"IRON DEFICIENCY ANAEMIA: OUTSTANDING QUESTIONS".

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My previous paper at this conference described some general developments particularly the concept of conditionally essential nutrients. This paper concerns developments in nutrition of a specific substance, iron, which is absolutely essential but like some other essential nutrients, is toxic when present in excess. General more detailed reviews have been published elsewhere (Wharton 1999)

Changes during development

Normal size babies
There is little increase in total body iron in the first 4 months or so of life. As the haemoglobin falls from around 18g/dl at birth to 14g/dl during the first 2 weeks of life the liberated iron is stored and then gradually reused as the total mass of circulating haemoglobin begins to increase with growth.

Low birthweight babies
Preterm babies are born with a lower concentration of haemoglobin so any physiological haemolysis liberates less iron for stores; erythropoietin if given increases iron requirements, and so does catch up growth.

Light for gestational age babies often have a raised haemoglobin at birth reflecting intrauterine hypoxia, and so initially post haemolysis iron stores are higher but the rapid catch up growth increases demands.

In a normal term baby the total haemoglobin mass doubles during the first year of life (from 180 mg at birth to 340mg at 1 year). In a preterm 1kg baby the increase is 6 fold (50 to 300mg). In a 2 kg baby born at term the increase is three fold (110-330mg).

Older infants and children
Between 4 - 12 months total body iron increases by about 130mg, and an external source of iron is necessary. If not met iron deficiency occurs and frank anaemia develops usually after the first birthday.
Infants who continue to receive only breast milk after the first 6 months of life are at increased risk. Breast feeding may continue after 6 months without difficulty so long as other foods providing available iron are introduced.

Boys as well as girls need more iron at adolescence because of the increase of muscle and myoglobin. Subsequently these increased requirements due to changes in body composition subside but increased requirements continue in girls following menarche.

Methods of diagnosis of iron status

Haemoglobin and RBC indices
Electronic counters based on impedance or light scattering are in common use in developed countries. The likelihood of iron deficiency may then be assessed from the indices. Increasing use is now made of histogram distributions of red blood cell volume rather than using only arithmetic summaries of size and variation in size such as mean corpuscular volume (MCV) and red cell distribution width (RDW). With some methods "Red cell cytograms" are also available in which red cell volume is plotted against red cell haemoglobin concentration for all red cells counted. Walters & Abelson (1996) have described the interpretation of full blood count and indices, possible artefacts (due to cold agglutinins, high white cell counts, and hyperosmolar plasma) crude checks for internal consistency (haemoglobin in g/dl about 3 x RBC; calculated and correct PCV about 3 x haemoglobin) and its interpretation in children. Hinchcliffe & Helliwell (1993) have described the use of distribution histograms and cell cytograms in children.

In older children with iron deficiency anaemia Hb, MCV are reduced, RDW is increased (i.e. microcytosis and anisocytosis) red cell haemoglobin distribution width (HDW) is increased (i.e. anisochromia), the ‘shape’ of the cell cytogram scatter is moved down and to the left with a large proportion of cells in the hypochromic microcytic zone. During a response to iron treatment double peaks are seen in the histograms for red cell volume and red cell haemoglobin and the cytogram shows more cells in the normocytic normochromic zone. The application of these more sophisticated methods in the newborn has not been evaluated.

Other investigations
EPP alone (or zinc protoporphyrin, ZPP) is used for screening and as an indication for a therapeutic trial of iron in some American paediatric practices but these descriptions are not in newborns (Benjamin et al. 1991; Siegal & Lagrone, 1994). In iron deficiency zinc fills the iron pocket in the protoporphyrin molecule. ZPP requires only 20 microlitres of blood and is
easily measured in a haematofluorimeter. It also remains abnormal for a week or so, even if iron therapy commenced before the test. However, it is also abnormal in the anaemias of inflammation and in lead poisoning.

Serum ferritin may also be determined on small blood samples but careful standardisation of methods and use of a reference ferritin preparation for calibration are necessary (Worwood, 1997). It is raised during acute infections, chronic disease and liver disease irrespective of the iron stores but iron deficiency is the only cause of a low concentration. Serum transferrin receptor concentration has raised considerable interest. The concentration reflects the number of transferrin receptors on immature red cells and so in most instances also reflects the rate of bone marrow erythropoeisis. Iron deficiency, however, also results in an "unproportional" increase in the concentration (Heubers et al 1990). An increased concentration provides an early and sensitive indicator of functional iron deficiency, sometimes before the plasma ferritin has fallen. (Skikne et al. 1990; Worwood, 1995, 1997). A major advantage is that it remains normal in many chronic disorders if iron deficiency is not present. However, it is raised in the thalassaemias even though iron deficiency is not present. As in adults, in infants and 11 - 12 year old boys, higher concentrations of the receptor were associated with a lower serum ferritin even within the normal physiological range for ferritin (Virtanen et al 1999). However, its use as an index of iron deficiency in infancy and adolescence has been questioned (Kuiper-Kramer et al. 1998; Kling et al. 1998; Kivivuori et al. 1993; Kuizon et al. 1996). It would be unwise to use the test alone without other measurements of ID as well.

