Should we have Newer Diagnostic Criteria for Preventable Anemia in Children?

Asha Nair Mooppil* and S Subramania Krishnamoorthy

Consultant Paediatricians, Al Jalila Children's Specialty Hospital, Dubai, UAE

*Corresponding Author: Asha Nair Mooppil, Consultant Paediatricians, Al Jalila Children's Specialty Hospital, Dubai, UAE.

Anemia has conventionally been defined as haemoglobin below the lower limit of normal range for the age and sex of any child. It is universally accepted that the cut off values of haemoglobin less than 10 mg/dl are confirmatory for the diagnosis of anemia at any age and/or sex and/or race of the child. With increasing body of evidence suggesting that iron deficiency produces irreversible changes in brain, resulting in poor cognitive functioning of the child, the focus now is on early diagnosis of anemia in children and measures to prevent iron deficiency before it eventually causes a fall in haemoglobin.

As you are aware, newborn babies have a head circumference around 35 cms at birth, which increases to about 46 cms by 1 year and around 49 cms by 2 years. Comparing to adult head circumference of about 58 cms, the growth in head size in the first 2 years is about 85% of the adult size. Needless to say, brain growth too is maximum during these years and conditions/practices that affect the developing brain could have maximum impact during this time. Iron is a key element in body metabolism at cellular as well as subcellular levels and deficiencies affect several aspects of body function including brain development. In fact, studies have shown that in iron deficient children at 2 years of age and above, the brain iron content is low and this does not reverse even following iron supplementation. Also, there are further studies which show that cognitive dysfunction manifested by lower IQ scores in iron deficient children does not equate to the scores in non-deficient children, even following adequate supplementation. All these studies emphasize the need for maintaining iron sufficiency early on in life.

Literature describes mothers as soft cornered and benevolent to their children! This journey starts from even from the time of conception. Studies show that body iron stores in term babies born to iron deficient mothers, equate to the levels in term babies born to mothers without iron deficiency. This means that iron gets transferred to the baby preferentially during pregnancy-- even at the expense of depleting maternal iron levels! However, it has been shown that the transplacental passage of iron is maximum in the later weeks of pregnancy from around 35-40 weeks. No wonder therefore that preterm babies born before 35 weeks of gestation have a lower iron endowment at birth and consequently are at higher risk of iron deficiency early on in infancy.

Currently there is a huge emphasis to promote breast-feeding all over the world, which indeed is very good from several perspectives. Although breast milk is a poor source of iron and does not meet the infant's requirements, studies have shown that breast milk iron is better absorbed. Maintenance doses of iron supplements given to babies right from birth has not been shown to have any detrimental effects in healthy term and preterm babies, giving weight to the recommendation that exclusively breast fed babies be given iron supplements early on.

Incorporation of iron into the heme molecule is an essential and rate-limiting step in haemoglobin synthesis and the body tries all measures to get to this stage, utilising all available iron. Hence, lack of iron leading to fall in haemoglobin is an understandable concept. However, many changes happen in the body before the manifestation of overt iron deficiency and fall in haemoglobin. Fall in storage iron, manifested by low Ferritin levels, has been used for several years as an index to document iron deficiency. Fall in storage iron

subsequently leads to lower levels of circulating iron (low serum iron levels) and consequent increase in iron binding capacity. Transferrin, the iron binding protein in circulation, is usually about 20 - 30% saturated with iron and low transferrin saturation is another indicator of iron deficiency. With continuing iron deficiency, body starts synthesising RBCs, which are smaller (leading to reduction in MCV), and less hemoglobinised (leading to reduction in MCH and MCHC). The pace of RBC production subsequently slows down due to continued deficiency of rate limiting substrate, leading to fall in RBC count and hemoglobin. It is therefore clear that many a water has flown under the bridge, in terms of iron deficiency, before the actual fall of haemoglobin, which has long been regarded as the indicator of anemia as per agreed definition. Hence the question-- is it time to think of an alternative definition or diagnostic criteria to detect early iron deficiency before it causes catastrophic changes in body and brain metabolism?

One of the early changes in iron deficiency is a change in RBC size and hemoglobinisation as already discussed. As RBCs have an average life span of 90 days, the sizes of RBCs during iron sufficiency and deficiency would vary and at any time, peripheral blood will contain different sizes of RBCs. Most automated blood counters are able to analyse the co-efficient of variation in RBC size and this is reported as Red Cell Distribution Width (RDW). Normal RDW is ranges from 12.5 - 14.5%. Increase in RDW beyond this range indicates higher variation in red cell sizes, suggesting possible iron deficiency. It would be worth noting that even when the RDW is elevated, the hemoglobin could still be normal, leading one to believe that elevation of RDW is one of the early changes in iron deficiency.

