Iron deficiency in childhood

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Publication date
2015
Document Version
Final published version

Part I

Iron deficiency in preterm infants born after 32 and 37 weeks of gestational age

Chapter 2

Iron deficiency in the first six months of age in infants born after 32 to 37 weeks of gestational age

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European Journal of Clinical Nutrition 2014; Oct 15. doi: 10.1038/ejcn.2014.217.


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ABSTRACT

Introduction
Preterm infants are at risk of iron deficiency (ID). In the Netherlands, preterm infants born after 32 weeks of gestational age (GA) do not receive iron supplementation on a routine basis. We hypothesized that dietary iron intake in these infants might not be sufficient to meet the high iron requirements during the first 6 months of life.

Methods
In a prospective cohort study we analyzed the prevalence and risk factors of ID in 143 infants born between 32+0 and 36+6 weeks GA who did not receive iron supplementation.

Results
ID at the age of 4 and 6 months was present in 27 (18.9%) and 7 (4.9%) infants. Results of a multivariable logistic regression analysis showed that ID was associated with lower birth weight, a shorter duration of formula feeding, more weight gain in the first 6 months of life, and lower ferritin concentrations at the age of 1 week.

Conclusion
Preterm infants born after 32 weeks GA have an increased risk of ID compared to those born at term, supporting the need of iron supplementation. Our results suggests that measurement of ferritin at the age of 1 week might be useful to identify those infants at particular risk, and could be used in populations without general supplementation programs. However, the efficacy and safety of individualized iron supplementation, based on ferritin concentrations at the age of 1 week, together with other predictors of ID, needs to be further investigated, preferably in a randomized controlled trial.

INTRODUCTION

Infants born prematurely are susceptible to iron deficiency (ID) because of insufficient iron storage at birth, frequent blood sampling during the first weeks of life and rapid growth after birth[1]. ID during infancy and iron-deficient anemia (IDA) may have a long-term detrimental influence on cognitive and psychomotor development, despite later iron treatment[2]. However, the potential risk of iron overload and the poorly developed anti-oxidant mechanisms in preterm infants argue against indiscriminate iron supplementation in this population[3,4]. Therefore it is important to identify those infants who may benefit from iron supplementation but also to avoid iron supplementation in cases where it is not necessary.

According to both European and American recommendations, all preterm infants should therefore be supplemented with 2–3 mg/kg per day of elemental iron from 2–6 weeks to at least 6 months of age[5,6]. However, these recommendations are mostly based on studies in infants born <32 weeks gestational age (GA)[6,7]. In the Netherlands, preterm infants born ≥32 weeks GA do not receive iron supplementation on a routine basis. We hypothesized that dietary iron intake might not be sufficient in all these infants to meet the high iron requirements during the first 6 months of life. In order to investigate this hypothesis, we analyzed the prevalence of ID in a population of late preterm infants where general iron supplementation was not used. Furthermore, we aimed to identify risk factors for ID, in order to explore the possibility of individualized iron supplementation, an approach that may be superior to the recommended general supplementation[6,8].

METHODS

Study design

We conducted a prospective cohort study in infants born between 32+0 and 36+6 weeks GA. As iron stores at birth are adequate until approximately the time that birth weight has doubled[9]. we expected to find an increased risk of ID at the age of 4–6 months. We defined ID at the age of 4 months and 6 months as a ferritin concentration <20 and <12 µg/L, respectively[1]. IDA was defined as ID in combination with anemia, defined as hemoglobin (Hb)<105 g/L[1]. The study was approved by the Medical Ethics Committee of South-West Holland.