Microcytosis
Apart from the thalassaemias hereditary causes of microcytosis are quite rare. Most are associated with iron overload of tissues but a small number of children have been described with deficiency because of a defect in absorption (see Table below).

**Hereditary causes of microcytic hypochromic anaemia**

### With iron overload

<table>
<thead>
<tr>
<th>Thalassaemias:</th>
<th>autosomal recessive</th>
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<tbody>
<tr>
<td>Atransferrinaemia:</td>
<td>autosomal recessive</td>
</tr>
<tr>
<td>Without iron in marrow:</td>
<td>2 siblings</td>
</tr>
<tr>
<td>With eliptocytosis:</td>
<td>sex linked recessive</td>
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<tr>
<td>Sideroblastic anaemias:</td>
<td></td>
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<tr>
<td>- some are pyridoxine responsive</td>
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<tr>
<td>- with hypolipidaemia</td>
<td>Spitzer et al., 1996</td>
</tr>
<tr>
<td>- with delta aminolevulinic acid synthetase deficiency</td>
<td>Aoki et al., 1973</td>
</tr>
<tr>
<td>- with cytomegalovirus</td>
<td>Goedseels et al 1997</td>
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</tbody>
</table>
Without iron overload

<table>
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<tr>
<th>Iron malabsorption*: 3 siblings</th>
<th>Buchanan &amp; Sheehan 1981</th>
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<tbody>
<tr>
<td>Iron malabsorption*: partial response to parenteral iron: 2 siblings</td>
<td>Hartman &amp; Barker, 1996</td>
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*some similarities to recessively inherited microcytic anaemia of the mk-mk mouse which may be due to a defective transferrin receptor leading to impaired cellular uptake of iron (Bannerman, 1981).

Some other factors (see Tsang et al., 1992)

Absorption
Preterm infants, absorb dietary iron well; depending on postnatal age, growth rate, hemoglobin concentration, and the type of feeding.

Iron fortification of formulas does not impair the absorption of copper and zinc to a nutritionally important degree

Blood transfusion
Blood transfusion decreases dietary iron absorption and often leads to raised serum ferritin. Limiting factors in the production of hemoglobin might be inhibited mobilization of storage iron by the high serum ferritin concentrations, and normal blood transferrin saturation. So provision of newly absorbed iron from the diet might be necessary for incorporation into red cells even though iron stores are more than adequate.

Red cell production and haemolysis
If haemopoietin (r-HuEPO) therapy is given dietary iron intake may need an increase.

Preterm infants were predisposed to develop vitamin E-deficiency haemolytic anaemia because of limited vitamin E stores at birth, and consumption of infant formulas with high polyunsaturated fatty acid (PUFA) and low vitamin E content. Intake of these formulas increased the PUFA content of the red cell membranes. The membranes were then more susceptible to lipid peroxidation because of the pro oxidant effect of iron and insufficient antioxidant protection of membrane PUFA’s. Modern formulas have the correct balance of PUFA, iron and vitamin E, so that this disorder has disappeared.

Prevention
At birth
Blood loss should be avoided. Effective umbilical clamping with devices which tighten as the cord withers usually prevent cord haemorrhage. The time of clamping may affect subsequent ID. In Guatemala infants in whom the cord was not clamped until pulsation had stopped had a higher haematocrit at 2 months of age; this manoeuvre had no effect on serum ferritin at 3 months of age in Indian children (Grajeda et al., 1997; Geethanath et al., 1997). Since three quarters of iron ‘stored’ at birth is in haemoglobin perinatal blood loss is a potent cause of anaemia in early and later infancy. Generally the other stores in newborns show little relationship to the mothers’ iron status although some studies in both the developed and developing world have shown one. Two papers have shown that poorer maternal iron status in pregnancy is associated with a poorer iron status in the infants at 1 year of age, (Strauss 1996; Colomer et al., 1990). This could reflect a longer term effect of reduced iron stores or that both mother and child have received an iron deficient diet.

Suckling period (0 - 4 months)
For normal sized babies there is little concern because total body iron does not increase during this time. If ID occurs then abnormal blood loss should be considered. This may occur in the perinatal period (e.g feto-maternal transfusion, cord accident) or later (e.g. reflux oesophagitis, bleeding from ectopic gastric mucosa in a Meckels diverticulum, rarely allergic colitis of infancy). Breast feeding is encouraged or failing that a modern infant formula is used. See above for the special requirements of low birth weight babies.

REFERENCES


