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102.IRON HOMEOSTASIS AND BIOLOGY

Nearly Half of Extreme Preterm Infants Are Iron Deficient at 4-6 Months of Corrected Age Despite Prophylactic Iron Supplementation

Hudson Barr, BA [1,2], Lisa Morrison, PDt [3], Ketan Kulkarni, MD [2,4], Satvinder Ghotra, MD [1,3]

[1] IWK Health, Halifax, Canada
[2] Dalhousie University, Halifax, Canada
[3] Dalhousie, Halifax, Canada
[4] IWK Health Center, Halifax, Canada

Background:
Iron deficiency (ID) is the most prevalent micronutrient deficiency globally and has been associated with negative neurodevelopmental and behavioral outcomes in infants and young children. Susceptibility to ID is heightened in preterm infants due to lower iron reserves at birth, rapid growth during the initial weeks of life, immature erythropoiesis, and frequent blood samplings during hospitalization. To mitigate this problem, international bodies recommend prophylactic iron therapy from 2-6 weeks of age until at least 6-12 months in preterm infants. Currently, the literature regarding iron status in extremely preterm infants (EPI, infants born less than 28 weeks gestational age) who receive prophylactic iron supplementation after birth is limited. Considering the potential long-term detrimental effects of ID on the developing brain of these high-risk preterm infants, examining the prevalence and risk factors for ID are crucial to implement prevention strategies.
Objective: To investigate the prevalence and risk factors associated with ID in EPI
Methods:
A retrospective cohort study was conducted using a population-based Provincial Perinatal Follow-Up database on all live EPIs born in Nova Scotia between 2005 and 2018. Infants with congenital malformations, chromosomal anomalies, blood disorders or those who died before outcome assessment were excluded. Prophylactic iron supplementation (2-3 mg/kg/day) starting at 2-4 weeks of chronological age was a standard of care for all included infants. Further, the dosage of iron was adjusted regularly during the hospital stay based on serum ferritin (SF) levels. Discharge instructions recommended continuing iron prophylaxis until 9-12 months corrected age (CA). At 4-6 months CA, all infants underwent blood tests to evaluate hemoglobin, and SF levels. ID was defined as SF levels below 20g/L or 12g/L at 4 and 6 months CA, respectively. A univariate analysis was performed by using a series of single-variable logistic regression models to identify the factors associated with presence of ID. Factors with a p-value < 0.20 in the univariate analysis were entered into a multivariable risk model using a backward selection procedure. Variables with a p-value < 0.05 were retained.
Results:
Among 146 infants, 67 (45.9%) had ID. Ferritin (16.4 μg/L vs 50.0 μg/L, p < .001) and reticulocyte hemoglobin equivalent (28.4pg vs 31.6pg, p < .001) were significantly lower in the ID group than non-ID group. The prevalence of ID decreased over time, from 59.7% in 2005-2011 to 40.3% in 2012-2018 (p = 0.52). Table 1 compares the antenatal and neonatal characteristics of the ID and non-ID groups. Table 2 compares sociodemographic variables and clinical variables at 4-6 months CA between two groups. Breastfeeding (exclusive or partial) versus formula alone at a 4-6 months CA was identified as an independent factor protective for ID (Odds: 0.2 (0.1 - 0.6), p = 0.003). Iron therapy at follow-up was also protective for ID but did not remain significant in the final model. Of note, iron therapy was stopped in 40 (27.4%) EPI before 4-6 months CA. Supplemental iron intake at 4-6 months CA was significantly lower in the infants receiving exclusive formula feeding (66.1%) compared with those breastfed (99.1%, p = 0.006).
Conclusion(s):
Despite prophylactic iron supplementation, nearly half of the EPI had ID at 4-6 months CA, and iron therapy was discontinued in roughly a quarter of all EPI before 4-6 months CA. Breastfeeding at 4-6 months follow-up was found to be protective for ID. High prevalence of ID in EPI highlights the need for further research in this area to avert the negative neurodevelopmental consequences of ID on the developing brain of these high-risk infants. Closer monitoring of iron status and early identification of children at high risk for ID is imperative to maximize the benefits of prophylactic iron supplementation in EPI. Further, there

is lack of sufficient data for iron requirements in EPI leading to a variability in iron therapy recommendations by different professional organizations. Future prospective studies to investigate specific iron requirements of EPI as well as risk factors for ID in this high-risk vulnerable population are essential to optimize their neurodevelopmental outcomes.

Disclosures No relevant conflicts of interest to declare.