Study population

Infants were recruited from March 2011 to April 2013 in the Juliana Children's Hospital and the Medical Center Haaglanden, both in The Hague, and in the Medical Center Alkmaar in Alkmaar. These are large level II hospitals in the western region of the Netherlands. Eligible infants were identified from delivery records. Exclusion criteria were infections (C-reactive protein (CRP) ≥5 mg/L), congenital malformations, chronic or inherited metabolic disease, hemoglobinopathies, active blood loss during delivery/major bleeding, twin to twin transfusion syndrome, hemolytic disease, (positive coombs) or blood transfusions in the first 6 months of life. The observational design of the study allowed pediatricians to prescribe iron supplementation in the way they considered appropriate. Infants receiving iron supplementation were registered but not included in the main analyses. Parents were contacted at the hospital after delivery, and written and oral information was provided by the investigators (MA, LU). Parents who accepted participation gave written informed consent.

Data collection

Infants visited the outpatient clinic for routine follow-up at the postnatal age of 1.5, 4 and 6 months, respectively. In the first week of life and at every visit, venous blood was collected (3 mL) and analyzed for ferritin, Hb and CRP. CRP was measured to detect cases of infection or inflammation, which usually is accompanied by an increase in ferritin. Anthropometric data were recorded after birth and at the postnatal age of 1.5, 4 and 6 months respectively; length was measured to the nearest millimeter by using a length board, weight was measured to the nearest 0.001 kg by using a digital scale (SECA Model 717 A, Hamburg, Germany) and head circumference was measured to the nearest millimeter by using a plastic measuring tape. Z-scores for anthropometric data were calculated, with correction for GA at birth, by using Dutch references[10]. The type and amount of feeding (mL per day) that infants received at the age of 1.5, 4 and 6 months, respectively, were recorded by using an unstandardized questionnaire. The period of breastfeeding was defined as the period from birth onwards, during which the infant received mother's own breast milk exclusively or in combination with water or complementary feeding but no formula. The period of formula feeding was defined as the period during which the infant received formula exclusively or in combination with breast milk, water or complementary feeding. Daily iron intake (mg/kg per day) from formula and breast milk was estimated, with an assumed iron content in breast milk of 0.3 mg/L and a total volume intake of 150 mL/kg per day[11]. Perinatal data and maternal characteristics (gestational diabetes, pregnancy induced hypertension, smoking habits and

use of iron supplementation during pregnancy) were recorded. Multivitamins containing iron were not monitored. However, these preparations in the Netherlands do not contain iron at therapeutic doses. Mothers of participating infants were asked to give written informed consent for access to their own medical records to verify these data. In this study, obstetricians performed early cord clamping (<60 s)[12], which was the standard procedure at the time of the study. Parents filled out a questionnaire concerning demographic data and parental education. When both parents were born in a western country (Europe, United States) infants were classified as 'western'. Educational level of the parents was classified as 'high' when they completed higher vocational education or university. Socioeconomic status (SES) was determined by postal code. SES scores are available for all postal code areas in the Netherlands for the year 2010. SES scores are provided by The Netherlands Institute for Social Research, a Dutch governmental organization, and based on the following items; (a) mean annual income in a postal code area, (b) the percentage of households with a low income, (c) the percentage of households with a low education, and (d) the percentage of unemployment. The SES was expressed as a score with a lower SES score representing a lower socioeconomic status[13,14].

Biochemical analysis

Venous blood was collected in an EDTA tube and analyzed for Hb, using a Sysmex XE-2100 (Sysmex Corporation, Kobe, Japan) automated hematology analyzer. Ferritin and CRP concentrations were analyzed in plasma, using a Unicel DxI 800 immunochemistry analyzer (Beckman Coulter, Fullerton, CA, USA). All analyses were performed within 4 h after sampling.

