Prevalence and causes of iron deficiency anemias in infants aged 9 to 12 months in Estonia

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Key words: anemia; infant; iron deficiency; risk factors.

Summary. Objective. To investigate the prevalence and causes of iron deficiency anemia in infants aged 9 to 12 months in Estonia.

Material and methods. Every second child aged 9–12 months was randomly selected from primary medical centers in seven counties from all over Estonia. A questionnaire concerning eating habits and lifestyle was sent to their parents. Sixty-five percent (n=195) of contacted families agreed to participate in the study. Mean corpuscular volume and hemoglobin, serum ferritin, and soluble transferrin receptor levels were measured in 171 infants. Anemia was defined when hemoglobin level was lower than 105 g/L, and iron deficiency when ferritin level and mean corpuscular volume were lower than 12 µg/L and 74 fL, respectively.

Results. The prevalence of iron deficiency was 14.0% and iron deficiency anemia 9.4%. Birthweight less than 3000 g was the main risk factor for iron deficiency (OR=9.4; P<0.0005). Infants fed with breast milk and solid food had lower ferritin concentration (18.5 µg/L, 95% CI 14.0–23.0) than infants fed with formula and solid food (32.8 µg/L, 95% CI 26.6–39) (P<0.005).

Conclusion. Iron deficiency anemia is common among 9–12-month-old Estonian infants. The main risk factor for iron deficiency was birthweight less than 3000 g.

Introduction

Iron deficiency anemia (IDA) in children is a common nutritional problem all over the world (1, 2). Infants and young children have a high risk for developing iron deficiency (ID) because they have high demand for iron during the period of rapid growth. This is aggravated by the insufficiency of iron in their diet (3). Iron deficiency develops most commonly in late infancy and during the second year of life (4, 5). The first stage of developing ID is the diminishing of storage iron (prelatent iron deficiency) seen by reduced plasma ferritin concentration. When iron stores are almost empty, a latent iron deficiency will develop which may lead to the manifestation of IDA (6). Recent studies have shown that IDA has an impact on psychomotor development and cognitive functions (7, 8) in children, as well as on growth (9). IDA has also shown to increase the risk of respiratory infections (10).

Recent studies have shown a big variance in the prevalence of IDA among developed countries (1–8%) (2, 5, 11–12). These figures may even be higher in some socioeconomic groups. Gregory et al. (13) found that up to 40% of infants aged 6–24 months living in socioeconomically deprived urban areas in the United Kingdom had IDA (9). A high prevalence (30–51%) of IDA has been also reported in low-income countries (14, 15). The differences in the prevalence of IDA may be partly explained by the different criteria used to define IDA. The previous study in Estonia in 1996 found that 18% of rural and 45% of urban children aged 3–4 years had microcytic anemia (16). However, the authors of this study used hemoglobin concentration and mean corpuscular volume (MCV) as indices of iron status, and serum ferritin concentration was not measured. Therefore, the real prevalence of IDA in Estonia is not known. This problem is especially important now when family doctors have replaced pediatricians in primary care settings. This change means a challenge for primary health care and highlights the importance to investigate the prevalence and associated background factors for ID and IDA.

Thus, the aim of this study was to estimate the prevalence and associated background factors for ID and IDA in infants aged 9 to 12 months in Estonia.

Methods

The study was performed in three periods: a pilot...
study was carried out in the county of Tartu between July 2002 and February 2003; a population-based study was carried out from October 2004 to March 2005. Family doctors from seven different counties from all over Estonia were asked to make a list of all children aged 9 to 12 months. Letters (n=300) were sent to every second parent from the list. An information letter with explanation about the study and questionnaire were sent to parents. The questionnaire contained 20 questions about living conditions, parents’ education, past illnesses, and baby’s feeding habits. We received back 225 filled questionnaires. Thirty parents refused from blood tests. Thus, 195 out of the 300 families (65%) gave their consent to participate in the study and to take blood tests from their infant. Enough blood for all tests was obtained from 174 infants. Three infants were excluded from the study because their C-reactive protein (CRP) level was increased.

Before blood tests, skin was anesthetized with EMLA 5% cream. Blood samples were obtained by sticking the vein once. Hemoglobin (Hb) and mean corpuscular volume (MCV) were analyzed on the Coulter Counter (Sysmex K-1000 and Sysmex XE 2100, Kobe, Japan). Concentration of serum ferritin was measured using a solid-phase, two-site chemiluminescent immunometric assay (Immulite® 2000, Diagnostic Products Corporation, Los Angeles, CA, USA). Serum soluble transferrin receptor (sTfR) assay was performed using a latex turbidimetry (Orion Diagnostica, Espoo, Finland) with analyzer Cobas Mira 400, Roche Diagnostics GmbH, Mannheim, Germany). All tests were analyzed at the United Laboratory of Tartu University Hospital, Tartu, Estonia.

