

## PERSONAL VIEW

## Iron deficiency anaemia in infancy and early childhood

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In inner cities in the UK, iron deficiency anaemia (IDA) occurs in infants with the same frequency as in developing countries. Evidence is now accumulating to show that IDA is associated with developmental delay, and that the association is causal. IDA is readily preventable, even in a profoundly socially disadvantaged population, by the provision of an iron supplemented formula in place of unmodified cows' milk. In the United States there has been a substantial reduction over the last 20 years in the prevalence of IDA among infants and young children from low income families.<sup>1-3</sup> None the less there is no evidence of a similar downward trend in the UK.<sup>4</sup> The lack of urgency in dealing with this problem in the UK is puzzling. We have therefore summarised the existing data on the epidemiology of IDA in the UK and on its causes and consequences. We also suggest some strategies for prevention. The special needs of preterm infants are well recognised, and have been specifically excluded.

### Definitions

After release from a relatively hypoxic intrauterine environment, mean haemoglobin concentration falls by 30% to 110 g/l by the eighth postnatal week, followed by a rise to 125 g/l at 4 months. Mean haemoglobin then increases gradually to 135 g/l in preadolescents.<sup>5</sup> The lower 95% limit of the reference range from 6 months to 4 years for haemoglobin is 110 g/l, with corresponding values of 32% for packed cell volume, and 72 fl for mean corpuscular volume (MCV). Iron deficiency without anaemia implies that haemoglobin synthesis is impaired, but that haemoglobin concentration has not fallen sufficiently to meet the definition of anaemia. It is usually recognised on the basis of criteria other than haemoglobin concentration: serum ferritin (<10 µg/l), erythrocyte protoporphyrin (>2.5 µg/g haemoglobin), MCV <72 fl, or a response to oral iron treatment (an increase in haemoglobin of at least 10 g/l one month after starting on oral iron: 3 mg/kg, as ferrous sulphate, once daily before breakfast).<sup>6</sup>

### Epidemiology

The UK data have been the subject of a recent comprehensive review.<sup>4</sup> A nationally rep-

resentative UK sample suggests a current prevalence of 12% of 1.5 to 2 year olds with haemoglobin less than 110 g/l and 28% with low ferritin levels.<sup>7</sup> However, in socioeconomically deprived populations, the prevalence of IDA between 6 and 24 months currently varies between 25 and 40%. This figure has remained remarkably consistent over the last few decades.

Experience in Birmingham over the past 10 years indicates that the problem is widespread in the inner city, mainly but not exclusively, in ethnic minorities. In 1985, 27% of Asian toddlers and 18% of other groups were anaemic in an inner city area.<sup>8</sup> Ten years later in a similar area of the city, 19% of white European, 27% of Asian, and 29% of Afro-Caribbean children were anaemic.<sup>9</sup>

### Iron requirements

In the normal term infant, total body iron changes little during the first four months of life. Even though blood volume increases, total haemoglobin iron increases only slightly, as haemoglobin concentration falls during this period. Consequently, IDA in this age group is uncommon, except in the presence of gastrointestinal blood loss. The need for iron supplementation in the first few months is therefore questionable.

By 4 months of age, neonatal iron stores have been reduced by half, and exogenous iron is required to maintain haemoglobin concentration during the rapid phase of growth between 4 and 12 months. Absorption of about 0.8 mg or iron per day from the diet is required, of which 0.6 mg is needed for growth, and 0.2 mg to replace losses.<sup>10</sup> The reference nutrient intake for iron (mg/day) is 4.3 (4-6 months) and 7.8 (7-12 months).<sup>11</sup>

### Iron absorption and losses

Iron in breast milk is present in low concentrations (0.06-0.09 mg/100 ml) but is uniquely well absorbed and utilised, for reasons that are unclear. The lower calcium and phosphate concentrations in breast milk, and the presence of lactoferrin may be partly responsible. However, the total amount of iron absorbed by breast fed infants is less than that absorbed by those receiving an iron supplemented formula,

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and by 9 months, there is evidence of iron deficiency in some breast fed infants, unless additional sources of iron are present in the diet.<sup>12</sup>

Although the absorption of iron from iron supplemented formulas is less efficient than breast milk, the use of such formulas is a reliable way of preventing iron deficiency.<sup>13</sup> The percentage of iron absorbed decreases as the concentration rises, so that 6% of iron is absorbed from a formula containing 0.6 mg iron/100 ml, compared with only 4% from a 1.2 mg/100 ml formula.<sup>14</sup>

