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Original Article

Iron profiles of preterm infants at two months of chronological age

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Abstract

Background Preterm infants are vulnerable to iron deficiency (ID) due to lack of maternal iron stores, repeated phlebotomy, and the body's increased demand for iron during growth. The risk of ID increases at 2 months of age, when hemoglobin (Hb) levels start to decrease.

Objective To describe iron profiles in preterm infants at 2 months of chronological age (CA).

Methods This cross-sectional study was conducted in 2-month-old infants, born at 32-36 weeks of gestational age, and who visited the Growth and Development Clinics at Cipto Mangunkusumo, Fatmawati, or Budi Kemuliaan Hospitals. Parental interviews and medical record reviews were done during the clinic visits. Complete blood count, blood smear, serum iron (SI), total iron binding capacity (TIBC), transferrin saturation (Tfsat), and ferritin level tests were performed.

Results Eighty-three subjects were enrolled in this study. The prevalence of iron deficiency anemia (IDA) was 6% and that of ID was 10%. The lowest Hb level found in IDA infants was 6.8 g/dL, the lowest ferritin level was 8.6 ng/mL. Median values for the other tests were: SI 48 μg/dL, TIBC 329μg/dL, and Tfsat 17%. Subjects with IDA were all male (5/5), mostly achieved more than twice their birth weight (4/5), were non-iron supplemented (3/5), born to mothers with low educational background (3/5), and of low socioeconomic status (3/5).

Conclusion The prevalence of IDA is 6% and that of ID is 10%. Most subjects with ID and IDA have low SI, high TIBC, low Tfsat, and low ferritin level. Most of the all-male IDA subjects weigh more than twice their birth weight, are non-iron supplemented, and born to mothers with low educational background and low socioeconomic status. **[Paediatr Indones. 2016;56:277-84. doi: 10.14238/pi56.5.2016.277-84]**.

Keywords: *anemia; iron deficiency; iron profile; preterm infants*

Preterm birth is a global concern, since it causes death mainly in children below 5 years of age.[1] In Indonesia, the preterm birth rate was reported to be 15.5 per 100 live births, making Indonesia the 5th highest country for preterm births in 2013.[2] Preterm birth has been associated with many morbidities, including anemia. Anemia in preterm infants is mainly caused by the increased demand for iron due to rapid growth, blood loss due to phlebotomy, and physiological decreases in Hb level at the age of 4-8 weeks CA.[3–5] Low body iron stores in preterm infants may be related to maternal iron status, birth weight, gestational age at birth, cord clamping time, iron supply, and gender.[6]

The prevalence of IDA varies among studies, depending on differences in preterm age, iron supplementation, nutritional support, and age at the time of blood collection. The prevalence of IDA was 26.5% in a Brazilian population aged 12 months, 42.8% in a Turkish population aged 4 months, and 9.9% in a Swedish population aged 6 months.[7–9] Iron deficiency

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may irreversibly impact motor development, as well as cognitive, behaviourial, and hearing function, in addition to the maturation of myelin.[10–12] In order to prevent the clinical manifestations of IDA, iron profiles in preterm infants should be obtained. We aimed to desrcibe the iron profiles in preterm infants at 2 months of age who were born at 32-36 weeks gestational age (GA), as well as any associated factors.

Methods

This cross-sectional study was performed in the Growth and Development Clinics of Cipto Mangunkusumo Hospital (CMH), Fatmawati Hospital, and Budi Kemuliaan Hospital from May to December 2014. Complete blood counts (CBC), erythrocytes indexes (mean corpuscular volumes/MCV, mean corpuscular hemoglobin/MCH, mean corpuscular hemoglobin concentration/MCHC) and iron profile (SI, ferritin, TIBC, and Tfsat) were performed at the Clinical Pathology Laboratory of CMH. Inclusion criteria were infants, aged 2 months (chronological age/CA), and born at 32-36 weeks GA. Exclusion criteria were infants with infection, diarrhea, cow's milk protein allergy as diagnosed based on history-taking, physical examination, and simple laboratory examination, major congenital anomalies, hemato-oncology-related diseases, those treated with oral or parenteral iron therapy, those whose parents refused to provide informed consent, or lacked maternal Hb records.

