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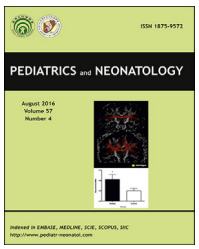

Original Article

Current practice of iron prophylaxis in preterm and low birth weight neonates: A survey among Italian Neonatal Units

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Key Words
iron;
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Background: Preterm babies are at high risk of iron deficiency.
Methods: We investigated current practices regarding iron prophylaxis in preterm and low birth weight newborns among Local Neonatal Units (LNUs, n = 74) and Neonatal Intensive Care Units (NICUs, n = 20) of three Italian Regions (Piemonte, Marche and Lazio).
Results: Birth weight is considered an indicative parameter in only 64% of LNUs and 71% of NICUs, with a significant difference between LNUs in the three regions (86%, 20% and 62%, respectively; $p < 0.001$). Iron is recommended to infants with a birth weight between 2000 and 2500 g in only 25% of LNUs and 21% of NICUs, and to late-preterm (gestational age between 34 and 37 weeks) in a minority of Units (26% of LNUs, 7% of NICUs).
Conclusions: Our pilot survey documents a great variability and the urgent need to standardize practices according to literature recommendations.

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1. Introduction

Preterm babies comprise the largest group of children at risk of iron deficiency and iron deficiency anemia because of both their low iron stores (due to the reduced third trimester iron transfer) and their increased demand (due to the proportionally more rapid postnatal growth than that of the term infant).[1]

As iron is essential for brain development, iron deficiency is demonstrated not to be only a hematologic disease, but a developmental disrupter with long-term poor neurocognitive outcome.[2–9]

For these reasons, both the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)[10] and the American Academy of Paediatrics (AAP)[11] recommend supplementation of preterm neonates and low birth weight infants with enteral iron. However, the optimal dose, as well as timing of beginning and cessation of iron supplementation, remains to be elucidated.[12–15] Recently, a higher risk of neurocognitive problems deriving from iron deficiency in marginally low birth weight preterm babies has been reported, further underlying the need for iron supplementation in this category of newborns.[16–19]

The aim of the present study was to investigate current practices regarding iron deficiency and iron deficiency anemia prophylaxis among Italian neonatologists.

2. Methods

Neonatologists members of three Regional Sections (Piemonte, Marche and Lazio) of the Italian Society of Neonatology (SIN) were recruited between January 2016 and March 2016 to complete a web-based survey examining knowledge, attitude and practices of their Neonatal Units regarding iron deficiency anemia prophylaxis in preterm and low birth weight babies. The design of the study was approved by Local SIN Sections.

Following a detailed review of the literature, two different online surveys, one for Local Neonatal Units (LNUs, i.e., neonatal units with a level of care equivalent to AAP Level I and II neonatal units), and one for Neonatal Intensive Care Units (NICUs; i.e., units with a level of care equivalent to AAP Level III) were drafted ad hoc by the Authors (see supplemental data 1 and 2). Both multiple-choice questionnaires examined iron prophylaxis indications, as well as type of iron salt and dosage schedule suggested (14 questions); in the NICUs questionnaire (34 questions) timing of commencement and cessation of iron supplementation as well as timing of follow-up controls and special situations were investigated, too.

In the period between January 2016 and March 2016, the survey was distributed to 75 hospitals that were included in the SIN list (www.biomedia.it), for a totality of 74 LNUs (Piemonte n = 25, Marche n = 13, Lazio n = 36) and 20 NICUs (Piemonte n = 8, Marche n = 1, Lazio n = 11). Each individual LNU and NICU was contacted by e-mail to a maximum of three attempts. Respondents were asked to answer with reference to what is specifically reported in their internal protocol, if any; where a protocol was not present, respondents were asked to answer in accordance to the "common practices" of their Units regarding these issues.

Data were reported as absolute frequencies and percentages. Differences in responses between groups were tested using Fisher Exact Test. A p value <0.05 was considered statistically significant.

3. Results

3.1. Response rate and demographic characteristics of enrolled units

Overall, there was a 66% (49/74) response rate for LNUs and one of 70% (14/20) for NICUs, with a participation of LNUs that was significantly higher in Piemonte and Marche than in Lazio (96%, 92% and 36%, respectively; $p < 0.0001$). Responses regarding demographic characteristics of enrolled Neonatal Units are reported in Table 1.

