

EDITORIAL

Iron deficiency and iron deficiency anaemia during infancy and childhood

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The present definition of iron deficiency and iron deficiency anaemia is under debate. Our present figures for the prevalence of iron deficiency in infants and toddlers are thus disputed.

Conclusion: Better understanding of the regulation of iron metabolism and requirement during the critical early period of growth and development is needed for relevant control of iron deficiency anaemia.

Key words: Iron deficiency, haemoglobin level, iron deficiency anaemia, infancy, childhood, pregnancy

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In a recently published “Medical Position Paper”, the ESPGHAN Expert Committee on Nutrition remarks that we may not know enough to define iron metabolism and iron requirements (1). The committee concludes that “the prevalence of iron deficiency during the first two years will not be known until we have a better understanding of the homeostasis and regulation of iron metabolism during this critical period of development”. Although iron deficiency (ID) and iron deficiency anaemia (IDA) have been intensely studied during the last century, the criteria for these conditions are still under debate.

In many reports on the prevalence of ID and IDA during infancy and childhood, adolescence, in adult males and females, and in pregnant women, the cut-off value for the haemoglobin level is <110 g/L, and for the serum ferritin level <12 microg/L. The fact that the Hb level changes markedly during infancy, that it differs in adults between men and women, and that it declines during pregnancy is not always taken into account. Nor is it generally considered that the Hb level increases with increasing altitude, that it is high in congenital heart disease with right-to-left shunt, and in lung diseases with reduced gas diffusion. The level is also elevated in the cord blood of fetuses who have been subjected to hypoxia (2).

Anaemia and iron status in high income countries

The ESPGHAN committee has good reasons to conclude that the cut-off points which are currently used for the definition of anaemia or for depleted iron stores overestimate the prevalence of these conditions (1). To elucidate whether this statement is correct, some recent reports on the prevalence of IDA and iron status at 12 mo of age in some European countries have been reviewed. The situation among newborns, infants, older children, adult men and women, and pregnant women in high and low income countries has been considered.

In the US, the prevalence of iron deficiency in early childhood has declined considerably over the last two decades, which may be attributed to improved infant feeding and more efficient preventive programmes (3, 4). Prevalence reported from different European countries varies, which may be due to differences in populations, different feeding practices and varying criteria for the definition of ID. Thus, in children between 1 and 2 y of age, the prevalence of ID has been reported to be 9–34% and that of IDA to 3–8% (5–7).

In a prospective longitudinal cohort study to assess the prevalence of ID in European children up to 16 mo of age, a cohort consisting of 488 normal term infants

Table 1. Prevalences of anaemia, abnormal iron indicators, iron deficiency and iron deficiency anaemia in European infants (from Male C et al. (8)).

	Cut-off value	Total (n = 488) % (n) % deficient	Girls (n = 277) % (n) % deficient	Boys (n = 261) % (n) % deficient
Anaemia	Hb <110 g/L	9.4	7.0	11.5
Low mean corpuscular volume	<70 fl	4.6	2.3	6.7
Low serum ferritin	<10 µg/L	15.6	12.8	18.0
Low transferrin saturation	<10%	15.0	13.5	16.3
High serum transferrin receptor	>4.4 mg/L	8.4	6.6	10.0
Iron deficiency ^a		7.2	4.8	9.2
Iron deficiency anaemia ^b		2.3	1.3	3.1

^a Two or more iron indicators are abnormal (MVC, SF, TSA, TfR)

^b Hb plus two or more iron indicators are abnormal

from primary health care centres were recruited from cities in 11 European countries (Athens, Bilbao, Budapest, Dublin, Madrid, Naples, Porto, Rostok, Santiago, Umeå and Vienna) (8). Socio-economic variables, feeding, anthropometry and morbidity were assessed at regular intervals from birth. From the estimation of the concentrations of Hb, serum ferritin, mean corpuscular volume (MCV), transferrin saturation (TSAT) and serum transferrin receptor (TfR) at 12 mo of age, the prevalence of anaemia was found to be 9.4%, of ID 7.2% and of IDA 2.3%. More than 40% of the infants who were anaemic although the iron status was normal had been subjected to recent infections. IDA was found in 5.1% of families of low socio-economic status but not at all in families of high status. Iron-fortified formula was the main factor which was positively correlated with iron status. Otherwise, the type of infant feeding did not play any role in the iron status. Main individual data from the European study are summarized Table 1.

In an Icelandic study with about the same design as the European study, iron status at 12 mo of age was correlated to the food intake, rate of growth and body size as well as to feeding (9). Twenty percent of the infants (27% of the boys and 12% of the girls) were considered to be iron deficient, and 2.7% were also anaemic. The cut-off levels and the percentage below this level are shown in Table 2. The female infants had significantly higher MCV and serum ferritin— 77.3 ± 4.1 fl and 19.8 ± 12.3 µg/L, respectively—than the male infants who had an MCV and serum ferritin level of 75.5 ± 4.2 fl ($p = 0.023$) and 14.8 ± 9.5 µg/L ($p = 0.018$), respectively. ID at 12 mo was associated

Table 2. Iron status in Icelandic infants at 12 mo of age (from Thorsdottir et al. (9)).

	Cut-off	Percent <cut-off
Hb	<105 g/L	9
MCV	<74 fl	29
SF	<12 µ	41
TfR	>8.5 µg/L	25

with fast growth and short duration of breastfeeding. From the results, it was concluded that the daily intake of cow's milk in 9–12-mo-old infants should not exceed 500 g.