Statistical analysis

The sample size was based on reported prevalence of ID in late preterm infants (10%)[15]. Using this data in a power analysis, a number of 200 infants would be sufficient to have 95% confidence limits of ±5%, with a dropout rate of 20%. SPSS (version 21.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All registered data were checked for normality using histograms and Kolmogorov–Smirnov test. Because ferritin values were not normally distributed, they were logarithmically transformed in all calculations and transformed back for presentation as geometric means and standard deviations. Blood samples were considered as incomplete when insufficient blood was obtained to analyze Hb, ferritin and CRP at the age 6 months. One-way analysis of variance was used for comparison of means between study sites. For comparisons between groups, we used a Student's t-test for continuous variables and Chi-square test

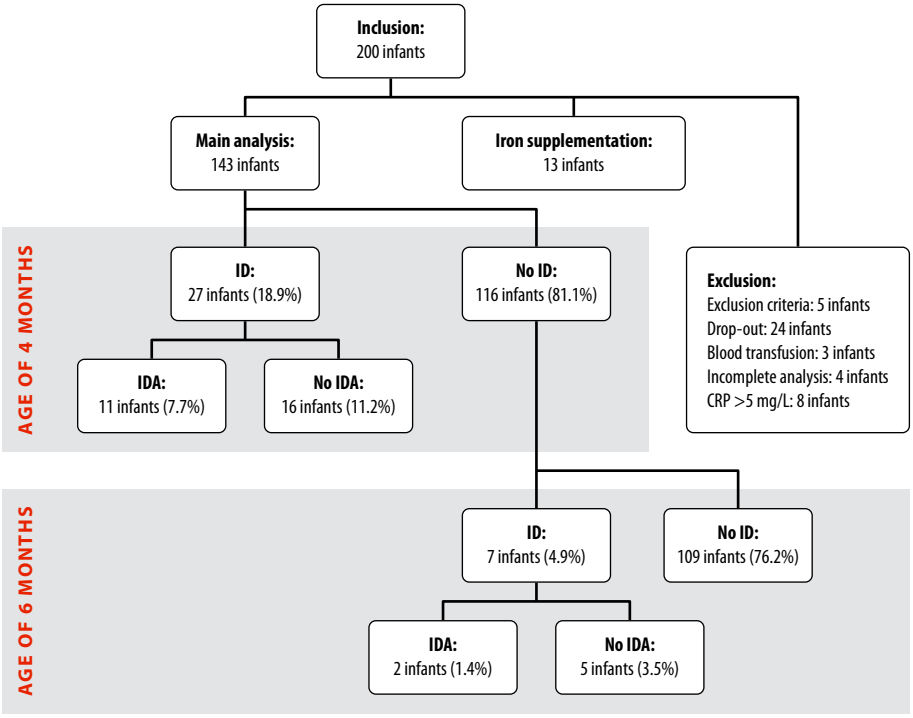
for dichotomous variables. Logistic regression analysis was used to analyze risk factors for ID. Risk factors with a P <0.10 in the univariate analysis were combined in a multiple logistic regression analysis, using a backward Wald method. Statistical significance was defined as a P <0.05. To visualize the efficacy of the risk factors to discriminate infants with ID from infants with no ID, we constructed a receiver operating characteristic curve.

RESULTS

Characteristics of excluded infants

Of the 200 infants who participated in the study (124 infants from the Juliana Children's Hospital, 58 infants from the Medical Center Haaglanden and 18 infants from the Medical Center Alkmaar), 5 infants were excluded because of congenital malformations (n=3) and ABO blood group immunization (n=2). During the follow-up period, 24 parents decided to withdraw their child from the study because of resistance against blood drawing (n=7), follow-up visits in another hospital for logistic reasons (n=10) or without giving any reason (n=7) (figure 1). Three infants received a blood transfusion at the postnatal age of 2–4 weeks (mean Hb 79.4 g/L (n=3), mean ferritin 64 µg/L (n=2)). Blood samples were incomplete in four infants, and elevated CRP concentrations (<5 mg/L) were present in eight infants (**figure 1**). Mean birth weight and GA of excluded infants were similar compared with those who completed the follow-up period (data not shown). Iron supplementation (2–3 mg/kg/day iron) was prescribed by the infants' pediatrician in 13 infants at the postnatal age of 3–8 weeks (figure 1). The main reason to start iron supplementation was a low Hb (median Hb 83.7 g/L, range 69.2–111.1 g/L). Ferritin was measured prior to start iron supplementation in six infants (median ferritin 68.5 µg/L, range 24.0–312.0 µg/L). Mean birth weight and GA were lower in infants who received iron supplementation as compared with infants who received no iron supplementation (1748 g (SD 465) versus 2305 g (SD 472), respectively, P <0.001), 34.0 weeks (SD 1.4) versus 34.9 weeks (SD 1.1), respectively, P <0.01). Iron supplementation was prescribed more frequently in infants born small for GA (birth weight <10th percentile) as compared with infants born appropriate for GA (5 of the 28 small for GA infants (17.8%) versus 8 of the 128 appropriate for GA infants (6.3%), P 0.04). No differences in dropout rates or use of iron supplementation between study sites were found (data not shown).