Even though in 10/14 (71%) NICUs there was an internal protocol regarding iron supplementation for specific categories of neonates, all respondent LNUs and NICUs declared that they would consider drafting of SIN guidelines about these issues very useful for their clinical practice. Three responding LNUs were excluded from subsequent analysis, as physicians declared that they never suggested iron prophylaxis, being unaware of the utility of iron supplementation in preterm neonates.

3.2. Indications of iron prophylaxis

When queried regarding conditions considered as indications for iron prophylaxis in their Units, the majority of respondents indicated gestational age (91% for LNUs and 93% for NICUs) and hematological parameters (91% for LNUs and 86% for NICUs) (Fig. 1).

Birth weight was considered an indicative parameter in only 64% of LNUs and 71% of NICUs, with a significant difference between LNUs in the three regions (86%, 20% and 62% in Piemonte, Marche and Lazio, respectively; $p = 0.001$). In particular, iron was recommended to infants with a birth weight between 2000 and 2500 g in only 25% of LNUs and 21% of NICUs, and to late-preterm (gestational age between 34 and 37 weeks) in a minority of Units (26% of LNUs, 7% of NICUs).

Table 1 Demographic characteristics of enrolled units. Data are expressed as number of respondent Units and percentage.

	Piemonte (n = 24)	Marche (n = 12)	Lazio (n = 13)	Total (n = 49)
Births/year				
<500	0	1 (8%)	0	1 (2%)
500–1000	11 (46%)	8 (67%)	3 (23%)	22 (45%)
1000–2000	10 (42%)	2 (17%)	5 (38.5%)	17 (35%)
>2000	3 (12%)	1 (8%)	5 (38.5%)	9 (18%)
Gestational age of assisted newborns				
>32 weeks GE	16 (67%)	6 (50%)	9 (69%)	31 (63%)
>34 weeks GE	8 (33%)	6 (50%)	4 (31%)	18 (37%)

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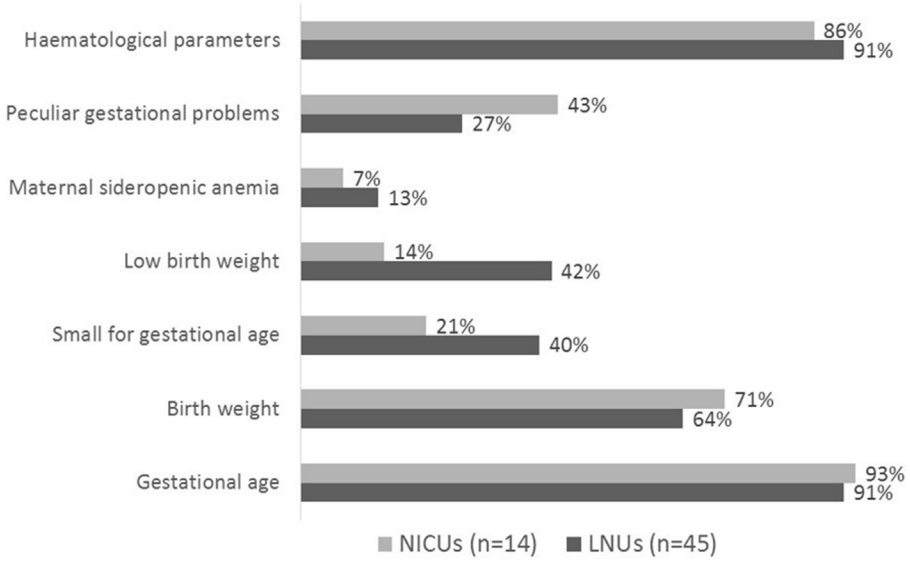

Figure 1 Conditions that respondents consider indications for iron prophylaxis. Data are presented as percentages of survey respondents.

3.3. Dosage and schedule

Sixty-nine percent of LNUs administered iron at a dosage of 2 mg/kg/day, while 43% of the NICUs recommended a dosage of 3 mg/kg/day; ($p = 0.01$) (Fig. 2). In 10/14 NICUs (71%) administration schedule was twice daily without milk, in contrast to 3/14 NICUs (21%) in which the administration was once daily without milk and to 1 Unit in which total daily dosage was split into 6 doses and administered with milk.