Subjects visited the Growth and Development Clinic for routine examinations. Some of the data were obtained from parental interviews and medical records. Venous blood specimens were obtained and sent to the Clinical Pathology Laboratory at CMH within one hour of drawing. Complete blood counts and iron profile results were available within 48 hours and reported to parents by email, mail, and/or telephone (per request). The cut-off points used in this study were: 45 ng/mL for ferritin level, 28% for Tfsat, and 9.8 g/dL for Hb. Iron depletion was diagnosed as ferritin level below the cut-off. Iron deficiency was diagnosed as ferritin level and/or Tfsat below the cut-offs. Iron deficiency anemia was diagnosed in iron deficient subjects as Hb level <9.8 g/dL.

Subjects diagnosed with iron deficiency and IDA were treated with 4-6 mg/kg BW/day of an elemental iron preparation and sent to the nearest health care facility or the original clinic for follow up. For subjects with normal iron test results, iron supplementation with 2-3 mg/kg BW/day of an elemental iron preparation was suggested. This study was approved by the Medical Research and Hospital Ethics Committee of Universitas Indonesia Medical School/Dr. Cipto Mangunkusumo Hospital, Jakarta.

Results

Of 83 subjects, 51% were male. Subjects' birth weights ranged from 1,180 g to 2,550 g. The majority of subjects had mothers >20 years of age (93%) with middle to high educational background (71%) and low socioeconomic status (66%). Maternal anemia was found in 27% of subjects.

Sixteen percent of our subjects were exclusively breastfed and 40% were iron-supplemented. Most subjects (76%) who received iron supplementation had good compliance. Subjects' nutritional statuses were undernourished (19%), malnourished (8%), and well nourished (73%). During hospitalization, 27% of subjects received packed red cell (PRC) transfusions. The prevalence of IDA in this study was 6% and the prevalence of iron deficiency was 10%.

Subjects' hematology and iron profiles are shown in **Table 1**. Anemia, defined as Hb level <9.8g/dL, was found in 70% of subjects. Most anemic subjects had normocytic normochromic anemia (54/58). Subjects with IDA mostly had microcytic hypochromic RBCs in blood smears (3/5), and all subjects with ID had normocytic normochromic RBCs.

We recorded the following characteristics of subjects: sex, birth weight, exclusive breastfeeding status, infant nutritional status, infant weight gain, PRC transfusion history, compliance to iron supplementation, and maternal factors including anemia status, age, educational level, and socioeconomic status (**Table 2**). All IDA subjects (5/5) and most ID subjects (7/8) either had poor compliance with iron supplementation or did not have iron supplementation.

Table 1. Hematology and iron profiles based on iron status

Variables	ID (n=8)	IDA (n=5)	Normal iron status (n=70)
Median Hb (range), g/dL	10.5 (9.1-12)	8.4 (6.8-9.4)	8.9 (6.8-12.8)
Median Ht (range), vol%	31.6 (25.2-34.5)	23.8 (21.5-27.8)	26.7 (20.1-37.1)
Median MCV (range), pg	82.7 (75.8-89.1)	84.5 (70-93)	86.7 (70 -98.7)
Median MCH (range), fl	28.5 (26.2-31)	28.4 (25-31.5)	29.1 (25.3-32.9)
Median MCHC (range), g/dL	34.5 (32.4-37)	33.6 (31.6-35)	33.5 (31.2-39)
Median SI (range), µg/dL	68 (50-87)	48 (27-115)	82 (27-195)
Median TIBC (range), µg/dL	280.5 (225-298)	329 (225-364)	233 (101-397)
Median Tf saturation (range), %	24.5 (17-38)	17 (8-35)	34 (11-100)
Median serum ferritin (range), ng/mL	28 .1 (16.5-44.7)	30.8 (8.6-37.3)	171.5 (49.4-1425)