Figure 1: *Flowchart of the study population.*



Abbreviations: CRP – C-reactive protein; ID – iron deficiency; IDA – iron deficiency anemia.

Characteristics of the study population

Mean birth weight and GA of the analyzed 143 infants were 2305 g (SD 473) and 34.8 weeks (SD 1.1) (**table 1**). The most frequently observed neonatal diagnoses were jaundice (n=46 (32.2%)), respiratory disorders (n=36 (25.2%)) and hypoglycemia (n=19 (13.3%)).

Table 1: *Characteristics of the study population (143 infants).*

	Mean or number	SD or percentage (%)
Gender (male)	87	60.8%
Gestational age (weeks)	34.8	SD 1.1
Birth weight (g)	2305.3	SD 472.5
Birth length (cm)	43.2	SD 2.7
Birth head circumference (cm)	31.8	SD 1.6
Small for gestational age	23	16.1%
Caesarian section	62	43.4%
Apgar score at 5 minutes	9.0	SD 1.3
Ethnicity (western)	77	53.8%
Socioeconomic status score	-0.6	SD 2.1
Educational level of the mother (high)	60	42.0%
Educational level of the father (high)	47	32.9%
Maternal age at delivery (years)	31.5	SD 5.1
Pregnancy induced hypertension	34	23.8%
Gestational diabetes	13	9.1%
Iron supplementation during pregnancy	48	33.6%
Smoking during pregnancy	25	17.5%
Breastfeeding ever given	118	82.5%
Duration of breastfeeding (weeks)	5.0	8.3
Duration of formula feeding (weeks)	19.3	8.1
Age at introduction of complementary feeding (weeks)	18.3	3.5

Prevalence of iron deficiency

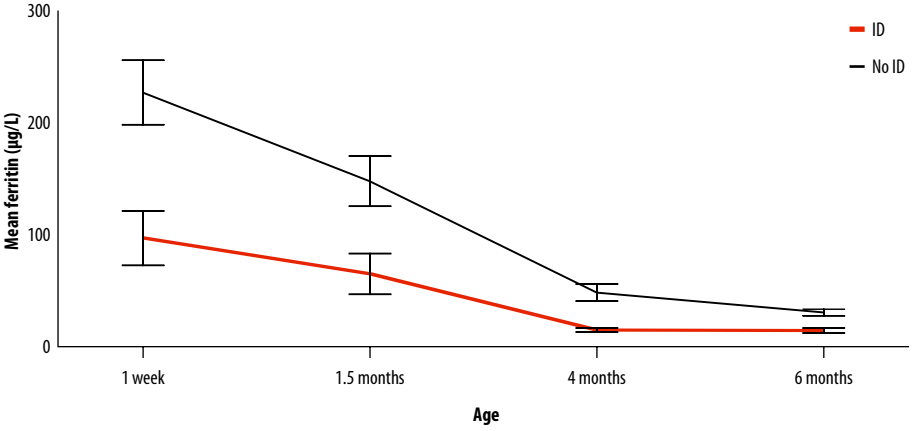
ID was present in 27 (18.9%) and 7 (4.9%) infants at the age of 4 and 6 months, respectively (figure 1). IDA was present in 11 infants (7.7%) at the age of 4 months and subsequently in 2 (1.4%) infants at the age 6 months (figure 1). When we additionally considered infants who received early iron supplementation as suspected ID, the cumulative prevalence of suspected or confirmed ID until 6 months of age was 32.9%.