Over 90% of iron in the diet of infants and young children is in the form of non-haem iron. The absorption of non-haem iron is enhanced by ascorbic acid, meat, fish and poultry, and inhibited by bran, tannin (in tea), calcium, and phosphate (present in high concentration in unmodified cows' milk). Thus, compared with water, orange juice will double the absorption of non-haem iron from a breakfast, whereas tea will reduce it by 75%.<sup>15</sup>

### Causes of iron deficiency

The early introduction of unmodified cows' milk as the major milk source at around 6 months of age is the most common dietary characteristic of infants found to have IDA at 1 year.<sup>16</sup> In the UK, iron deficiency is more common in those children consuming over one litre of cows' milk, and in those in whom unmodified cows' milk was introduced before 8 months.<sup>17</sup>

Cows' milk is low in iron, but the existing evidence suggests that factors other than low iron concentration are at least as important in causing IDA. For example, Stevens and Nelson found that anaemia was no more common in infants receiving a modified formula to which no iron had been added, compared with those receiving an identical formula which was supplemented with iron.<sup>18</sup> Evidence that cows' milk causes significant gastrointestinal blood loss remains equivocal.<sup>19</sup>

### Manifestations of iron deficiency

Iron deficiency anaemia produces many systemic abnormalities: blue sclerae, koilonychia, impaired exercise capacity, urinary discoloration by betanin in beetroot, increased lead absorption, and an increased susceptibility to infection. Abnormal developmental performance and poor growth are particularly important features and are considered in more detail.

### Iron deficiency anaemia and developmental delay

There are now convincing data to show that IDA in infancy and early childhood is causally associated with developmental delay. The evidence has recently been reviewed comprehensively by Lansdown and Wharton.<sup>20</sup>

In the experimental animal with IDA, usually the rat, there is a reduction in spontaneous activity and a diurnal reversal in the pattern of activity, which rapidly returns to normal following iron treatment. Of the few studies on cognitive behaviour in the rat, none

has demonstrated a deficit. Instead, non-cognitive behaviours, such as reactivity and arousal, appear to be impaired.<sup>21</sup>

In man, development in the first two years of postnatal life may be particularly vulnerable to iron deficiency, as this is the time when the most important changes in neuronal multiplication take place. This period also coincides with the peak prevalence of iron deficiency.

Interpretation of studies addressing a causal relationship between IDA and developmental delay is hampered by a number of confounders. IDA frequently coexists with environmental and psychosocial deprivation. Moreover, the means of assessing iron status and development vary between studies. Of those non-interventional studies seeking an association between iron deficiency and development, the majority find in favour, and come from both industrialised and developing countries. Many of those failing to support the hypothesis can be criticised on the basis of potentially confounding variables such as protein energy malnutrition, insensitive tests of development, and small sample size. Of those studies which support an association, most have shown the Bayley mental scale to be more impaired than the motor scale in IDA. In infants with moderate IDA (haemoglobin <110 g/l) the differences in the Bayley mental scales compared with iron replete subjects have been both consistent and large, varying between 0.5 and 1.5 standard deviations.<sup>22</sup> In general however, the mean score for IDA infants was still within the reference range expected for normal, healthy infants.

In contrast to non-intervention, observational studies, only randomised, double blind trials can address causality. These have been of three kinds. In the first, short term responses to oral or intramuscular iron were assessed after 7–15 days. In other words, before anaemia could be corrected. In the second, long term treatment with iron was assessed, and in the third, a longitudinal cohort study design was used, with random assignment to an iron supplemented or non-iron supplemented formula.

Results from the short term studies are conflicting. In one study, intramuscular iron was associated with a one standard deviation increase in the Bayley mental developmental scale seven days after administration. However, a non-significant improvement occurred in the placebo group, such that the difference between groups in the size of the improvement was not statistically significant.<sup>23</sup> A somewhat larger study by Lozoff *et al.*,<sup>24</sup> failed to show a significant improvement using oral iron therapy, whereas a study by Walter *et al.* showed a response to oral iron in anaemic, but not in non-anaemic iron deficient infants.<sup>25</sup>

Not all long term studies have shown an improvement after iron therapy, but most have concluded in favour of a significant effect.<sup>20</sup> Two double blind randomised trials show a clear causal link between developmental delay and iron deficiency. In a study from inner city Birmingham, iron deficient toddlers with anaemia were randomly assigned to receive either iron and vitamin C, or vitamin C (as placebo)

for three months.<sup>8</sup> Thirty one per cent of the treated group, but only 12% of placebo group, achieved an average rate of development, assessed by the Denver developmental screening test. Similarly, the expected rate of development was achieved by 37% of those whose haemoglobin rose by at least 20 g/l, compared with only 16% whose concentration rose by less than 20 g/l. However, some children who showed a haematological response to iron, failed to show an improvement in development, suggesting that factors in addition to iron may be responsible for slower development in inner city children.