3.4. Type of iron salt

Sixty-one percent of LNUs and 71% of NICUs preferred the administration of isolated iron salt to the association of iron and vitamins. Important differences regarding the type of iron salt recommended within and between the three regions are clear form analysis of data (Table 2).

3.5. Timing of prophylaxis

Timing of commencement and cessation of iron supplementation were investigated only for NICUs in detail. Prophylaxis was initiated in 50% of the NICUs ($n = 7$) on a specific day of life (variable between Units, depending on birth weight and gestational age); in four Units (29%) commencement of iron administration depended on specific different hematological parameters (i.e., reticulocyte hemoglobin content-CHr, ferritin, absolute reticulocyte

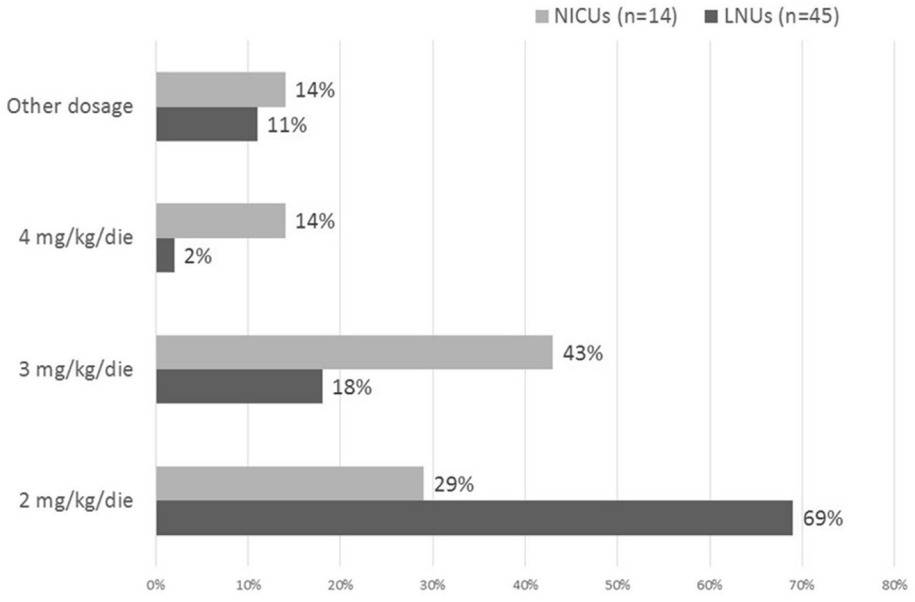

Figure 2 Dosage of elemental iron suggested for prophylaxis. Data are presented as percentages of survey respondents.

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Table 2 Type of iron salt recommended in different Neonatal Units. Data are expressed as absolute number of respondents.

	Piemonte	Marche	Lazio	p-value
Iron sulphate	0	1	4	0.01
Iron pidolate	5	0	1	>0.05
Liposomiale Iron	3	6	3	0.03
Iron gluconate	1	2	4	>0.05
Iron bisglicynate chelate	13	0	0	<0.0001

count-ARC, Hematocrit-Ht, Hemoglobin-Hb, and mean corpuscular volume-MCV). Seven of fourteen NICUs (50%) recommended prophylaxis until 12 months of age and three of fourteen (21%) until the introduction of complementary food; in the remaining Units iron was discontinued at the achievement of specific cut-offs of different hematological parameters. The great variability of analysed parameters and relative cut-offs between different regions and even within the same region is reported in Table 3.

3.6. Follow-up analysis

In 9/14 (64%) NICUs periodic follow-up analysis were performed during prophylaxis and timing of hematological controls greatly varied within Units (from every 2–6 weeks). Three out of fourteen (21%) Units performed blood controls only before suspending iron administration. The parameters analysed in the majority of Centres were complete blood count (100%) and reticulocyte count (92%); some Units consider CHr (46%) and ferritin (38%).

