=32) of the cases. Necrotizing enterocolitis (NEC) developed in 9.8% (n=20) of cases during neonatal intensive care. The prognosis of the infants who developed NEC was good. Total parenteral nutrition support was given to 26.1% (n=53) of the infants. Blood transfusions (erythrocyte suspensions) were given to 13.7% (n=28) in the neonatal intensive care unit. EPO treatment was given to 5.4% (n=11). Intracranial hemorrhage (i.e., periventricular hemorrhage or intraventricular hemorrhage) was detected in 4.4% (n=9) in the neonatal intensive care unit. Two of those patients had grade 3 periventricular/intraventricular hemorrhage. Posthemorrhagic hydrocephalus developed in one patient and an external ventricular drain was inserted in the Neurosurgery Unit. Surfactant treatment (i.e., Curosurf or Survanta) was given to 24.1% (n=49) in the neonatal intensive care unit. At 12 months of follow-up, it was observed that 78.3% (n=159) had received iron prophylaxis regularly. It was also observed at 12 months of follow-up that 76.8% (n=156) had received vitamin D prophylaxis regularly. When breastfeeding durations were evaluated retrospectively at 12 months of follow-up, it was found that 56.6% (n=115) of the mothers continued to breastfeed their infants and 43.4% (n=88) had discontinued breastfeeding before the 6th month. The mothers breastfed their infants for an average of 4.5 months. Furthermore, it was found that 52.3% (n=107) infants had started complementary feeding at the 6th month, while 47.7% (n=96) had started before the 6th month. The mean time to start complementary feeding was 5.5 months (Table 1). The mean hemoglobin value of all infants at the time of the first CBC was 16.3±0.2 g/dL (range: 8.8-20.4 g/dL). The mean hemoglobin value in CBCs performed at 12 months of follow-up was 10.9±0.3 g/dL (range: 7.8-13.9 g/dL). The mean hematocrit value from the first CBC was 49.8±0.2% (range: 30.1-62.6%), and that at 12 months of follow-up was 38.9±0.4% (range: 28.8-41.2%) (Table 2). When hemoglobin values were compared between children who did and did not receive iron prophylaxis, statistical significance was found in terms of anemia (p=0.04). No statistical significance was found upon comparing the mothers' breastfeeding durations (>6 months) and the hemoglobin values of the infants (p=0.38). No statistical significance was found upon comparing the time to start complementary feeding (<6 months) and the hemoglobin values of the infants (p=0.54).

DISCUSSION

Preterm infants need iron supplementation for brain and cognitive development in the postnatal period. Iron deficiency and IDA can affect dendritic growth, synaptogenesis, myelination, and neurotransmitter functions (10).

Table 1. Characteristics of the patients

Characteristics		n	%	p
Sex	**Male**	102	50.2	0.24
	Female	101	49.8	0.32
Twins		12	5.9	0.44
Preterm	**Extremely early**	13	6.4	0.35
	Very early	40	19.7	0.28
	Moderately	38	18.7	0.38
	Late	112	55.1	0.45
Birth weight	**LBW**	141	69.4	0.12
	VLBW	13	6.4	0.18
	ELBW	128	63	0.23
Comorbidities	**RDS**	149	73.3	0.87
	NEC	20	9.8	0.78
	PVH/IVH	9	4.4	0.92
	ROP	8	3.9	0.68
	BPD	6	2.9	0.66
Breastfeeding duration	**<6 months**	88	43.4	0.44
	6-12 months	115	56.6	0.38
Start of complementary feeding	**<6 months**	107	52.3	0.54
	≥6 months	96	47.7	0.45
Blood transfusion	**Yes**	28	13.7	0.34
	No	175	86.3	0.56
Erythropoietin (EPO)	**Yes**	11	5.4	0.24
	No	192	94.6	0.46
Surfactants	**Yes**	49	24.1	0.58
	No	154	75.9	0.56
Euprotin	**Yes**	11	5.4	0.47
	No	192	94.6	0.29
Respiratory support (CPAP, mechanical ventilation)	**Yes**	149	73.3	0.35
	No	54	26.7	0.45
Operation	**Yes**	19	9.3	0.32
	No	184	90.7	0.65
Iron prophylaxis	**Yes**	159	78.3	**0.04**
	No	44	21.7	0.36
Vitamin D prophylaxis	**Yes**	156	76.8	0.54
	No	147	23.2	0.49