Table 2. Factors potentially related to iron deficiency

Variables	ID (n=8)	IDA (n=5)	Normal iron status (n=70)
Gender, n			
Male	3	5	34
Female	5	0	36
Birth weight, n			
< 1,500 grams	0	1	12
≥ 1,500 grams	8	4	58
Infant weight gain, n			
<twice BW	3	0	39
≥ twice BW	5	5	31
Exclusive breastfeeding, n			
Yes			
No	2	1	10
	6	4	60
Infant nutritional status, n			
Normal			
Undernourished/	7	4	49
malnourished	1	1	21
Iron supplementation, n			
Yes	3	2	28
No	5	3	42
PRC transfusion history, n			
Yes	1	0	21
No	7	5	49
Maternal anemia, n			
Yes	2	0	20
No	6	5	50
Maternal age, n			
≤ 20 years old	0	0	6
> 20 years old	8	5	64
Maternal education, n			
Elementary (low)	1	3	20
Middle high	7	2	50
Maternal nutritional status, n			
Normal	7	4	49
Undernourished	1	1	21
Socioeconomic status, n			
Low to middle-low	3	3	56
Middle to high	5	2	14

Discussion

This study was performed at outpatient clinics where subject inclusion depended on subject compliance for visiting the clinic. Approximately 20-30% of the total preterm infants born each month visited the Growth and Development Clinic at CMH at 2 months CA. This low percentage was due to bureacratic procedures that made it challenging to reach our tertiary hospital. In order to increase the sample size, we extended the study to other clinics at Fatmawati and Budi Kemuliaan Hospitals.

Iron profile was determined based on a combination of Hb, Tfsat, and serum ferritin level. A population study conducted in the US suggested using a combination of two iron markers, Tfsat and the zinc protoporphyrin-ferritin ratio, to diagnose iron deficiency, as these markers can be used to detect iron supply disregulation in erythropoesis before anemia occurs.[23] Serum ferritin is an acute phase protein, which increases during infection or inflammation.[13] In our study, infection was diagnosed by clinical manifestations and simple laboratory examinations; patients with infection were excluded. We did not assess for acute infection markers, such as C-reactive protein.

The gold standard for iron deficiency diagnosis is an iron marker examination of bone marrow aspirate. We did not perform this test on our subjects, as it is an invasive procedure. Other biomarkers for iron deficiency that are not affected by infection or inflammation, such as sTfR, could not be performed due to the high cost and lack of available tests, as well as lack of well-defined cut-off points for preterm infants.

Cut-off points for iron biomarkers (SI, TIBC, Tfsat, and serum transferrin) for preterm infants are still debatable. Past studies have used 10-12 ng/dL for serum ferritin and 10 or 16% for Tfsat as cut-off points to diagnose iron deficiency.[13–15] A Turkish study used the lowest percentile of serum ferritin from the study as the cut-off point (20 ng/mL), while Sidappa *et al*. used a ferritin cut-off point of 35 ng/mL.[9,16] *The European Society for Paediatric Gastroenterology Hepatology And Nutrition* (ESPGHAN) recommended different ferritin cut-off points for term infants based on age grouping as follows: 40 ng/mL (0-2 months), 20 ng/mL (4-6 months), and 10-12 ng/mL (6 months-5 years).[17] Cut-off points used in this study were serum ferritin < 45 ng/mL and Tfsat < 28%.[18]

Most subjects had birth weight >1,500 grams (84%) and good nutritional status (73%). Thirteen subjects were exclusively breastfed (16%), higher than in a previous study in Brazil in preterm infants aged 6 months, which showed that only 8.3% subjects received exclusive breastfeeding. However, that study had different age and birth weight inclusion criteria from our study, which may have led to differing results.[8]

Iron supplementation for preterm infants has become a standard recommendation in Indonesia. A Cochrane meta-analysis showed no significant difference in Hb or serum ferritin level between early iron supplementation (given at 2 months CA) and late iron supplementation (given at 4 months CA). Based on history-taking, subjects who received iron supplementation typically started at 28-30 days of age.[19] Forty percent of our subjects were iron supplemented and 76% of those had good compliance. Since the data were collected by history-taking without actually measuring the iron preparations consumed, there was a potential risk of bias.

