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Iron status in a group of Norwegian children aged 6–24 months

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An adequate iron status is of vital importance for health and development in infancy and early childhood. Iron status was evaluated in a group of full-term Norwegian children followed longitudinally, at the ages of 6 mo ($n = 278$), 12 mo ($n = 249$) and 24 mo ($n = 231$) by measuring haemoglobin (Hb), mean cell volume (MCV) and serum ferritin. At 6, 12 and 24 mo of age, 3, 10 and 12%, respectively, had iron deficiency anaemia (IDA) defined as Hb <110 g/l in combination with ferritin <15 μg/l. With more restrictive criteria for defining IDA (Hb <110 g/l or <105 g/l in combination with ferritin <12 μg/l), the prevalence decreased to 1–2% at 6 mo and 2–5% at 12 and 24 mo of age. If children with a history of fever in the previous month were excluded, the proportion of children with depleted iron stores (ferritin <10 μg/l) increased from 2 to 3% at 6 mo, from 5 to 7% at 12 mo and from 9 to 13% at 24 mo.

Conclusion: Mild iron deficiency anaemia exists among otherwise healthy Norwegian infants and toddlers. The prevention and early treatment of iron deficiency should be a priority for the child health services.

Key words: *Iron deficiency, iron status, anaemia, haemoglobin, serum ferritin*

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Adequate iron status is of special importance during pregnancy and the first two years of life to ensure optimal development of the brain and nervous system. Iron deficiency anaemia (IDA) in this period is associated with delayed mental and motor development. Evidence is accumulating to show that the association is causal (1, 2). It is uncertain whether such consequences are reversible (3–5). Prevention of IDA may therefore prove to be of profound importance for the health and development of infants and toddlers. Rapid growth and a high iron requirement may exceed the dietary intake during the first years of life. After the age of two, the growth rate decreases and thereby also the risk of IDA (6).

IDA develops when the concentration of haemoglobin (Hb) decreases as a result of iron deficiency. Anaemia is defined as Hb concentration below an established cut-off value. IDA refers to an anaemia that is associated with additional laboratory evidence of iron deficiency, such as low serum ferritin concentration (ferritin), transferrin saturation or mean corpuscular volume (MCV) or an elevation in erythrocyte protoporphyrin or transferrin receptor levels (TfR) (7). However, these indicators are difficult to interpret in infants and young children (8). Anaemia can also be caused by deficiency of other nutrients or arise following infection, inflammation or vaccination (9–11). A combination of several tests increases specificity (6).

This paper describes iron status from 6 to 24 mo of age. The overall aim of the survey was to describe the iron status and dietary factors influencing iron status in a group of apparently healthy Norwegian children followed longitudinally from birth to 2 y of age. Recent data on iron status in large groups of Norwegian infants and young children have been lacking.

Subjects and methods

Subjects

All pregnant women booked to deliver at Aker University Hospital in Oslo between April and June 1997 were invited to participate in the study. At the time of the study, this hospital had the largest maternity ward in Oslo and provided care for 14 of the 25 local authorities within the city of Oslo. Invitations were sent to 471 pregnant women with Norwegian or other Nordic origin. By the time of delivery, 78% of the invited women agreed to be interviewed and contacted again when the baby was 6 mo old. Another 67 women (of Nordic origin) who were not booked at the hospital when the invitations were distributed, were recruited at the maternity ward when they were admitted to the hospital for delivery. A total of 364 mothers fulfilled the following inclusion criteria: singleton birth, gestational period of 37–42 wk and child's birthweight over the 2.5

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percentile (2600 and 2700 g for girls and boys, respectively) (12).

The study design was approved by the Regional Committee for Research Ethics in Norway and the Norwegian Data Directorate. The parents were informed that they could withdraw from the study at any time without explanation, and informed written consent was obtained prior to the blood sampling.

Blood sampling

Venous blood samples were drawn at the ages of 6 mo ($n = 284$), 12 mo ($n = 249$) and 24 mo ($n = 231$). A total of 197 children participated at all stages.

All infants were presumed to be healthy at the time of blood sampling. If a child had fever (indication of infection) shortly before blood sampling, a new appointment was made. The common cold (without fever) was not considered reason enough to postpone the blood sampling.

