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Nutritional Anemia in Infancy in Childhood

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Abstract

Pregnant anemic women transfer low iron stores, this deficiency affects fetal brain iron and neurotransmitters, irreversibly. In lactation, breast milk traps iron for the baby. Deficiencies of nutrients responsible for erythropoiesis i. e. iron, vitamins folic acid, B_{12}, A, C and amino acids affect hemoglobin level, resulting in anemia. The nutritional anemia in infancy and childhood are reviewed i. e. iron deficiency, megaloblastic, and possible approaches for diagnosis, prevention, food fortification, control of infections and infestations.

Keywords: Anemia; Pregnancy; Iron; Vitamins deficiency (Megaloblastic anemia); Food fortification; Control infections/ infestations

Prevalence of anemia in pregnant women of Assam, Himachal Pradesh, Madhya Pradesh, Orissa, Kerala, and Tamil Nadu states in India, during 2002-2003 was 86.1%, with 9.5% of women having Hb < 7.0 g/dL. 81.7% women lactating up to 3 months had anemia of these 7.3% had Hb<7.0 g/dL (1). National Family Health Survey (NFHS-4) 2015-2016 evaluated maternal and child health and nutrition in 13 states (viz., Andhra Pradesh, Madhya Pradesh, Goa, Bihar, Haryana, Karnataka, Meghalaya, Tamil Nadu, Sikkim, Telangana, Tripura, Uttarakhand, and West Bengal) and two union territories (viz. Puducherry and Andaman and Nicobar Islands) found that more than 50% of children in 10 of the 15 states/union territories and greater than 50% of women in 11 states/union territories were anemic Under/Malnutrition (UN/Mn) and anemia in Indian children from recent NFHS surveys are Summarized**:** On Dec 21, 2020, Indian Express newspaper reported NFHS findings showing worsening of child nutrition and maternal anemia (2).

The effects of pregnancy anemia on fetal outcome and brain growth are reviewed (3-8)

- Transport of iron from mother to fetus remains proportionate to the degree of maternal hypoferriemia,
- Placenta- iron content reduces significantly. Pathology shows decrease in- Villous surface area, Volume of villi and length of blood vessels- Maturation arrest,
- Fetal Liver iron stores are reduced significantly in maternal hypoferremia. The tissue iron content increases steeply in last 8 weeks of gestation. Infant born before 36 weeks of gestation, had half the iron content in hepatic reserve
- Fetal brain iron and neurotransmitters decreased, irreversibly in fetus of latent iron deficient rat mother.
- Iron also plays an essential role in myelination and influences dendritic growth in the hippocampus (9).

Definition and etiology of anemia (10- 14)

Anemia is a condition in which the number of red blood cells (and consequently their oxygen-carrying capacity) is insufficient to meet the body's physiologic needs. The cells in your child's muscles and organs need oxygen to survive, as decreased numbers of red blood cells can place stress on the body. It can make your child appear pale in color and feel cranky, tired, or weak. Specific physiologic needs vary with a person's age, gender, residential elevation above sea level (altitude), smoking behavior, and different stages of pregnancy. Iron deficiency is thought to be the most common cause of anemia globally, but other nutritional deficiencies i.e. protein (all amino acids are essential in hemoglobin synthesis) and vitamins- folic acid, B_{12}, C, and A are also.

Once anemia develops it indicates severe degree of multiple nutritional deficiencies. In addition rapid growth may be a potential cause of anemia, in the first years of life and adolescence, as growth has priority for nutrients.