In the most recent long term study, 12–18 month old Indonesian infants with IDA were randomly allocated to receive oral iron or placebo for four months.<sup>26</sup> A similar treatment randomisation was performed among iron deficient, non-anaemic subjects, and among an iron sufficient group. Before treatment, the infants with IDA had scores on Bayley mental and motor scales that were significantly lower than the other two groups. After treatment, deficits in both mental and motor scales were reversed in the IDA infants who received iron, but were unchanged in the placebo group. Changes in the scores of the iron deficient, non-anaemic, and iron sufficient subjects were unchanged. This study therefore confirms the negative impact of IDA on mental and motor development, but is also consistent with previous studies which suggest that IDA, and not merely iron deficiency without anaemia, is important in generating this effect. It is possible however, that sample size in this and other studies, was not large enough to detect a developmental delay which was smaller than in the IDA group. Moreover, these data, and those of Aukett *et al*<sup>8</sup> suggest that IDA among 12–18 month olds causes a developmental delay which can be reversed by treatment.

A third type of study, also implicating iron deficiency in the aetiology of developmental delay, has recently been published from Canada.<sup>27</sup> Socioeconomically disadvantaged Native American infants aged 0–2 months, were randomly allocated to receive either an iron fortified or a non-iron fortified formula from birth, and followed up to 15 months of age. Stable deterioration in iron status in the group receiving the non-iron supplemented formula by 6 months of age was associated with impaired psychomotor development at 9 months, although this was no longer significant by 15 months. This corresponded to an improvement in some indices of iron status. Mental development and behaviour were unchanged.

In summary, IDA in infants and young children under 2 causes a developmental delay that is reversible by long term oral iron treatment; the results of short term treatment with iron are unconvincing. At present, there is little evidence to implicate iron deficiency without anaemia in this effect, although studies to date may have lacked sufficient sensitivity to detect a smaller effect.

### Mechanisms

The mechanisms whereby IDA produces developmental and behavioural defects are uncertain. There are several hypotheses.

Early iron deficiency may have specific effects on the central nervous system. In the rat, a brief period of iron deficiency during the brain growth spurt (10–28 days) causes a lasting deficit in brain iron, which persists into adulthood despite correction of the anaemia. Altered neurotransmitter function is present in the brains of iron deficient rats. The activity of monoamine oxidase, which is responsible for noradrenaline degradation, is reversibly diminished, as is the activity of aldehyde oxidase, which catalyses serotonin degradations.<sup>28, 29</sup> Moreover, serotonin induces drowsiness and altered attention and cognitive function in the rat. The functional activity of dopamine D<sub>2</sub> receptors is reduced in the iron deficient rat. Moreover, many dopamine mediated behaviours are modified in the iron deficient rat.<sup>30</sup>

Myelination may also be adversely affected in the iron deficient rat. Marked changes in the fatty acid composition of myelin specific lipids, such as cerebrosides, are found that are consistent with reduced desaturase activity.<sup>31</sup> Moreover, there is also evidence of impaired essential fatty acid metabolism in peripheral tissues, including red cells, in the moderately iron deficient rat.<sup>32</sup>

### Iron deficiency and growth

In the study by Aukett *et al*, treatment of IDA with oral iron for 2 months was associated with a significantly greater increase in weight velocity compared to the placebo group.<sup>8</sup> Other studies from Indonesia have confirmed these observations, and also suggest that correction of anaemia is associated with a reduction in the increased morbidity (fever, respiratory tract infections, diarrhoea) seen in children with IDA.<sup>33, 34</sup>

The mechanisms of these growth effects are uncertain, but presumably include reduced morbidity, increased food intake, and possibly a direct effect of iron. Nor is it clear why the longitudinal cohort study reported by Moffatt *et al* on Canada in this issue has failed to detect any growth delay in infants with IDA.<sup>27</sup>

### Prevention

There are two approaches: primary and secondary prevention (screen and treat).