Abbreviations: LBW: Low Birth Weight; VLBW: Very Low Birth Weight; ELBW: Extremely Low Birth Weight; RDS: Respiratory Distress Syndrome; NEC: Necrotizing Enterocolitis; PVH/IVH: Periventricular Hemorrhage/Intraventricular Hemorrhage; ROP: Retinopathy of Prematurity; BPD: Bronchopulmonary Dysplasia; CPAP: Continuous Positive Airway Pressure. Values of p<0.05 are significant; Mann-Whitney U test

In Turkey, within the scope of the "A Turkey Like Iron" project, it is recommended to begin administering drops containing elementary iron to preterm infants at 2 mg/kg/day from the 2nd month of life and continue iron prophylaxis until 1 year of age. According to data from the WHO, 98% of the iron requirements of infants aged 6-23 months should be met by complementary foods. Complementary foods can satisfy this level of iron requirement. These foods should include large amounts of meat, fish, and eggs and foods rich in vitamin C. One common mistake in infant nutrition is providing cow milk to infants in the early period and in excess. The absorption of iron from cow milk is much lower than that from breast milk. Cow milk often replaces more iron-rich foods in the diet, and the calcium and casein in cow milk may impair iron absorption (14,15).

Randomized controlled studies have shown that iron intake of 1-3 mg/kg/day (or 1-2 mg for LBW and 2-3 mg for marginally VLBW infants) is required to effectively prevent iron deficiency. There is

Table 2. Laboratory results of patients

Variable	Mean±SD (range): 1st measurements	Mean±SD (range): 12-month follow-up
Erythrocyte count (×10^6)	4.45±0.72 (2.10-6.63)	5.32±0.72 (3.2-6.84)
Hemoglobin (g/dL)	16.3±0.2 (8.8-20.4)	10.9±0.3 (7.8-13.9)
Hematocrit (%)	49.8±0.2 (30.1-62.6)	38.9±0.4 (28.8-41.2)
MCH (pg)	35.5±0.3 (23.4-45.7)	26.6±0.2 (16.6-37.8)
MCV (fL)	106.7±0.7 (72.3-131.6)	78.9±0.2 (49.4-111)
RDW (%)	15.9±0.4 (12.5-20.3)	15.1±0.4 (12.1-22.8)
Ferritin (ng/mL)	-	41.8±1.4 (30-75)
Iron (µg/dL)	-	57.2±1.2 (4.3-247.5)
Iron binding capacity (µg/dL)	-	381.6±7.7 (145-550)
Transferrin saturation (%)	-	7.9±0.73 (1.4-40)

recent evidence that such levels of iron intake will specifically prevent behavioral problems and other neurodevelopmental outcomes and some of the adverse health outcomes associated with LBW (16).

In a study by Rocha et al. it was determined that there was a relationship between mortality and early anemia in ELBW infants (17).

In our study, all preterm and low-birth-weight infants were started on iron prophylaxis in the recommended months. Their families reported that prophylaxis was given regularly in 78% of cases. When the group receiving iron prophylaxis regularly was compared to the other group in terms of hemoglobin values at the 12th month, a statistically significant difference was observed between the groups ($p<0.05$).

In line with the WHO's targets for 2025, we recommend exclusive breastfeeding to families for the first 6 months (4). In this study, we observed that more than 50% of the families continued breastfeeding as recommended. We did not detect a statistically significant difference between breastfeeding duration and the presence of anemia. This might be attributed to the mothers generally being anemic themselves with inadequate nutritional status.