3.7. Particular situations

Fifty-eight percent of NICUs increased iron dosage during eritropoietin administration. In 71% of the NICUs, it was mandatory to exclude an excessive iron overload with ferritin dosage before starting iron prophylaxis in neonates who had previously received red blood cell transfusions. In 9/14 NICUs (64%) iron was not discontinued in the presence of retinopathy of prematurity.

4. Discussion

Both the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)[10] and the American Academy of Paediatrics (AAP)[11] recommend supplementation of preterm neonates and low birth weight infants with enteral iron as a beneficial intervention. The aim of this pilot study was to present a snapshot regarding current practices of neonatal iron prophylaxis among Neonatal Units of three Italian Regions (Piemonte, Marche and Lazio).

Despite the limited number of contacted Units, the good response rate observed (more than 60% both for LNUs and NICUs) confers on our survey an acceptable external validity and allows us to draw some preliminary conclusions.

We found a poor adherence to recommendations in the literature.

Particularly, our data indicate the need for a special attention to late preterm and low birth weight infants. Even though these two categories of neonates are proven to be at high risk of developing iron deficiency and iron deficiency anemia, less than a quarter of respondent Units routinely prescribed iron therapy for them.

Moreover, in contrast with AAP and ESPGHAN recommendations, more than 90% of both LNUs and NICUs considered hematological parameters prior to beginning iron administration.

Recommended dosage significantly varies with the levels of care, with NICUs prescribing higher dosages (i.e., elemental iron 3 mg/kg/day or more) than LNUs.

In recent years, we have seen the advent of several new formulations of oral iron (sulphate, pidolate, gluconate,

Table 3 Parameters and relative cut-offs considered indicative of efficacy of prophylaxis. Data are expressed as value considered, number of respondent Units and percentage. Total number of respondent Units in the three regions is 13. Multiple answers were possible.

	Piemonte Cut-offs (n/tot; %)	Marche Cut-offs (n/tot; %)	Lazio Cut-offs (n/tot; %)
ARC (n/mmc)	>100,000 (1/13; 8%)	Not considered	>100,000 (1/13; 8%)
CHr (pg)	>29 (1/13; 8%) >30 (2/13; 15%) >29–32 (1/13; 8%)	Not considered	>25–28 (1/13; 8%)
Ht (%)	Not considered	Not considered	>25 (1/13; 8%) >30 (1/13; 8%) >32 (1/13; 8%)
MCV (fl)	Not considered	Not considered	>80 (1/13; 8%) >100 (1/13; 8%)
Ferritin (ng/ml)	>10 (1/13; 8%) >60 (1/13; 8%)	Depending on age (1/13; 8%)	>50 (1/13; 8%) >150 (1/13; 8%)
Hb (g/dl)	Depending on age (1/13; 8%)	Not considered	>9.5 (1/13; 8%) >10 (1/13; 8%) >11 (1/13; 8%)

ARC = absolute reticulocyte count; CHr = reticulocyte hemoglobin content; Ht = Hematocrit; MCV = mean corpuscular volume; Hb = Hemoglobin.

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liposomial, bisglicinate chelate); however, the bioavailability of these different products, as well as their efficacy in terms of hematological response, remains to be elucidated. Our survey demonstrates a significant variability in prescribing attitudes, depending on geographic location more than on levels of care in different Units.

Timing of beginning and ending of supplementation and of follow-up controls need to be standardized, too. Special attention must be paid to assessment of hematological response. In more than 60% of respondent NICUs, periodic follow-up analyses were performed during prophylaxis. Neonatologists should be careful to minimize frequency and quantity of phlebotomy losses. Since a single parameter is a poor indicator of iron status of the newborn,[20] neonatologists should take advantage of micro methods to simultaneously evaluate different indicators. Moreover, they could consider CHr, which has been proposed as suitable marker, superior even to ferritin, for latent iron deficiency in preterm infants at 3—4 months corrected age.[21]

In conclusion, this pilot survey documents a great variability in the approach to iron prophylaxis of preterm and low birth weight infants, and underlines the urgent need for standardization.

A larger nation-wide survey is ongoing in order to obtain more detailed information of Italian neonatologists' attitudes regarding these issues. Simultaneously, authors are working with Neonatal Hematology Study Group of Italian Society of Neonatology in order to define updated shared protocols and to spread them across Italian Neonatal Units.

Conflict of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pedneo.2018.01.013.