#### PRIMARY PREVENTION

Sufficient dietary iron must be available from 4 months of age and throughout the weaning period. Primary prevention can be achieved by giving supplementary iron, by the fortification of foods, and by dietary education changing feeding practice. Although prophylactic medicinal iron is recommended in this country for preterm infants, it is not in routine use outside this indication. There have been concerns about accidental overdosage and gastrointestinal disturbance, as well as some evidence that growth rates may be slowed if iron replete children are given iron supplements.<sup>35</sup> Moreover,

experience in North America indicates that low dose iron supplements have no advantage over iron fortified infant formulas.<sup>36</sup>

In the United States there has been considerable success in reducing iron deficiency by the WIC Program, which supplies iron fortified drinks and cereals to infants and toddlers from disadvantaged families free of charge.<sup>1</sup> Recent studies in Birmingham have indicated that this approach can also be highly successful in the UK.<sup>37</sup>

In line with the COMA Working Group's recommendations,<sup>38</sup> infants from families in receipt of income support currently receive iron supplemented formula free of charge up to the age of 12 months. Some caretakers switch to free, unmodified cows' milk during this period, probably because it is more convenient to use. This ability to switch, which promotes the early introduction of an unsuitable dietary component, is undesirable, and should no longer be available. Beyond 12 months, intake of iron remains low, particularly among socioeconomically deprived infants.<sup>7, 37</sup> For example, in inner Birmingham, only 16% of 24 month olds currently achieve the reference nutrient intake of iron.<sup>37</sup> This reflects the difficulty of providing iron rich finger foods to toddlers at a time when their eating behaviours and preferences are becoming firmly established, and the non-availability of subsidised iron supplemented formulas to families on income support beyond 12 months.

There is therefore a strong argument for continuing the use of iron supplemented formula to 24 months of age. In families receiving income support, this should be provided free of charge. It seems implausible that this measure would be any more costly than a truly comprehensive screening and treatment programme for at-risk toddlers. Whether or not the higher iron content of follow-on formulas is of benefit in the second year of life has not been adequately tested.

While an attractive way of preventing IDA is through dietary education, there has been little evaluation of such an approach. Some success using health visitors in this way has been reported from a primary health care setting in Bristol.<sup>38</sup> Nutrition education was combined with screening in a predominantly Afro-Caribbean and European population with few Asian families. A recent study in Birmingham, which aimed to see if a nutrition education programme using existing resources could effectively reduce the prevalence of iron deficiency anaemia in a large group of inner city toddlers, was unable to replicate these findings.<sup>9</sup> There was no difference in the prevalence of anaemia between the control and intervention groups, and no difference in feeding practices (for example age of introduction of unmodified cows' milk; use of iron containing weaning foods) between the two groups. There was a high percentage of Asian children (78%), poorly educated mothers (35%), and a preponderance of low socioeconomic groups, especially unemployed (61%).

An understanding of why such studies fail is clearly of crucial importance. Parents get

advice on how to feed their children from a variety of sources: the extended family and friends; their own education; food advertising; the media; as well as from health professionals. Much of this advice is conflicting. The traditions and cultural views of different ethnic groups within the community as a whole also need to be considered. Advice which does not heed such beliefs will not be taken.

#### SECONDARY PREVENTION: SCREEN AND TREAT

This has not received universal support. The COMA Working Group recommended that there should be an assessment of the need for, and feasibility of, universal or subgroup screening for IDA in infants and young children.<sup>39</sup> The current edition of *Health for All Children* does not recommend universal screening for IDA in the UK.<sup>40</sup> Instead, it suggests that in districts or localities where there is severe socioeconomic deprivation, screening programmes should be continued if they are adequately monitored and are accompanied by continuing efforts at primary prevention. A meeting of experts convened by the Department of Health in February 1995 failed to reach a conclusion on this point.

Screening is acceptable and popular with parents.<sup>41</sup> A test is available (measurement of haemoglobin by haemoglobinometer) which is simple and relatively cheap, and effective treatment is available. However, screening has been criticised on several counts. First, the accuracy of the results obtained by haemoglobinometer (Hemocue) will vary, and are dependent on good sampling technique. Second, the use of haemoglobin alone will underestimate the frequency of iron deficiency, and the addition of other, more sensitive parameters is more costly and complex to organise, nor does it provide an instant result. Third, the timing of the test is a problem. Some children found not to be anaemic at 12–18 months will become so later,<sup>42</sup> while others found to be anaemic may improve spontaneously, or if treated, relapse. There is no clear evidence about the optimal age. In practice, this would need to be linked with one of the preschool surveillance checks or immunisations, although the target group are exactly those who are likely to be poor clinical attenders.