The blood samples were drawn by trained laboratory technicians at the hospital at least 1 h after the application of the local anaesthetic cream EMLA® from Astra Zeneca. The infants were also given 2 ml of a concentrated sucrose solution on the tongue as an anaesthetic (if the parents wanted it). In a few cases at 6 mo ($n = 12$) a vein could not be found due to subcutaneous fat, and the blood was sampled from a finger tip. There was no significant difference in mean values of iron indices between the capillary and venous samples, and the capillary samples were hence included.

All analyses were performed at the central laboratory at the hospital. Red blood cell indices including Hb and MCV were measured using a Sysmex 8000/9000 haematology machine. Ferritin was analysed using an immuno-chemical method from Chiron Diagnostics (ACS: 180 Ferritin assay). The laboratory regularly underwent quality controls within international programmes (Labquality, Helsinki and Murex, USA).

Definition of iron status

Because of the methodological and biological problems regarding the definition of iron deficiency and identification of iron deficient subjects in infancy and childhood, iron status is described by using different cut-off values and combinations of values for Hb, MCV and ferritin. This approach was chosen also to facilitate the comparison with results from other surveys. The cut-off value for Hb established by the World Health Organization is 110 g/l up until 5 y of age (13). However, this cut-off value is being questioned (8). In children, ferritin below 10 μg/l indicates depleted iron stores. In combination with anaemia, a value of less than 15 μg/l indicates IDA (7).

Information to subjects about results

After the blood sampling at all ages, the parents were informed about their child's iron status, and received free diapers and some other consumer products for children (not food products). Children with Hb <110 g/l in combination with ferritin <15 μg/l, or with ferritin <10 μg/l were recommended a liquid iron preparation (5 ml of Nycoplus Neofer® from Nycomed, containing 45 mg of iron) twice a day for 2 mo to improve iron status.

Statistics

Iron indices are presented as means with standard deviations and as proportions of the entire sample. Student's *t*-test and Fisher's exact test were used to compare independent groups. Pearson's correlations were applied to correlate two variables. Computing and statistical analyses were performed by using SPSS® 10.0 for Windows.

Results

Iron status

The mean age (min–max; 10th–90th percentile) at blood sampling was 189 (155–215; 182–197) d at 6 mo, 382 (344–431; 373–392) d at 12 mo and 725 (693–785; 705–745) d at 24 mo.

Mean values (with standard deviations) for Hb, MCV and ferritin and the proportions of children with Hb, MCV and ferritin below cut-off values are shown in Table 1. At 6 mo, girls had significantly higher mean values than boys: Hb:117 vs 113 g/l; MCV: 78.6 vs 76.6 fl; and ferritin: 67 vs 49 μg/l ($p \leq 0.001$). At 12 and 24 mo, the gender difference was significant only for MCV (77.6 vs 75.9 fl at 12 mo; $p < 0.001$; 77.5 vs 76.2 fl at 24 mo; $p < 0.01$).

The proportion of children aged 6–24 mo with Hb <110 g/l was 26–39%, with MCV <73 fl 9–12% and with ferritin <10 μg/l 2–9%. At 6 mo of age, signifi-

Table 1. Laboratory tests for iron status in a group of Norwegian children, aged 6–24 mo, presented as means (SD) and proportions of children with values below cut-offs (*n*; %).

Iron status indices	N	Mean (SD)	Below cut-off, *n* (%)		
Haemoglobin (g/l)			<105 g/l	<110 g/l	
6 mo	284	115 (9)	26 (9)	74 (26)	
12 mo	249	112 (8)	41 (16)	98 (39)	
24 mo	231	113 (7)	24 (10)	72 (31)	
MCV (fl)				<73 fl	
6 mo	284	77.5 (3.2)		26 (9)	
12 mo	249	76.7 (3.3)		28 (11)	
24 mo	221	76.8 (3.4)		26 (12)	
Ferritin (μg/l)			<10 μg/l	<12 μg/l	<15 μg/l
6 mo	281	57 (38)	7 (2)[a]	11 (4)	17 (6)
12 mo	249	27 (19)	13 (5)[a]	26 (10)	53 (21)
24 mo	231	23 (15)	21 (9)[a]	29 (13)	68 (29)

[a] When all children with fever in the previous month are omitted, the percentages with ferritin <10 μg/l were 3 at 6 mo, 7 at 12 mo and 13 at 24 mo.