Mothers in our study were mostly >20 years of age, not working outside the home, and with middle-to-high educational level. The prevalences of maternal anemia in two previous Turkish studies were 27.8% and 28.3%.[9,20] Similarly, we found that the maternal anemia prevalence was 27%. However, this prevalence was lower than that in the 2013 National Health Report [*Riset Kesehatan Dasar (Riskesdas)*] which reported 36.4% of pregnant women in Indonesian urban areas to be anemic.[21] Riskesdas used the same criteria to diagnose anemia in women (Hb level <11 g/dL), but the sampling was performed in infants of any gestational age, unlike our study. Also, we measured maternal Hb level data just before labor started. The type of anemia in mothers could not be determined because we collected data only on maternal Hb levels. Previous research reported that 50% cases of anemia in pregnancy were caused by iron deficiency.[22] Most subjects came from low (11%) and middle-low (66%) socioeconomic background. Socioeconomic background was also reported to affect the prevalence of IDA. Honduras, a low-income country, had a higher IDA prevalence compared to Sweden, a high-income country (28% *vs.* 2%, respectively). Level of income is associated with iron supply available from the diet, which may affect maternal nutritional status, and later impact the amount of iron transferred to the fetus.[8]

The prevalence of IDA in this study was 6% and the prevalence of ID was 10%. No iron depletion was found in our subjects. The IDA prevalence in our study was lower than that in Turkey (42.8%), Brazil (26.5%), or Sweden (9.9%).[7–9] Differences may be due to differing subject characteristics, age when sampling was performed, diet, iron supplementation programs, and ferritin cut-off point used. The Turkish study included 4 month CA preterm, non-iron supplemented infants, and used a ferritin cut-off point of <20 ng/mL.[9] Subjects in the Brazilian study were very low birth weight infants born at 30.4±2.3 weeks GA; ferritin cut-off point used was <10 ng/mL; and blood sampling was performed at 12 months CA.[8] Those subjects received iron supplementation from the time of hospital discharge, but 31.4% of them were given cow's milk at the age of 6 months. Cow's milk consumption is associated with IDA (RR 1,687; 95%CI 1,146-2,483; P=0.008).[8] A Swedish study included 200-2,500 gram preterm infants, who were non-iron supplemented, and used a ferritin level of <10 ng/mL to diagnose IDA.[7]

Preterm infants may have a negative iron balance because of the increased demand for iron due to rapid growth, especially when the body weight reaches twice the birth weight. This occurrence usually happens at 2 months of age. At that time, the rapid production of erythrocytes, muscle mass, and enzymes consume a lot of iron.[5,16] Most of our subjects (51%) had not reached twice their birth weight when the blood was drawn, so this negative iron balance had not yet occurred. Nonetheless, 40% of subjects received

oral iron supplementation since 1 month of age. A Cochrane systematic review reported that preterm infants receiving iron supplementation had 6 g/dL higher Hb level compared to non-iron supplemented infants at the age of 6-9 months.[19]

Prevalence of IDA is also associated with maternal factors. Most of our subjects were born to mothers age >20 years (93%), with good pre-pregnancy nutritional status (72%), and middle-to-high educational level (71%). These maternal factors contributed lower risk of IDA.[6] Iron supplementation for pregnant women is also routinely given, as Riskesdas data shows that iron consumption among pregnant women reached 89.1% in Indonesia.[21]