In summary, iron deficiency is still disturbingly common in socioeconomically disadvantaged infants and toddlers in the UK. Iron deficiency anaemia is causally associated with developmental delay and with poor growth, both of which are reversible with treatment, at least when treatment is offered early in childhood. We would therefore advocate an approach which combines primary prevention and screening, particularly in the inner city. Avoidance of unmodified cows' milk and the use of iron supplemented formulas offer an easy method of primary prevention which is yet to be implemented in at-risk groups. Evidence now indicates that iron supplemented formulas should be provided to children up to the age of 24 months in families receiving income support. Switching to unmodified cows' milk should not be an option.

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### Commentary

The authors of this review suggest that iron deficiency is an important problem in our society and advocate screening for IDA in toddlers, especially in the inner cities. While many in the field share this view it seems appropriate to add some words of caution.

We need to be clear what we mean by IDA. Although most studies use the standard World Health Organisation definition (haemoglobin <110 g/l), this is not unproblematic. IDA is not a disease like cystic fibrosis but one end of a population distribution. It is meaningful to regard IDA as a problem only to the extent that a particular definition has prognostic implications and any discussion of prevalence must reflect this. The authors quote 110 g/l as being the lower 95% limit of the reference range but the source of this figure is unclear. Clearly it cannot be a reflection of the population distribution as in the UK around 12% of young children have concentrations below this.<sup>1</sup> It presumably depends on some 'ideal' distribution, something that needs to be spelt out in terms of prognostic significance.

There is little argument about the adverse consequences of extreme iron deficiency but the position is less clear with regard to less severe deficiency. The authors conclude unequivocally that IDA (presumably haemoglobin <110 g/l) 'causes developmental delay' but this is perhaps too strong an interpretation of the evidence presently available. Without presenting a systematic review of the evidence the discussion is complex but it is worth making some specific points. The observational data are hopelessly confounded by social factors and, although they raise questions, are not useful as evidence of a causal relationship. There are also a number of intervention studies, some of which are quoted here, of both short and longer term iron treatment or supplementation. Most are non-randomised and based on comparing responses in children later classified as being deficient before treatment with those not deficient. This is not a design that can easily be interpreted. There are some randomised studies but few of high quality.

The two published randomised controlled trials of iron treatment in toddlers with IDA which stand up well to critical appraisal are a study from Birmingham<sup>2</sup> published in the 1980s and a recent trial from Indonesia.<sup>3</sup> The Indonesian study suggests a causal relationship between iron treatment and improved development over a two month period. The interpretation of the Birmingham study is less straightforward as the differences reported between treated and placebo groups are based on a post hoc analysis which could be challenged while the more obvious analysis appears to show no significant effect of treatment. There is, in addition, a well conducted trial of iron supplementation from birth in bottle fed infants,<sup>4</sup> quoted here as reference 27, which does suggest some differences at 9 months between groups but these differences disappear on follow up and for this reason, in my view, cannot be said to support a relationship between iron status and development. The non-randomised studies that have followed up cohorts of children with IDA after treatment have shown conflicting results with some suggesting that developmental scores will rise at least in the subgroups with the biggest haematological responses while others show no response (see Lozoff *et al* for a summary<sup>5</sup>). On the basis of the evidence currently available I suggest that a causal relationship between mild to moderate iron deficiency and developmental deficits remains unproved.

There are two further problems with any proposed screening programme in toddlers. Firstly, the natural history is complicated as children appear to move in and out of 'IDA' over time so that identification either as having IDA or as 'normal' at one point is a poor predictor of whether a child will still be in the same category a few months later.<sup>6</sup> Secondly, al-

though as the authors comment it has been shown that screening programmes for IDA can be run well in both general practice and community clinics, this may not be true when attempts are made to move such programmes to services not run by enthusiasts.<sup>7</sup>

Many children in our society have haemoglobin concentrations lower than those regarded as ideal and these 'deficits' can be reversed by iron treatment. What remains less clear is whether such deficits are a cause of deleterious effects on development or whether the relationship is due to confounding by other disadvantageous circumstances. Even if we are convinced that we should attempt to improve such children's iron status, it may be more appropriate to consider a population based approach rather than screening.

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