In the May issue of *Acta Paediatrica*, iron status among Norwegian 6-, 12- and 24-mo-old full-term children has been reported (10). At these ages 3, 10 and 12%, respectively, had IDA defined as Hb <110 g/L in combination with ferritin <15 µg/L. It was thus concluded that mild IDA is not at all rare among otherwise healthy Norwegian infants and toddlers. It is, however, quite logical that the authors of the Norwegian paper agree with the ESPGHAN Committee on Nutrition that the cut-off level for Hb as recommended by WHO and others (11, 12) may be too high. Thus, they suggested more restrictive criteria for anaemia in infants and toddlers, i.e. Hb <110 g/L in combination with a ferritin level <12 µg/L. Previously, Michaelsen et al. have proposed <105 g/L as a more realistic value for the definition of anaemia (6). Based on breastfed iron-unsupplemented infants, Domellöf et al. suggested a cut-off value for Hb of 105 g/L at 6 mo, and 100 g/L at 9 mo of age (13).

The gender difference in iron indicators as found in the Icelandic (9) and Norwegian (10) studies as well as in a Swedish study (14) have been suggested to be due to faster growth velocity in boys with higher iron requirement than in girls. Other reasons may be differences in behaviour and breastfeeding patterns. The gender difference of TfR at 6 mo of age may indicate different iron status and an increase in the prevalence of infections, as MCV and ferritin levels are influenced by infections in contrast to TfR. This fact, as well as the difference in iron status, may also explain why mean MCV and ferritin levels are lower in boys than in girls at 6 and 9 mo of age (8).

Prevalence of anaemia and iron deficiency in low income countries

The prevalence of anaemia of nutritional origin is extremely high among children in many low income

countries. For instance, with a cut-off level for Hb of 110 g/L it has been reported to be 82% among 0–4-y-old children in Bangladesh (15), 38–73% among Indonesian children of the same age (16), and 23% among Chinese kindergarten children (17). Anaemia may also have been considered to be nutritional, although it has been caused by occult blood losses due to hook-worm parasites or other intestinal infections.

Anaemia and iron deficiency during pregnancy

Anaemia and ID during pregnancy, which not only affects the mother but also her foetus and newborn infant, has attracted great concern. For instance, 75% of pregnant women in Uzbekistan have been reported to be anaemic (18). IDA in pregnancy also has a high prevalence in Africa (44–55%) and in India (62–88%), and may even be as high as 18% in industrialized countries (19). However, when evaluating haematological data in pregnant women, it should be remembered that the fall of the Hb level is associated with an increase in the plasma volume of up to 50% at 34–37 wk of gestation. In reality, dilution anaemia is associated with an increase of the total amount of Hb by 30% (18). However, the total iron requirement during pregnancy increases not only because the blood volume of the mother increases but also due to the requirement of the foetus, which is about 1000 mg up to term. The daily requirement during the first trimester is estimated to be 1–2 mg, during the second 2 mg, and during the third 6 mg (19). During pregnancy, ID is defined when the ferritin level is $<12 \mu\text{g/L}$. Since specificity and sensitivity of the ferritin level is low because it increases during infections and falls during pregnancy, the soluble transferrin receptor level has been recommended as a better parameter for assessment of erythropoietic activity in maternal blood and neonates. As it increases during pregnancy, a level above <8.5 has been recommended (20, 21).

The mechanism for the iron balance between mother and foetus during pregnancy is still unclear. The flux of iron from mother to foetus is regulated by HFE, which is linked to a beta 2-microglobulin. As the requirement of iron of the foetus is a priority, moderate IDA in the mother has no negative effect on the haematological indicators in cord blood. On the other hand, severe IDA in the mother is followed by reduced iron store in the foetus. Thus, if the maternal Hb level drops $<60 \text{ g/L}$, the Hb level in cord blood may be reduced to 110–120 g/L (22, 23).

Haemoglobin levels during early postnatal life

The criteria used by WHO for the definitions of anaemia and ID are inaccurate during early infancy. Thus, in healthy full-term infants, the mean Hb concentration declines by approximately 30%, i.e. from about 170 to

110 g/L within the first 6–8 postnatal wk (24). In preterm infants, this postnatal fall is still more pronounced, and the lower the gestational age, the more pronounced is the postnatal fall of the Hb level. In infants with a birthweight between 1500 and 2000 g, the lowest level is 94 g/L, and in infants with a birthweight between 1200 and 1500 g, it is 90 g/L (25). In full-term infants, the mean Hb level is 126 g/L at 1 y of age if the feeding has been correct and there has been no blood loss during delivery from early clamping of the cord. Infants born at a high altitude of about 4000 m, for instance in Bolivia or Tibet, have the same cord blood Hb level as infants born at sea level (26). However, postnatally, their oxygen sensors respond to the low environmental oxygen tension by increasing the Hb level instead of letting it decline. The difference in the postnatal course of the Hb level as found between infants born at sea and high altitude level demonstrates that the Hb level is related to demand. However, as the oxygen-carrying capacity depends upon the total amount of circulating Hb, Hb does not always give accurate information as to whether the physiological requirement is met, a fact which is obvious during pregnancy. In newborns, the consequence of sludge of red cells should also be considered (27).

Functional consequences of iron deficiency and anaemia

Dallman, the grand old man within the field of nutritional child anaemia, has asked the question whether ID matters unless there is also anaemia (28). However, studies on the relation between working capacity and ordinary haematological data, including the total amount of Hb, in school children of both genders may give new aspects on this problem.

Each haem molecule contains one atom of iron, which means that Hb synthesis will be reduced in ID. But cellular oxidizing enzymes such as cytochrome C also contain iron, which means that deprivation of iron reduces the intracellular bioenergetic capacity in the brain and other vital organs. Thus, in attempts to clarify the functional consequence of ID and anaemia, not only should the working capacity be considered but also processes which are of central importance during early life such as neurotransmission and myelin formation (29). Studies on the relation between iron status and early psychoneurological development may give further information about iron requirement in early life (30–33).

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