Table 2. Correlations between iron status indices in a group of Norwegian children aged 6–24 mo.

	Hb			MCV			Ferritin		
Age (mo)	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*
6–12	229	0.38	<0.01	229	0.80	<0.01	225	0.34	<0.01
6–24	209	0.32	<0.01	200	0.75	<0.01	204	0.08	0.26
12–24	212	0.51	<0.01	203	0.79	<0.01	210	0.10	0.13

cantly more boys than girls had Hb, MCV and ferritin below cut-off values (Hb: 53 vs 21, $p < 0.001$; MCV: 21 vs 5, $p < 0.01$; ferritin: 7 vs 0, $p < 0.05$). At 12 and 24 mo, this was the case for MCV (23 vs 5, $p < 0.01$ and 20 vs 6, $p < 0.05$, respectively), but not for Hb or ferritin.

The correlations between measurements of Hb, MCV and ferritin at different ages are shown in Table 2. The correlations were significant for all three measurements at 6–12 mo as well as for Hb and MCV at 12–24 mo and 6–24 mo. No correlation was found, however, in ferritin at 12–24 or 6–24 mo.

Both Hb and ferritin measurements at 6, 12 and 24 mo were obtained from 190 children. IDA according to the criteria set by Dallman et al. (7)—Hb <110 g/l in combination with ferritin <15 µg/l—was found at both 6 and 12 mo in one child, at both 6 and 24 mo in one child and at both 12 and 24 mo in four children. Three out of these four children had not been given iron medication as recommended at 12 mo.

Out of 192 children with ferritin measurements at all three ages, values lower than 10 µg/l were found at both 6 and 12 mo in two children, at both 6 and 24 mo in two children and at both 12 and 24 mo in one child. No one had low values according to these criteria at all three age stages.

Table 3 shows the proportion of children with low iron status, defined by different combinations of Hb, ferritin and MCV. There were only small differences between the genders. The number of children with IDA increased from 3% at 6 mo of age to 10% at 12 mo and 12% at 24 mo of age. If the number of children with depleted iron stores, defined as ferritin <10 µg/l but not low Hb, were added, the proportions of children with “low iron status” were 4% at 6 mo, 12% at 12 mo and 17% at 24 mo. The number of children with IDA was lower if MCV <73 fl is added as an additional criterion, or if a lower cut-off value for ferritin (12 µg/l) and/or Hb (105 g/l) is used. With these more restrictive criteria for defining IDA, the prevalence in this group of children decreased to 1–2% at 6 mo of age and 2–5% at 12 and 24 mo of age, as shown in Table 3.

Anaemia related to recent illness and vaccination

There was no significant difference in the prevalence of anaemia (Hb <110 g/l) or mean Hb between children with or without reported fever in the previous week at any age, or reported fever in the previous month at 12–24 mo. At 6 mo, a larger proportion of infants with than without reported fever during the previous month had anaemia at the time of blood sampling (35% vs 21%; $p < 0.05$), but this may be a random finding.

Fever did, however, influence mean ferritin values. The ferritin-raising effect of reported fever (both during the previous week and the previous month) was highly significant at 12 mo (39 vs 25 µg/l and 33 vs 24 µg/l, respectively) as well as at 24 mo (42 vs 21 µg/l and 28 vs 19 µg/l, respectively) ($p < 0.01$), but less pronounced and not significant at 6 mo. When children with fever in the previous month were excluded, the proportion with ferritin values below 10 µg/l increased somewhat, from 2 to 3% at 6 mo, from 5 to 7% at 12 mo and from 9 to 13% at 24 mo. The higher figures can be considered to apply to infants in this population without antecedent infections.

The proportion of infants with anaemia was not significantly higher in the group that had been vaccinated at the 1-y-old check-up (78 out of 96 infants) than in the group that had not yet been to this check-up at the time of the blood sampling (111 out of 147 infants) ($p = 0.15$).

Discussion

This study has succeeded in following longitudinally a large group of Norwegian infants from birth until 2 y. Assessment of iron status and comparison of iron status between different surveys is difficult for several reasons. The prevalence of IDA depends on the cut-

Table 3. Proportions of Norwegian children aged 6–24 months (*n*; %) with low iron status, defined by different combinations of Hb, ferritin and MCV.