There were no iron-depleted subjects in our study, possibly due to the diagnosis criteria for iron depletion being a low ferritin level. Ferritin resembles iron stores in the tissues and mostly affected by infection and inflammation. Infants with infection and inflammation in this study were excluded by history-taking and simple laboratory examinations. These screening methods may not have accurately detected infection and inflammation conditions. Iron deficiency is diagnosed by normal hemoglobin level accompanied by low Tfsat, or low ferritin level. Studies in Turkey and Brazil also did not report on iron depletion prevalence. However, the prevalence of ID in Brazil was 48% at the infant age of 12 months.[8,9]

Most subjects in our study were anemic (70%), with Hb level <9.8 g/dL as the cut-off point.[22] Blood smears showed normocytic normochromic RBCs in most subjects (87%). All subjects with ID had normocytic normochromic RBCs without anemia, and subjects with IDA were normocytic normochromic (2/5) and microcytic hypochromic (3/5). One subject with normal iron store had a microcytic hypochromic smear (1/53). Physiologically, Hb level decreases because of bone marrow hypoactivity by the age of 6-8 weeks and erythrocytes have normal morphology. Erythropoesis increases in activity after 8 weeks of age, which implies that most of our subjects would be anemic. Anemia in our subjects was not symptomatic. Erythrocytes change to a microcytic hypochromic morphology at the end of the spectrum of iron deficiency, as shown in our ID and IDA subjects. One subject with normal iron store and microcytic hypochromic morphology was advised to undergo hemoglobin analysis to rule out thalassemia.[23]

Serum iron and TIBC profiles in our subjects were consistent with IDA pathogenesis, i.e., low SI and high TIBC. Serum iron level is affected by diurnal variation (higher in the afternoon), and iron content in diet.[24] Serum iron to TIBC ratio is known as transferrin saturation (Tfsat). Low Tfsat is reflective of an iron deficiency state. Subjects' ferritin level in our study encompassed a wide range: 8.6-37.7 ng/dL in the IDA group, 16.5-44.7 ng/dL in the ID group, and 49.4-1425 ng/dL in the normal iron stores group. The ferritin cut-off point used in this study was <45 ng/mL. This cut-off point is higher than the cut-off point used in the Turkish, Brazilian, and US studies, since there is not yet agreement in this area.[8,9,17] This wide range may also be caused by acute or chronic infection in subjects who were asymptomatic, or by PRC transfusion history, as 27% of subjects received PRC transfusion during hospitalization. At 2 months, late-preterm infants had lower serum ferritin and median Hb compared to term infants [(serum ferritin: 145 mg/dL *vs.* 195 mg/dL, respectively; (P=0.001) and Hb: 10.1 g/dL *vs.* 11.6 g/dL; respectively; (P<0.001)].[9] Median Hb level in our study was lower than in a Turkish study because of the difference in subjects' gestational ages.[9]

Iron deficiency is diagnosed by a combination of two markers, Tfsat and ferritin.[25,26] The Tfsat is affected by diurnal variation, but blood collection was performed in the morning until afternoon. Another factor affecting Tfsat is iron in the diet. Infants have to be fed every 2-4 hours so it is difficult to control the effect of iron from diet. Low birth weight infants experiencing IDA at 2-3 months age and serum ferritin level <50 ng/dL are predictive factors of iron deficiency in preterm infants.[27] Thus, it is recommended to screen infants at the time of hospital discharge or at the age of 2 months.[23] The recommendation of the *American Association of Family Physicians* (AAFP) for iron deficiency is to screen preterm infants who do not consume iron-fortified formula at 6 months of age, and to screen low birth weight infants at 9 months of age.[28] Iron and hematology profiles were high at 2 months of CA in our study.

Iron-supplemented infants had higher Hb level and iron stores compared to non-iron-supplemented infants. They also had a lower risk to develop IDA.[19,29] Gender, birth weight, exclusive breastfeeding, compliance to iron supplementation, maternal age,

education, anemia, and socioeconomic status were not associated with ID in preterm infants aged 2 months.