The criteria for IDA were Hb<105 g/L, ferritin<12 µg/L and MCV<74 fL, and for ID ferritin<12 µg/L and MCV<74 fL. Infant who had either ferritin or MCV or both above these cutoff points were classified as iron-sufficient. The cutoff values for Hb (105 g/L) and for MCV (74 fL) have been used in earlier studies (2, 11, 17, 18). These values deemed to be appropriate for this age group. The value for serum ferritin (12 µg/L) was used according to the WHO criteria (19). Infants were categorized into one of four groups: iron-sufficient, not anemic (group 1); iron-sufficient, anemic (group 2); iron-deficient, anemic (group 3); and iron-deficient, not anemic (group 4).

CRP concentration of <5 mmol/L was used as a criterion to exclude cases with possible increase in ferritin concentration due to infection. Serum sTfR concentration higher than 3.3 mg/L was used to detect latent ID (20).

Parents and family doctors were informed about the results by letter, and written recommendations on feeding, if necessary, were given. If a blood test showed any abnormalities, infant was referred to their family doctor or to a pediatrician.

The Human Research Ethical Committee at the University of Tartu approved the study, and informed consent from the parents was obtained before blood tests.

Statistical analysis
Data were analyzed using statistical program R Development Core Team Version 1.7.0 (2003). Student’s t test for parametric continuous variables and Wilcoxon two-sample test for nonparametric continuous variables were used to compare the difference between the groups. The results are shown as a mean with 95% confidence interval. A stepwise regression analysis and Fisher’s exact test were used to define the determinants of iron status and the associated background factors for ID and to find odds ratios (OR). A P value of <0.05 was considered statistically significant.

Results
A total of 171 infants were included into the final analysis. There were 117 infants (68.4%) with Hb and either ferritin or MCV or both above the cutoff points composing the control group (group 1). Fourteen infants (8.2%) had anemia without ID (group 2); 16 infants (9.4%) had IDA (group 3). Twenty-four infants (14.0%) had ID without anemia (group 4). The concentration of serum sTfR was increased in 6 infants (3.5%) (Table 1). Seven out of the 171 babies were preterm infants born at 34th (n=1), 36th (n=1), and 37th (n=5) gestational weeks with a birth weight (BW) of more than 2000 g in all subjects.

In the analysis of associated background factors for ID and IDA, groups 3 and 4, i.e. iron deficient groups, were analyzed together. The mean BW in the iron deficient group was significantly lower than in the control group (3393 g (95% CI 3227–3559) vs. 3627 g (95% CI 3534–3720); P<0.01). The weight gain since birth was statistically higher in the iron deficient group (mean age of 10.8 months) than in the control group (mean age of 10.4 months) (6825 g (95% CI 6349–7301) vs. 6288 g (95% CI 6059–6516), P<0.05). The weight gain in infants with BW<3000 g was not different within the group (ID vs. control) as well as from those with BW>3000 g. Birthweight of less than 3000 g was a significant risk factor for ID: OR=9.4 (95% CI 2.7–33.0) (P<0.0005). Twenty-five
out of the 92 (27.2%) boys were iron-deficient while only 10 (12.6%) of the 79 girls had ID. The boys had a tendency to have a lower ferritin concentration than girls, but the difference was not statistically significant (21.0 μg/L (95% CI 16.8–25.4) vs. 27.0 μg/L (95% CI 22.1–31.9); P=1.3). Socioeconomic variables such as age and educational level of the mother, living in urban or rural area, did not have an effect on iron status (Table 2). In the analysis of feeding habits, we found that 36 (21%) of the 171 infants were exclusively breastfed up to 6 months and 68 (39.8%) of the 171 were partly breastfed, i.e. were fed with breast milk and solid food at the time of the study. Duration of exclusive breastfeeding (3.6 months (95% CI 2.9–4.7)) or duration of total breastfeeding (7.0 months (95% CI 5.5–9.2)) was similar in the iron deficient group and in the control group. However, infants who were exclusively breastfed until the age of 6 months had significantly lower Hb (113 g/L (95% CI 111–115)) and ferritin (18.7 μg/L (95% CI 15.2–22.3)) levels than infants who were exclusive breastfed only until the age of 3 months (117 g/L (95% CI 115–119) 28.0 μg/L (95% CI 22.7–33.4), respectively) (both P<0.05). The same tendency was seen in Hb values between the groups defined by the age of introducing solid food: the infants fed with solid food before 6 months had statistically higher Hb values than infants whom the solid food was introduced after 6 months of life (118 g/L (95% CI 115–120) vs. 114 g/L (95% CI 110–117), respectively; P<0.05). Infants fed with breast milk and solid food had a lower ferritin concentration (18.5 μg/L (95% CI 14.0–23.0)) than infants fed with formula and solid food (32.8 μg/L (95% CI 26.6–39)) (P<0.005). The ORs are seen in Table 2. Nearly every third infant (56 of the 171) was fed with cow’s milk before 9 months of age, and 16 of those had ID. Their ferritin concentration was lower compared to the infants who had not received cow’s milk (18.8 μg/L (95% CI 14.3–23.7) vs. 26.1 μg/L (20.5–40.1) (P<0.05)).