Table I. Antenatal and neonatal characteristics of the ID and non-ID groups

Antenatal Variables	ID % (n=67)	Non-ID % (n=79)	OR or mean difference (95% CI)
Birth Epochs			
2005-2011	59.7 (40)	54.4 (43)	1.2 (0.6 – 2.4)
2012-2018	40.3 (27)	45.6 (36)	Ref
Maternal age, years, mean ± SD	30.14 ± 5.6	28.6 ± 6.1	-1.6 (-3.5 to 0.4)
Maternal anemia	9.0 (6)	3.8 (3)	2.5 (0.6 – 10.4)
Gestational hypertension ª	17.9 (12)	6.3 (5)	3.2 (1.1 – 9.7)
Maternal Diabetes	7.5 (5)	5.1 (4)	1.5 (0.4 – 5.9)
Smoking	31.3 (21)	30.4 (24)	1.1 (0.5 – 2.3)
Antepartum hemorrhage	26.9 (18)	19.0 (15)	1.6 (0.7 – 3.4)
Multiple gestation	20.9 (14)	30.4 (24)	0.6 (0.3 – 1.3)
Mode of delivery			
Vaginal	41.8 (28)	51.9 (41)	Ref
Cesarean section	58.2 (39)	48.1 (38)	1.5 (0.8 – 2.9)
Neonatal Variables			
Gestational age, weeks, mean ± SD	25.7 ± 1.2	25.8 ± 1.2	0.1 (-0.28 to 0.5)
Birth weight, grams, mean ± SD	868.2 ± 193.6	907.8 ± 192.5	39.6 (-23.8 to 103.0)
Length of hospital stay, days, mean ± SD	109.1 ± 49.3	106.9 ± 33.5	-2.2 (-15.9 to 11.5)
Need of any blood transfusions	85.1 (57)	86.1 (68)	1.0 (0.6 – 1.5)
Number of blood transfusions, median (IQR)	3 (5)	3 (4)	—
Hemoglobin at discharge, g/L, mean ± SD	111.0 ± 17.2	106.6 ± 16.1	-4.4 (-9.9 to 1.0)
Ferritin at discharge, µg/L, mean ± SD ª	76.2 ± 58.0	106.6 ± 96.4	30.5 (0.3 – 60.6)
Iron Dose at discharge, mg/kg/day, mean ± SD	3.1 ± 1.2	3.3 ± 1.1	0.2 (-0.1 to 0.6)
Male sex	50.7 (34)	59.5 (47)	0.7 (0.4 – 1.4)
BPD requiring oxygen at 36 weeks	40.3 (27)	40.5 (32)	1.0 (0.5 – 1.9)
HS - PDA	43.3 (29)	54.4 (43)	0.6 (0.3 – 1.2)
Necrotizing Enterocolitis	9 (6)	3.8 (3)	2.5 (0.6 – 10.4)
Culture positive sepsis	32.8 (22)	26.6 (21)	1.4 (0.7 – 2.8)
Any IVH	32.8 (22)	46.8 (37)	0.56 (0.28 – 1.09)
Cystic brain injury	10.4 (7)	8.9 (7)	1.2 (0.4 – 3.6)

Note: ª indicates p<0.05, OR: odds ratio, CI: confidence intervals, ID: iron deficient, IQR: interquartile range, IVH: intraventricular hemorrhage, SD: standard deviation, BPD: bronchopulmonary dysplasia, HS-PDA: hemodynamically significant patent ductus arteriosus, µg: microgram, g: gram, L: litre, mg: milligram, kg: kilogram.

Table II. Post discharge characteristics at 4-6 months corrected gestational age in the ID and non-ID groups

Clinical Variables	ID % (n=67)	Non-ID % (n=79)	OR (95% CI)
Feeding type at follow-up			
Breastfeeding (exclusive or partial) ª	11.9 (8)	36.7 (29)	0.2 (0.1 – 0.6)
Exclusive Formula	88.1 (59)	63.3 (50)	Ref
Receiving iron at follow up ª	62.7 (42)	81.0 (64)	0.4 (0.2 – 0.8)
Reflux medication	46.3 (31)	51.9 (41)	0.8 (0.4 – 1.6)
Sociodemographic Variables			
Single parent	14.9 (10)	19.0 (15)	0.8 (0.3 – 1.9)
Married (incl. common law)	77.6 (52)	75.9 (60)	1.3 (0.5 – 3.1)
Urban dweller (vs rural) ª	74.6 (50)	89.9 (71)	0.3 (0.1 – 0.8)

Note: ª indicates p<0.05, OR: odds ratio, CI: confidence intervals

Figure 1

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