- Decrease in hemoglobin (Hb), hematocrit (Hct), erythrocyte count < 2SD below age specific norm.
- Mechanism-i) Nutritional-deficiency of iron, vitamin B_{12}, folic acid or in protein energy malnutrition (PEM), ii) hemorrhage, iii) hemolytic or iv) infective hematopoietic**.**
- Mechanism-i) Nutritional-deficiency of iron, vitamin B_{12}, folic acid or in protein energy malnutrition (PEM), ii) hemorrhage, iii) hemolytic or iv) infective hematopoietic.
- **Erythropoiesis** is the process in which new erythrocytes are produced. These new erythrocytes replace the oldest erythrocytes (normally about one percent) that are phagocytosed and destroyed, each day. Folate, vitamin B_{12}, and iron have crucial roles in erythropoiesis. Erythroblasts require folate and vitamin B_{12} for proliferation during their differentiation. Deficiency of folate or vitamin B_{12} inhibits purine and thymidylate syntheses, impairs DNA synthesis, and causes erythroblast apoptosis, resulting in anemia from ineffective erythropoiesis. Erythroblasts require large amounts of iron for hemoglobin synthesis. The iron gets recycled daily with hemoglobin breakdown from destroyed old erythrocytes. Many recently identified proteins are involved in absorption, storage, and cellular export of nonheme iron and in erythroblast uptake and utilization of iron. Erythroblast heme levels regulate uptake of iron and globin synthesis such that iron deficiency causes anemia by retarded production rates with smaller, less hemoglobinized erythrocytes. In addition to erythropoietin, red blood cell production requires adequate supplies of substrates, mainly iron, vitamins B_{12}, folate and heme.
- In Protein – deficiency there are a) decreases: of erythrocyte production / reticulocyte count and 'Fe' utilization by erythrocytes, b) erythroid hypoplasia in bone marrow, c) hypoxic response to erythropoietin production disappears.

- All 10 essential amino acids are needed for hematopoiesis. Deficiency of methionine -causes megaloblastic anemia.
- In breast milk infant receives sufficient iron up to 6 months and all vitamins, except K , D and B_{12}.

Erythrocytes survive about 120 days.

WHO 2001 Age/sex cut off for HB to diagnose Anemia

- Children 6-59 mo (both sexes) 11.0 gm/dl
- Children 5-11 years (both sexes) 11.5 gm/dl
- Children 12-14 years (both sexes) 12.0 gm/dl
- Non pregnant woman >15 12.0
- Pregnant woman 15 11.0
- Men >15 13.0

Hemoglobin (Hb) concentration alone cannot be used to diagnose iron deficiency. However, the concentration of hemoglobin should be measured, even though not all anemia are caused by iron deficiency. The prevalence of anemia is an important health indicator and when it is used with other measurements of iron status the hemoglobin concentration can provide information about the severity of iron deficiency.

Stages of inadequate iron nutritive are:

- First Stage- Iron stores are absent but the Hb concenration remains above the anemia cut off. -low serum ferritin (SF) concentration (<12 µg/L) in CRP –ve.. Ferritin being an acute phase reactant rises in inflammatory/infectious diseases.
- Second stage- Iron deficient erythropoiesis, Hb concentration above the anemia cut off levels. There is an increase in the transferrin receptor (sTfR) concentration and increased free protoporphyrin (FEP) in RBC (umol/mol of heme) <5 yr >70; >5yr >80.
- Third and most severe form of deficiency is iron deficiency anemia (IDA). Iron supply inadequate for Hb synthesis, Hb concentration below the established cut off levels. MCV, MCH and MCHC decreases.

About 25% of the iron in the body is stored as ferritin, found in cells and circulates in the blood. The average adult male has about 1,000 mg of stored iron (enough for about three years), whereas women on average have only about 300 mg (enough for about six months).

Laboratory Diagnosis for Iron deficiency

- Measurement of serum ferritin (SF) is currently the test for diagnosing iron deficiency in absence of an associated disease CRP-ve, a low SF value is an early and highly specific indicator of iron deficiency. WHO criteria for depleted storage iron (SF) are 12µg/L for children under 5 years and 15µg/L for those over 5 years. A higher threshold of 30µg/L is used in the presence of infection.
- TfR index-ratio of sTfR to the log of ferritin, value >1.5 "Iron deficiency; <1.5 anemia chronic diseases.
- EPP- Erythrocyte Porphyrin increases in iron deficiency, lead poisoning and chronic inflammatory anemia. WHO age <5 years, levels 61 µmol/mol haem; for all other subjects, levels should be > 70 µmol/mol haem
- Absence of bone marrow iron content. Low hepatic iron content (MRI – hepatic iron content (15).