We suspected secondary IDA in two infants with poor weight gain, but no underlying disease was found.

### Table 1. The indices of iron status at the age of 9–12 months (n=171)

<table>
<thead>
<tr>
<th>Index</th>
<th>Mean</th>
<th>95% CI</th>
<th>Median</th>
<th>5th percentile</th>
<th>95th percentile</th>
<th>N (%) &lt;cutoff*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb, g/L</td>
<td>112.9</td>
<td>111.5–114.5</td>
<td>114.5</td>
<td>98.0</td>
<td>127.0</td>
<td>30 (17.5)</td>
</tr>
<tr>
<td>MCV, fl</td>
<td>73.4</td>
<td>72.7–74.2</td>
<td>73.9</td>
<td>65.5</td>
<td>80.0</td>
<td>85 (49.7)</td>
</tr>
<tr>
<td>Ferritin, μg/L</td>
<td>22.5</td>
<td>19.7–25.3</td>
<td>17.9</td>
<td>2.1</td>
<td>55.0</td>
<td>54 (31.6)</td>
</tr>
<tr>
<td>sTfR, mg/L</td>
<td>2.2</td>
<td>2.1–2.3</td>
<td>1.8</td>
<td>1.55</td>
<td>3.2</td>
<td>6 (3.5)</td>
</tr>
</tbody>
</table>

*Cutoff values were as follows: for hemoglobin (Hb) <105 g/L; mean corpuscular volume (MCV) <74 fl.; ferritin <12 μg/L; soluble transferrin receptors (sTfR) >3.3 mg/L.

### Table 2. Different factors associated with the risk of iron deficiency (n=171)

<table>
<thead>
<tr>
<th>Determinant</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight &lt;3000 g</td>
<td>9.4</td>
<td>2.7–33.0</td>
<td>0.0003*</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.2</td>
<td>0.9–5.3</td>
<td>0.058</td>
</tr>
<tr>
<td>Preterm</td>
<td>8.5</td>
<td>0.6–457.9</td>
<td>0.060</td>
</tr>
<tr>
<td>Urban area</td>
<td>1.1</td>
<td>0.4–3.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Maternal education</td>
<td>1.4</td>
<td>0.7–3.2</td>
<td>1.00</td>
</tr>
<tr>
<td>Anemia in pregnancy</td>
<td>0.8</td>
<td>0.3–1.9</td>
<td>0.68</td>
</tr>
<tr>
<td>Exclusive breastfeeding</td>
<td>1.5</td>
<td>0.7–3.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Partly breastfeeding</td>
<td>3.8</td>
<td>1.7–8.8</td>
<td>0.005*</td>
</tr>
<tr>
<td>Introduction of solid food</td>
<td>0.9</td>
<td>0.4–2.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Formula feeding</td>
<td>0.7</td>
<td>0.6–0.9</td>
<td>0.01*</td>
</tr>
<tr>
<td>Cow’s milk</td>
<td>1.6</td>
<td>0.7–3.7</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Statistically significant factor.

OR – odds ratio; CI – confidence interval.
Discussion
This is the first population-based descriptive epidemiological study to estimate the prevalence and causes of ID and IDA in Estonian infants. We found that the prevalences of ID and IDA in infants aged 9–12 months were 14.0% and 9.4%, respectively, which is disturbingly high. The mean prevalence of IDA in developed EU countries has been reported to be around 2% (2, 5), in Scandinavian countries between 0 and 5% (11, 17, 21). However, the prevalence of ID in Estonia was lower than in some socioeconomically deprived areas in the United Kingdom (9, 13) and in countries such as China and Albania (14, 15). The prevalence of ID in our study was higher than the average of 7% in the developed EU countries (5), but lower than in Sweden (19%) (11) or Iceland (20%) (2). One reason for such high prevalence of IDA in Estonia may be the fact that feeding with iron-fortified cereals is not common in Estonia. Cow’s milk, particularly in rural areas, is still common practice. The second reason might be that Estonia does not have a direct program for prevention of IDA in infants. Our results show that prevention program of IDA may be useful, particularly in primary health care system. The value of the direct program for prevention of IDA is approved in Denmark. In Danish infants aged 9 months, the prevalence of ID and IDA was near to zero (17).