	Total	
Combination of iron status indices	*N*	*n* (%)
6 mo		
Hb <110 g/l + ferritin <15 µg/l [a]	278	9 (3)
Hb <110 g/l + ferritin <15 µg/l + MCV <73 fl	278	2 (1)
Hb <110 g/l + ferritin <12 µg/l [b]	278	6 (2)
Hb <105 g/l + ferritin <12 µg/l [c]	278	2 (1)
Ferritin <10 µg/l (and Hb ≥110 g/l)	278	4 (1)
12 mo		
Hb <110 g/l + ferritin <15 µg/l [a]	249	24 (10)
Hb <110 g/l + ferritin <15 µg/l + MCV <73 fl	249	7 (3)
Hb <110 g/l + ferritin <12 µg/l [b]	249	13 (5)
Hb <105 g/l + ferritin <12 µg/l [c]	249	5 (2)
Ferritin <10 µg/l (and Hb ≥110 g/l)	249	5 (2)
24 mo		
Hb <110 g/l + ferritin <15 µg/l [a]	229	27 (12)
Hb <110 g/l + ferritin <15 µg/l + MCV <73 fl	219	9 (4)
Hb <110 g/l + ferritin <12 µg/l [b]	229	12 (5)
Hb <105 g/l + ferritin <12 µg/l [c]	229	4 (2)
Ferritin <10 µg/l (and Hb ≥110 g/l)	229	11 (5)

References: [a] (7), [b] (15), [c] (30)

off values used for the different iron tests. The cut-off values, and hence the definition of iron deficiency and IDA, vary among different studies. Lack of standardization among the tests and a paucity of laboratory proficiency testing limit comparison of results between laboratories (14).

According to the definitions by Dallman (7) of IDA (Hb <110 g/l in combination with ferritin <15 μg/l) and of depleted iron stores (ferritin <10 μg/l), the prevalence of low iron status was high in this group of otherwise healthy Norwegian infants and children. Using these definitions, a total of 4, 12 and 17% of the children had IDA or were iron depleted at the ages of 6, 12 and 24 mo, respectively.

Iron status compared to other studies

The prevalence of IDA and low Hb and ferritin values found in this survey is compared with other Nordic studies in Table 4. At 6 mo, the prevalence of IDA was low and similar to that found in groups of Danish and Swedish infants. The significant gender difference at 6 mo, not only in mean Hb and proportion of infants with Hb below cut-off, but also in MCV and ferritin, suggests that Hb even at this age may be indicative of iron status. The lower Hb and MCV could have been explained by a possible gender difference in antecedent infection, but then the ferritin values should have been higher, not lower as was found in this group.

The prevalence of IDA at 12 mo in the present study was similar to that found in previous (small) Norwegian studies, as well as studies of Swedish and Icelandic infants (15, 16), in spite of the strikingly higher prevalence of anaemia in the present study. The proportion of children with depleted iron stores (SF <12 μg/l; 10%) was similar to that found in previous Norwegian studies, but lower than that found among Swedish and Icelandic children (26 and 41%, respectively) (15, 16), and also lower than that found in the Euro Growth study (ferritin <10 μg/l: 16%) (17).

At 24 mo, the prevalence of IDA and depleted iron stores was similar to that found in previous (small) Norwegian studies and also similar to that found in a Swedish study of 2.5-y-olds (including immigrant children). The prevalence of anaemia was still high at 24 mo.

Anaemia: Hb cut-off

The prevalence of anaemia depends on the cut-off value used for haemoglobin. The ESPGHAN Committee on Nutrition (8) recently concluded that a Hb cut-off of 110 g/l may be too high and that there is a need to define more appropriate cut-off values for anaemia in infants and young children. Michaelsen proposed 105 g/l as a more realistic value for defining anaemia (18). Domellöf suggested new cut-off values for Hb of 105 g/l at 6 mo and 100 g/l at 9 mo based on iron-replete, breast-fed, unsupplemented infants (19). Some authors have argued, however, that it would be hazardous to assume that reality is better than it appears (20). Without any functional outcome measures, the selection of reference criteria for defining an iron replete population in Domellöf's study (as in others) seems arbitrary and based on assumptions. Lowering the Hb cut-off would result in identifying fewer individuals with anaemia due to causes other than iron deficiency (false positives), but also in overlooking more individuals with iron deficiency (true positives) (21).