Risk factors for iron deficiency

To identify risk factors for ID, we compared infants with confirmed ID at the age of 4 or 6 months (n=34, 23.8%) with infants without ID at the age of 6 months (n=109, 76.2%) (**table 2**). We found no differences in the reported presence of pregnancy-induced hypertension, gestational diabetes, smoking or use of iron

supplementation during pregnancy between infants with and those with no ID (data not shown). At the age of 1 week, ferritin concentrations were already lower in infants who developed ID at the age of 4 or 6 months compared with infants who did not (table 2 and **figure 2**). Results of a multivariable logistic regression analysis with birth weight, GA, weight gain, duration of breastfeeding and formula feeding and ferritin at the age of 1 week as independent factors showed that ID was associated with a lower birth weight (β 0.999 (95% confidence interval (CI) 0.997–1.000), P 0.04), a shorter duration of formula feeding (β 0.882 (95% CI 0.820–0.950), P 0.001), more weight gain in the first 6 months of life (β 0.366 (95% CI 1.163–4.815), P 0.02) and lower ferritin concentrations at the age of 1 week (β 0.988 (95% CI 0.981–0.995), P 0.01). Socioeconomic factors were no confounders for the observed associations. Using a similar regression model with suspected and confirmed ID as outcome variable, ID was associated with a lower birth weight (β 0.998 (95% CI 0.997–0.999), P <0.001), a shorter duration of formula feeding (β 0.918 (95% CI 0.867–0.973), P <0.01) and lower ferritin concentrations at the age of 1 week (β 0.994 (95% CI 0.989–0.998), P <0.01).

Figure 2: *Ferritin concentrations (µg/L) during the first 6 months of life in infants who developed ID[A] at 4 or 6 months compared with those with no ID[B] at the age of 4 and 6 months, respectively. Mean ferritin was significantly lower in infants with ID than in those with no ID (P <0.001 at the age of 1 week, 1.5, 4 and 6 months, respectively). Error bars represent 95% confidence interval.*



Abbreviations: ID – iron deficiency, No ID – no iron deficiency.

[A] Iron deficiency: ferritin <20 µg/L or ferritin <12 µg/L at the age of 4 or 6 months respectively.

[B] No iron deficiency: ferritin ≥20 µg/L and ferritin ≥12 µg/L at the age of 4 and 6 months respectively.

Table 2: *Characteristics of infants with ID[A] and those with no ID[B]. Number (percentage) or mean (SD).*

	ID (n=34)	SD	No ID (n=109)	SD	P-value
Gender (male)	24 (70.6%)	NA	63 (57.8%)	NA	0.18
Gestational age (weeks)	34.4	1.0	35.0	1.1	0.02
Birth weight (g)	2161.8	477.0	2350.1	464.2	0.04
Birth weight (Z-score)	-0.44	1.05	-0.28	0.92	0.40
Cesarian section	17 (50.0%)	NA	45 (41.3%)	NA	0.37
Multiple pregnancy	9 (26.5%)	NA	29 (26.6%)	NA	0.99
Small for gestional age	7 (20.6%)	NA	16 (14.7%)	NA	0.41
Weight gain in 6 months (kg)	5.2	1.1	4.9	0.9	0.09
Dietary characteristics					
Breastfeeding (yes)	28 (82.4%)	NA	90 (82.6%)	NA	0.98
Duration of exclusively breastfeeding (weeks)	7.5	10.0	4.2	7.6	0.04
Duration of formula feeding (weeks)	16.5	9.9	20.1	7.2	0.02
Introduction complementary feeding (weeks)	18.1	3.8	18.4	3.5	0.71
Mean iron intake from 6 weeks to 6 months (mg/kg per day)	0.56	0.40	0.64	0.35	0.27
Biochemical results					
Ferritin (µg/L) at the age of 1 week[C]	90.1	2.1	185.0	2.0	<0.001
Hb (g/L) at the age of 1 week	169.3	26.6	168.2	25.3	0.83
Ferritin (µg/L) at the age of 1.5 month[C]	53.3	2.0	121.9	1.9	<0.001
Hb (g/L) at the age of 1.5 months	97.8	13.4	103.8	15.0	0.05