In familial anemias like thalassemia traits, the RDW could be moderately elevated. With underlying iron deficiency, RDW values tend to be much higher. Hence, measurement of RDW values alone or along with iron studies could help to clinch the diagnosis of iron deficiency early enough in any situation to institute appropriate intervention.

Let us now consider if we can do any better to reach an earlier diagnosis even before dysmorphism of RBCs happen. The precursors of RBCs are the reticulocytes and when there is an increased RBC demand, reticulocytes are released into circulation early. An elevated reticulocyte count in peripheral circulation has always been viewed as a response of the body to falling RBC numbers due to any cause. Reticulocytes are in fact, hemoglobinsed RBCs, which just need to undergo maturational transformation before release into circulation. Hence, hemoglobinisation of reticulocytes too would be affected by iron deficiency and detection of this change promises to be a very early indicator of iron deficiency. This is what is measured in modern day coulter counters (DxH 900) as the 'Reticular Hemoglobin Index' (CHr)- with excellent reliability and reproducibility, using blood sample as low as 1 ml with ability to perform as many as 300 tests in an hour! CHr less than 27.5 pg has been found in several small studies to be an excellent indicator of iron deficiency.

With this relatively new finding, we need large scale randomised controlled studies to document usefulness of CHr as an early marker in iron deficiency. Stated otherwise, intervention at this stage (when CHr drops) with iron supplementation, holds the key to possibly minimising the cognitive damage due to established iron deficiency. Hence, can we rethink of defining anemia as a fall in CHr below the mean for the age, sex and race of the population rather than as a fall in Hemoglobin to help hapless children grow into productive adults in society? Why should we hesitate to introduce this intervention if the costs in mass diagnosis and reliable supplementation are justified? We can certainly start at this point, as there is no apparent harm in iron supplementation early to otherwise healthy children. And, if we are able to prove through follow up studies that iron supplementation can halt the progression from low CHr to full-fledged fall in Hemoglobin in a matter of 2-3 months, we would be crossing the first hurdle.

If standard cognitive performance tests done pre and post supplementation (at low CHr levels vs at low Hemoglobin levels) do show a significant difference, the evidence becomes more concrete to justify the testing as well as the early intervention [1-9].

Knowing these facts now, should we wait any longer?

Disclaimer

This article has been written using available scientific evidence now. Reference to any commercial product is by no means, a recommendation to purchase the same. Authors do not have any conflict of interest to disclose with regard to this article.

Bibliography

1. Robert D Baker., *et al*. "Diagnosis and Prevention of iron deficiency anemia in infants and young children (0-3 yrs of age)". *Paediatrics* 126.5 (2010): 1040-1050.

2. Michael Low., *et al*. "Effects of daily iron supplementation in primary-school aged children: systematic review and meta-analysis of RCTs". *Canadian Medical Association Journal* 185.17 (2013): E791-E802.

3. Leila M Larson., *et al*. "Iron and Cognitive Development: What is the evidence?" *Annals of Nutrition and Metabolism* 71.3 (2017): 25-38.

4. Sant-Rayn Pasricha. "Should we screen for iron deficiency anemia? A review of the evidence and recent recommendations". *Pathology* 44.2 (2012): 139-147.

5. Joyce C McCann and Bruce N Ames. "An overview of evidence for causal relation between iron deficiency during development and deficits in cognitive or behavioral function". *American Journal of Clinical Nutrition* 85.4 (2007): 931-945.

6. Michael J Wenger., *et al*. "Effect of iron deficiency on simultaneous measures of behavior, brain activity and energy expenditure in the performance of a cognitive task". *Nutritional Neuroscience* 22.3 (2019): 196-206.

7. MD Akkermans., *et al*. "Red Blood cell Distribution Width and the Platelet count in Iron deficient children aged 0.5-3 yrs". *Pediatric Hematology/Oncology* 32.8 (2015): 624-632.

8. Carlo Brugnara., *et al*. "Reticulocyte hemoglobin Content to diagnose Iron deficiency in children". *Journal of the American Medical Association* 281.23 (1999): 2225-2230.

9. Christina Ulrich., *et al*. "Screening Healthy infants for iron deficiency using Reticulocyte Hemoglobin content". *Journal of the American Medical Association* 294.8 (2005): 924-930.