However, such high prevalence of ID and IDA might be also that the criterion standard for ID (ferritin <12 μg/L, MCV <74 fL) and for anemia (Hb <105 g/L) was too high for infants in Estonia. In our study, we found that for diagnosis of ID, ferritin concentration should be less than 11 μg/L and MCV <71 fL and diagnosis of anemia, Hb concentration should be less than 101 g/L (23). The other authors have also shown the possibility that the cutoff values diagnosing ID or IDA might be too high (24). Using our own population-based cutoff values, 6% (n=12) of infants had ID and 2% (n=3) IDA.

The prevalence of iron sufficient anemia in our study was 8.2%. It is known that the second most common cause of anemia at this age is infection. The comparative study of Estonian and Swedish children showed that the frequency of respiratory illnesses during the first 2 years of life was significantly higher in Estonian children (median range 6.2) than in Swedish children (3.6) (22). This may explain why the prevalence of iron sufficient anemia in Estonia was such high.

The concentration of serum soluble transferrin receptors is a sensitive marker to diagnose latent ID and to differentiate IDA from anemia caused by infection (20, 25–27). However, in our study, serum sTfR concentration was increased only in six infants, and all of them had Hb concentration of less than 100 g/L and serum ferritin level lower than 1.5 μg/L. One possible explanation for the small number of cases with increased serum sTfR levels may be the inappropriate cutoff level. The published cutoff value for sTfR that we used was 3.3 mg/L (20).

We found that infants with BW of <3000 g had nearly a 10-fold increased risk for developing ID. It is known that the majority of children born small for gestational age (SGA) do catch up in weight and length during the first 2 years of life. Thus, the increased requirement for iron during this rapid period of growth may lead to ID. We also found that infants with ID had lower BW, but gained weight much more than the control babies did. Morasso et al. (28) also found a relationship between low BW and ID in infants. In addition, a positive correlation between BW and serum ferritin concentration has been previously reported (2, 5). Therefore, infants with low BW may need primary prevention of IDA. Gender apparently plays also an important role in infant’s iron status (2). We found that boys had a tendency to have lower ferritin concentration than girls, but the difference was not statistically significant. The other authors have reported similar sex difference (2, 5, 24).

Nearly 40% of our infants were partly breastfed at the time of the study. Infants fed exclusively with breast milk until the age of 6 months had lower Hb and serum ferritin levels than the infants fed with breast milk for a shorter period. Infants at the age of 9–12 months who were partly breastfed had nearly a 4-fold increased risk of ID. This appears to be contrary to the study carried out in Iceland, where infants with ID had shorter total duration of breastfeeding (5.3 months vs. 7.9 in the iron sufficient infants) (2). According to our study, formula feeding has a positive effect on iron indices and is slightly protective against ID (OR=0.7, P=0.01). Therefore, infants after the age of 6 months should have high-iron formula or iron-fortified food. It is known that cow’s milk is the main dietary risk factor for ID in infancy (2, 5, 9, 17). We found that nearly every third child in our study was fed with cow’s milk and not with formula before the age of 9 months. We did not find cow’s milk as a risk factor for ID, but infants who received cow’s milk had significantly lower serum ferritin levels than those who had not received it.

Conclusion
Iron deficiency and iron deficiency anemia are...
common in Estonian infants aged 9–12 months. Special attention should be paid to infants with a birth weight of less than 3000 g who are at high risk for developing iron deficiency. Directed program for early discovery and prevention of IDA of infancy should be planned in primary healthcare system in Estonia.

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Geležies stygiaus mažakraujystės paplitimas tarp 9–12 mėnesių amžiaus kūdikių Estijoje ir jos priežastys

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Raktažodžiai: mažakraujystė, kūdikis, geležies stygius, rizikos veiksnių.


Rezultatai. Geležies stygiaus paplitimo rodiklis – 14 proc., o geležies stygiaus mažakraujystės – 9,4 proc. Mažesnis nei 3000 g gimimo svoris buvo pagrindinis geležies stygiaus rizikos veiksnių (OR=9,4; p<0,005). Krūtimi ir tirschtu maistu maitintų kūdikių feritino rodiklis buvo mažesnis – 18,5 μg/l (95 proc. PI 14–23), palyginti su pieno mėsiniams ir tirschtu maistu maitintų kūdikių feritino rodikliu – 32,8 μg/l (26,6–39) (p<0,005).


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