Abbreviations: Hb – hemoglobin, ID – iron deficiency, no ID – no iron deficiency.

[A] Iron deficiency: ferritin <20 µg/L or ferritin <12 µg/L at the age of 4 or 6 months respectively.

[B] No iron deficiency: ferritin ≥20 µg/L and ferritin ≥12 µg/L at the age of 4 and 6 months respectively.

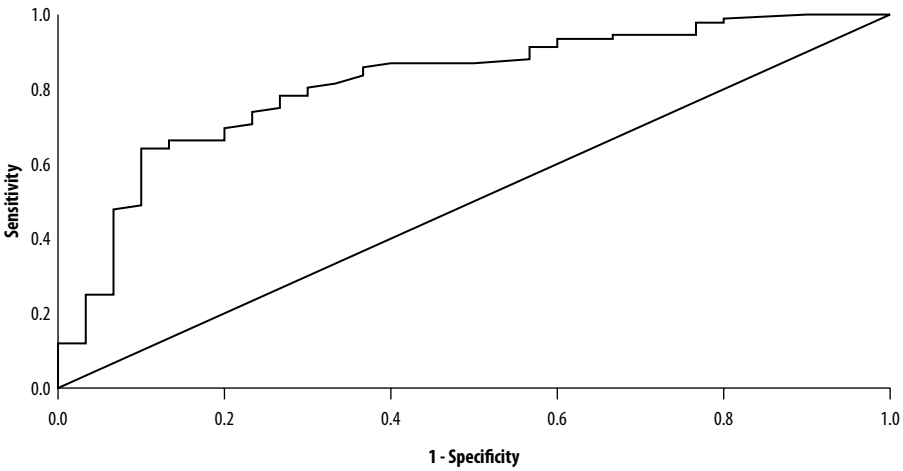
[C] Geometric mean concentrations of ferritin.

Predictive value of ferritin at the age of 1 week

We constructed a receiver operating characteristic curve to investigate the predictive value of ferritin at the age of 1 week for the development of ID (**figure 3**). A cutoff value of ferritin <150 µg/L provided the most balanced sensitivity and specificity of 69.2% and 72.4%, respectively. Considering both suspected and confirmed ID as outcome variable did not change these results but decreased the area under the curve from 0.769 to 0.705. The addition of birth weight or any other background variable included did not improve the predictive value of our model. Infants with a ferritin <150 µg/L at the age of 1 week had

a 5.9 times higher risk to develop ID compared with infants with ferritin concentrations ≥150 µg/L (95% CI 2.3–14.9, P <0.001).

Figure 3: *Reveiver operating characteristic curve for ferritin at the age of 1 week. Area under the curve is 0.769 (95% CI 0.678 – 0.860).*



DISCUSSION

In this study, ID and IDA at the age of 4 or 6 months were present in 23.8% and 9.1% of the included infants, respectively. Our population was representative for the Dutch population considering SES and parental educational level[14,16]. Ethnicity of our study population was more representative for the multi-ethnic composition of the population living in the urbanized, western region of the Netherlands[17].