In the meta-analysis conducted by Jin et al. it was emphasized that starting iron prophylaxis in the early period and initiating enteral nutrition for preterm and low-birth-weight infants will reduce the development of anemia (18). In our unit, enteral nutrition is started in the early period and iron prophylaxis is started at the end of the first month.

In this study, 3.9% of the infants (n=8) followed in the intensive care unit died. Of those infants, 3% (n=6) were ELBW and 0.9% (n=2) were LBW. These infants died in the neonatal period and all of them had clinical signs of respiratory distress syndrome (RDS). They received mechanical ventilation and surfactant support. In 3 cases, blood transfusions were performed in the intensive care unit. Although prematurity and inadequate lung development were considered to be major factors in these deaths, it is possible that anemia might have also increased the likelihood of death. We could not start prophylaxis in these cases because the infants were under 1 month of age.

In a study by Ferri et al. IDA was found in 48% of preterm infants. In these cases, increased cow milk consumption in the 6th month, low maternal age, high number of pregnancies, and being small for gestational age were found to be associated with anemia (19). In our region, there are high numbers of Syrian refugees and individuals under temporary protection, and the education level of the mothers in this study was generally low. We observed that in a significant portion of cases in our study, exclusive breastfeeding was discontinued at an early stage (<6 months) and the introduction of cow milk occurred early. We also found that mothers tended to have high numbers of pregnancies and the period between pregnancies was generally insufficient (<18 months).

Maternal anemia during and before pregnancy is associated with preterm birth, LBW, and the infant being small for gestational age (20). Maternal anemia is recognized as a risk factor for pregnancy outcomes, especially in the first trimester of pregnancy. It has been emphasized that interventions performed during this period may be particularly meaningful in terms of pregnancy outcomes (21). In the first 1000-day period, and especially during pregnancy, the mother's consumption of iron-rich foods will also protect the fetus from anemia. This will be important for the subsequent brain development of the infant (22).

The nutritional status of the mothers of the infants we followed was generally not good. Since mothers in our region have many children and frequent pregnancies, we assumed that their access to meat products during pregnancy and while breastfeeding was not sufficient.

A study comparing early and late initiation of iron supplementation found no difference in cognitive outcomes but did report an increased rate of abnormal neurological findings in the late iron group at age 5. Studies comparing high and low iron doses have shown no significant hematological benefits of exceeding the "standard" iron doses (i.e., 2-3 mg/kg/day) (23).

Anemia is associated with neurodevelopmental delays and brain damage in infants and young children, but whether preterm anemia has a similar effect in newborn preterm infants is still unknown. A cohort study from China found no association between early anemia and brain damage. Early anemia was not associated with neurodevelopment including behavioral ability in VLBW infants (24).

In the design of our study, there was no neurodevelopmental follow-up for the preterm infants. If we had conducted developmental tests at 12 months of follow-up or later, we could have compared infants using iron prophylaxis with other infants.

For preterm infants, it is recommended to start complementary feeding between the chronological ages of 5 and 8 months (25). In a randomized controlled trial, the time of initiation of solid foods had no effect on ferritin levels or other hematological parameters important for iron status in the first year of life of VLBW preterm infants. However, a higher incidence of iron deficiency was seen at 12 months of corrected age in the group that received solid foods earlier. Parents should be informed about the importance of iron supplementation and the early introduction of meat products and iron-rich solid foods through nutritional counseling. The recommended timing of the introduction of complementary feeding for preterm infants varies among pediatricians. Contradictory advice is often given to mothers and more studies are needed to determine the optimum age (26).

We found that mothers were uninformed about appropriate practices for complementary feeding and 52% of them switched to complementary feeding before the 6th month. In complementary feeding, we also observed that meat products were introduced late (>9th month). We did not detect a statistically significant difference between the time of starting complementary feeding and anemia and this may be attributed to the late introduction of meat products in our region.

CONCLUSION

In order to prevent anemia in preterm and low-birth-weight children, iron prophylaxis should be started in the early period. Families should be informed about immunization, nutrition, and follow-up. It is important to intervene when anemia develops with close cooperation among neonatologists, pediatricians, and family physicians.

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