Even if lowering the Hb cut-off would result in a more realistic proportion of children with anaemia, this will not explain the difference between this survey and other comparable surveys. It is hard to say whether the diverging anaemia prevalence is due to methodological incompatibility or actual differences in haemoglobin concentration. It is possible to imagine that the currently used cut-off values are not adjusted to currently used laboratory methodology, although analyses from laboratories subjected to quality control should be comparable.

Iron deficiency is by far the most common cause of anaemia in children. If the prevalence of iron deficiency declines, the proportion of anaemia due to other causes increases (14). Some individuals have an optimal level of haemoglobin below the cut-off of 110 g/l (22). Common infections and inflammations can lower the values of haemoglobin (infection anaemia) and MCV and increase ferritin (10, 23). Mild infections are common in the first years of life and are difficult to avoid in a blood sampling setting. Lacking good diagnostic tools to separate infection anaemia from anaemia due to other causes and thus separate false high ferritin values from true high values, all children were included in this paper. An elevated concentration of C-reactive protein (CRP) is sometimes used as an exclusion criterion because it is a marker for infection. However, a normal CRP cannot preclude falsely high ferritin values due to infection, presumably due to a longer half-time of serum ferritin than CRP, making CRP an unreliable criterion regarding iron status assessment (24).

The much higher proportion of children with low Hb values compared to low MCV or ferritin values, in addition to the fact that a history of fever did not seem to influence the prevalence of anaemia, may indicate that the anaemia is caused by other nutritional deficiencies. MCV is low in IDA, but normal (or raised) in anaemia caused by mixed nutritional deficiencies (25), e.g. folate, vitamin B12 and copper deficiencies (22). It could also indicate that the cut-off for Hb (110 g/L) is too high.

Ferritin

Ferritin, as opposed to Hb, was elevated in children aged 12 and 24 mo who were reported to have had fever in the previous week or previous month. The proportion of children with depleted iron stores (ferritin <10 μg/l) increased if children with reported fever in the previous month were excluded. Recent infection in this group thus seems to have led to a certain underestimation of depleted iron stores, from 1% at 6 mo to 4% at 24 mo.

Saarinen and Siimes (26) found that milder cases of IDA in infants can appear before body iron stores are exhausted and/or ferritin has reached a subnormal level. Difficulties in mobilization of storage iron and resulting high ferritin values may inhibit iron absorption from the gastrointestinal tract, which in turn can increase the risk of developing iron deficiency (27). In a study of the

Table 4. Proportions of children with iron indices below cut-off values in surveys from Nordic countries.

		IDA						
		Hb + SF		Hb		Ferritin		
Age (mo)	Country, *n*	g/l μg/l	%	g/l	%	μg/l	%	Ref.
6	**Norway,**	**110 + 15**	**3**	**<110**	**26**	**<10**	**2**	**This survey**
	Hb: *n* = 284	**110 + 12**	**2**	**<105**	**9**	**<12**	**4**	
	SF: *n* = 281	**105 + 12**	**1**	**<100**	**5**	**<15**	**6**	
	Hb + SF: *n* = 278							
6	Denmark	105 + 13	0	<110	32	<13	0	(18)
	Hb: *n* = 57			<105	5			
	SF: *n* = 47							
4–9	Sweden	110 + [a]	3					(31)
	n = 70							
9				<110	20			
12	**Norway**	**110 + 15**	**10**	**<110**	**39**	**<10**	**5**	**This survey**
	***n* = 249**	**110 + 12**	**5**	**<105**	**16**	**<12**	**10**	
				<100	**3**	**<15**	**21**	
12	Norway		4[c]	<110	7	<10	5	[b]
	Hb: *n* = 190			<100	1	<12	13	
	SF: *n* = 159							
12	Norway	110 + 15	0	<110	9	<10	0	(32)
	n = 33					<15	15	
12	Norway	110 + 15	2	<110	11	<10	13	[b]
	Hb: *n* = 93					<15	34	
	SF: *n* = 93							
12	Sweden	110 + 12	3	<110	13	<12	26	(15)
	Hb: *n* = 76			<105	8			
	SF: *n* = 56			<100	1			
12	Iceland	105 + iron deficiency[d]	3	<105	9	<12	41	(16)
	Hb: *n* = 114							
	MCV: *n* = 114							
	SF: *n* = 111							
24	**Norway**	**110 + 15**	**12**	**<110**	**31**	**<10**	**9**	**This survey**
	Hb: *n* = 231	**110 + 12**	**5**	**<105**	**10**	**<12**	**13**	
	SF: *n* = 231			**<100**	**3**	**<15**	**29**	
	Hb + SF: *n* = 229							
24	Norway	110 + 15	9	<110	16	<10	16	[b]
	Hb: *n* = 44							
	SF: *n* = 44							
24	Norway	110 + 15	0	<110	5	<10	9	(33)
	n = 37					<15	32	
30	Sweden	110 + iron deficiency [e]	7	–				
	Hb: *n* = 367					<12	10	(34)
	SF: *n* = 367							
	(32% immigrants)							