Infants with ID at the age of 4 or 6 months already had significantly lower ferritin concentrations at the age of 1 week compared with infants with no ID. These results suggest that ferritin at the age of 1 week is closely associated with future ID but not sensitive enough to be used as a single predictor in an individualized supplementation program.

The prevalence of ID and IDA observed in our population is higher compared with the prevalence of ID reported in term infants[18] but lower compared with the prevalence observed in a study of Swedish marginally low-birth-weight infants (birth weight of 2000–2500 g)[19]. In that study, ID at the age of 6 months (defined

as ≥2 indicators of iron status outside the reference range: ferritin <12 µg/L, mean corpuscular volume (MCV)<71 fL, transferrin saturation <10%, transferrin receptor >11 µg/L) was present in 18 of the 44 preterm infants (40.9%) who did not receive iron supplementation. However, the Swedish infants also had a different dietary profile. At the age of 6 weeks, formula feeding (exclusively or in combination with breastfeeding) was reported in 45.7% of these infants, whereas in our study formula feeding was reported in 71.3% of the infants aged 6 weeks. In accordance with other studies[19-21], we conclude that formula feeding is associated with lower prevalence of ID, probably due to its higher iron content compared with breast milk. Furthermore, we conclude that the observed differences in prevalence of ID between countries during the first 6 months of life could, at least partly, be attributed to differences in feeding practices.

The long-term benefits of protecting infants from ID was illustrated in the aforementioned Swedish study. However, dietary iron intake in these predominantly breastfed Swedish infants was lower, and the prevalence of ID was higher compared with our population of predominantly formula-fed infants[19]. Therefore more Swedish infants might have an advantage of iron supplementation. Furthermore, although adverse effects of iron supplementation, such as increased oxidative injury[22,23], a slower rate of weight gain[24] and length growth[11], have not been observed in low-birth-weight infants[19,25], this must be considered also in preterm infants, and the benefits of iron supplementation should be compared with the possible risks. Considering the observation that the majority (>75%) of our predominantly formula-fed preterm infants of ≥32 weeks GA received no iron supplementation and were iron-replete at the age of 6 months, individualized iron supplementation, with consideration of local feeding practices and personal needs of an infant, might be an alternative to standardized iron supplementation for all infants with a birth weight of <2500 g. However, it remains to determine how such individualized supplementation could be performed.

As observed in other studies[15,20,26], we found that lower ferritin concentrations at the age of 1 week were associated with an increased risk of ID at 4 or 6 months. Infants with a ferritin <150 µg/L at the postnatal age of 1 week had a sixfold increased risk of ID. If individualized iron supplementation would be used, our data suggest that it seems justified to supply iron to those late-preterm infants with ferritin concentrations <150 µg/L at the postnatal age of 1 week. However, this approach would only have a sensitivity of about 70%, and a randomized controlled trial on individualized iron supplementation, based on ferritin

concentrations at the age of 1 week, together with other possible predictors of ID, is necessary to investigate the efficacy and safety of this approach. At this time, all preterm infants with a birth weight <2500 g should receive standardized iron supplementation according to current guidelines[1,5]. In this study, we have showed that ID and IDA at the age of 4 or 6 months are common in preterm infants of ≥32 weeks GA, supporting the need of general iron supplementation, as currently recommended by several authorities. However, the prevalence of ID in this population of predominantly formula-fed infants was relatively low compared with prevalence rates previously observed in infants who were mainly breastfed during the first 6 months of life. Furthermore, we showed that infants with a ferritin <150 µg/L at the age of 1 week had a sixfold increased risk of ID, suggesting that measurement of ferritin at this age might be useful to individualize iron supplementation to late preterm infants in populations where iron enriched formula is commonly used, and general supplementation is not implemented. However, the sensitivity of ferritin alone may not be high enough, and the efficacy and safety of such individualized iron supplementation as an alternative to general supplementation needs to be further investigated, preferably in a randomized controlled trial.

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