All subjects with IDA were male (5/5), consistent with a previous study in Norway that reported male infants to have lower MCV and higher hypochromic erythrocyte percentage compared to female infants.[16] These factors may be predictive of the ID status in preterm infants at the age of 6 months. Men have higher metabolism and larger body mass composition which consume more iron than women do.[5]

All subjects with ID had birth weights >1,500 grams and 5 of them had reached twice their birth weight when study was performed. Most subjects with IDA (4/5) had birth weights >1,500 grams, and all had reached more than twice their birth weight when the study was performed. Increased body mass would increase iron consumption which may reduce the total iron body stores.[29,30]

The amount of iron contained in breast milk is lower than in fortified formula. However, the iron in breast milk is more easily absorbed in the infant gut. Fractional iron absorption from breast milk varies according to age and diet.[13] A meta-analysis in exclusively breastfed and partially breastfed preterm infants showed a 4.1 g/dL difference in Hb level between the iron-supplemented and non-iron supplemented subjects at the age of 6-8 weeks.[19] In addition, a study of 6-week-old preterm infants in Sweden who were exclusively breastfed reported an IDA prevalence of 18% in non-iron supplemented subjects.[31] Subjects who did not receive breast milk in our study were given formula or formula mixed with breast milk. No subjects were given any other kind of milk. Most subjects who developed ID and IDA were not breastfed. Since we did not record the volume of formula consumed by the infants, we could not measure the amount of iron consumed daily. Moreover, 40% of our subjects were iron-supplemented, which may have lowered the prevalence of ID and IDA in our study.

Maternal anemia is not related to ID and Hb level in infants.[32] In our study, subjects with ID and IDA were born to mothers who were not anemic. However, another study reported that infants born to iron-deficient mothers showed lower Hb and ferritin level compared to infants born to mothers with normal iron stores ($P<0.01$; $P<0.03$).[33] We did not record maternal iron profiles because these examinations are not routinely performed in Indonesia. In addition, a study in East Turkey reported that 50% of the anemia in pregnant women was IDA.[20]

Iron deficiency in preterm infants at the age of 12 months was independently associated with younger maternal age (RR 0.95; 95%CI 0.923 to 0.983; $P=0.003$), small for gestational age infants (RR 1.578; 95%CI 1.068 to 2.331; $P=0.022$), multiparity (RR 1.256; 95%CI 1.122 to 1.406; $P< 0.001$), cow's milk consumption at the age of 6 months (RR 1,687; 95%CI 1,146 to 2,483; $P=0.008$).[8] Another study showed infants born to mothers younger than 20 years of age had a 1.58 times higher risk to develop iron deficiency (95%CI 2.07 to 21).33 None of our ID and IDA subjects had mothers ≤20 years old. Most infants were born to families of low and middle-low socioeconomic backgrounds, but most were well-nourished and the mothers also had good pre-pregnancy nutritional status.

Subjects without iron supplementation or with poor compliance to iron supplementation had ID (7/8) and IDA (5/5). Compliance was assessed by parental interviews, without measuring the amount of iron consumed during the study. Iron supplementation also depends on parental knowledge and awareness, as well as the clinician's monitoring. Those factors were not investigated in our study.

In conclusion, most preterm infants aged 2 months CA with ID and IDA show low SI, high TIBC, low Tfsat, and low ferritin level. The prevalence of IDA in preterm infants aged 2 months CA is 6%, and the prevalence of ID is 10%. Preterm infants with IDA are all males, mostly gained ≥twice their birth weight, are non-iron supplemented, and born to mothers with low educational background and low socioeconomic status.

Compliance to iron supplementation needs to be increased by monitoring the preterm infants during outpatient clinic visits and educating the parents of the importance of iron supplementation. Iron deficiency anemia in preterm infants cannot be diagnosed by serum ferritin and transferrin saturation alone. Further cohort studies on preterm infants at the age of 6 and 9 months CA need to be conducted to further study the relationship between iron deficiency and risk factors.

Conflict of Interest

None declared.

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