[a] Ferritin <12 μg/l + MCV <70 fl.
[b] Personal communication, B Borch-Iohnsen.
[c] Multiple criteria.
[d] Ferritin <12 μg/l + MCV <74 fl.
[e] Ferritin <12 μg/l + one abnormal iron test, or ferritin 12–19 μg/l + two abnormal iron tests.

effect of increased meat intake on iron status in infancy, Engelmann found that haemoglobin was affected directly by an increase in meat intake, although no difference in ferritin or TfR was found (28). It is thus likely that the haemoglobin concentration in infants can be decreased by a shortage in iron supply even if iron stores are not exhausted. If this is the case, the apparent increase in anaemia in the present study compared to previous Norwegian studies may reflect a decrease in available iron for Hb synthesis among Norwegian infants, even though ferritin levels are comparable.

Gender

A gender difference in iron indicators was found consistent with better iron status among girls. This difference may be related to faster growth velocity among boys, and hence a larger need for iron. Another possible explanation is that the gender of the infant may influence the mother's behaviour towards her baby with regard to breastfeeding pattern and/or other aspects of infant nutrition.

A similar gender difference in iron status was also found in Swedish 6–9-mo-old infants (29) and Icelandic 12-mo-olds (16). Domellöf et al. (29) conclude that some of the differences may be genetically determined while others seem to reflect an increased incidence of true iron deficiency in boys.

The results presented in this paper apply to a group of children followed from birth to 2 y of age. The groups at each age stage cannot be viewed as independent and random samples. Even if dietary advice was not given, the individual child's iron status at each stage was reported to the parents, together with advice on use of iron medication when needed. One possible consequence of this is that iron deficiency at the first or second blood test would have been corrected before the next blood test, and that this might have lowered the prevalence of IDA compared to what would have been the case if iron deficiency was not treated. It is also possible that participation in the project has led to increased awareness of the importance of adequate iron supply. On the other hand, normal iron status at one test may have lead to a feeling of false safety from iron deficiency. It is also possible that some parents may have had increased anxiety about iron or other nutrients because of their child's regurgitation or poor appetite. It is unlikely that reward in the form of free diapers and other infant products has had any influence on the infant's diet in the families who participated. The high percentage of families participating at all stages (78, 68 and 63% of those invited at 6, 12, and 24 mo, respectively) strengthens the credibility of the results.

Conclusion

Mild iron deficiency anaemia exists among otherwise healthy Norwegian infants and toddlers. The prevalence, however, depends on the definitions and criteria chosen for IDA. With the use of the criteria suggested by the ESPGHAN committee (8), the prevalence of iron deficiency anaemia in this group of children was 1–2% at 6 mo and 2–5% at 12 and 24 mo of age. The iron status yielding optimal functional outcome, regarding physical and mental development in infants and toddlers, is, however, not yet established. The high prevalence of low Hb values (<110 g/l) may support the view that this cut-off value for haemoglobin is too high. On the other hand, mixed nutritional deficiencies may have contributed in some cases of anaemia.

The prevention and early treatment of iron deficiency should be a priority for the child health services. Health personnel should encourage a diversified and nutrient-dense diet to ensure adequate intake of all essential nutrients.

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