Reticulocyte Indices

- Immature reticulocyte fraction (IRF) based on reticulocytes RNA content- Marker of Erythropoiesis, : increase in IRF precedes the increase in total reticulocyte count by several days, monitors response to iron therapy .
- Mean Reticulocyte volume- Iron-deficient erythropoiesis "decreases (↓)"; On iron therapy 'increases (↑)".
- Reticulocyte Hemoglobin Equivalent -(RET-HE) / CHr-Measured by coulter detects functional iron deficiency because reticulocytes are the earliest erythrocytes released into blood and circulate for only 1 to 2 days.
- Delta HE- difference between RET-HE and RBC-HE;(↑)-improved erythropoiesis and (↓)- suppressed erythropoiesis.

Hepcidin in Body Iron Regulation (16)

- Hepcidin is a regulator' of dietary uptake and iron metabolism low levels in serum <10ng/ml- useful indicator of iron deficiency anemia (IDA). It increases in infections thus guides safe iron supplementation in high infection burden. This seems to have evolved as a defense mechanism to protect the host from infections/infestations.
- Hepcidin blocks iron flow into plasma: duodenal absorption, release from macrophages recycling old red blood cells, and mobilization of stored iron from hepatocytes, blocking of iron flow is achieved by hepcidin causing degradation of its receptor, the iron transporter ferroportin.

Vitamin(s) Deficiency in Nutritional Anemia

- A- mobilises Fe from stores & improves utilization (need 100 IU/d)
- C- Fe^{+++} to Fe^{++} & releases Fe from stores (25mg/d).

- Vitamins-- B_{12} and folic acid – megaloblastic anemia-
- B2- Bone marrow hypoplasia- normocytic-normochromic, decrease in reticulocyte, vacuolization of normoblasts
- B6- macro/microcytic anemia,
- Anorexia Nervosa-affects all cell lines. Thus, in protein energy malnutrition and other hematopoietic nutrient(s) deficiency. Anemia on 'Fe- supplementation' –alone – will have poor response.

Vitamin B_{12} and Folic acid (FA) in Hemoglobin Synthesis(17)

- Deficiency of vitamin B_{12} and or Folic acid inhibits purine and thymidylate syntheses, impairs DNA synthesis – apoptosis-'-ineffective erythropoiesis'.
- Nucleus matures poorly relative to cytoplasmic maturity (Dissociation of RNA/DNA synthesis). Megaloblastic changes are most apparent in rapidly dividing cells such as blood cells and gastrointestinal cells. In addition to large nucleated red blood cells megaloblasts, hypersegmented neutrophils, and large platelets can be seen in peripheral smears, and in bone marrow (Megaloblastic dysplasia).

What are the common signs and symptoms of anemia?

- Insidious onset- even Hb <8g/dl, child patient may be comfortable; physical activity even <6g/dl- remains in adjustment.
- Rapid – breathlessness, dizziness, faintness, fatigue, congestive heart failure, heart murmurs-systolic in timing heard at pulmonary area.
- Pallor eyelids, nail bed, hand creases (changes less common below 6 yr.) PICA—iron def, angular stomatitis or glossitis seen in megaloblastic anemia. tongue (large beef like).
- Psychoneurological changes- B_{12} and or Folic acid deficiency- Megaloblastic anemia.
- Dyspigmentation /pigmentation- megaloblastic anemia. Knuckle pad hyperpigmentation is much more frequent than of the palms -large nuclei in keratinocytes.
- Can cause developmental delay, hypotonia, tremor, seizures, failure to thrive, reduced IQ, and mental retardation.
- Children with B_{12} deficiency exhibit speech, language, and social delays, behavioral issues, and problems with fine and gross motor movement.
- MRI scans reveal brain atrophy, which commonly reverses after B_{12} therapy.
- Breast-fed get less B_{12}, develop deficiency within the first year of life.

(Note: Adult B_{12}, 2-5 mg (50% in liver); lasts 3-5 yrs if not fed. Newborn has 25mcg, only).

Besides Vitamins B_{12} and FA Deficiency//megaloblastic anemia in a child? could be due to:

a) Digestive diseases. Celiac disease, chronic infectious enteritis, and enteroenteric fistulas. Pernicious anemia - body can't absorb B_{12} as intrinsic factor is normally made in the stomach.

b). Inherited congenital folate malabsorption. A genetic problem - infants cannot absorb folic acid.

c) Intake of **antiepileptic,** interfere with folic acid absorption.

d) **Diet.** Certain restrictive diets Vegans can develop low levels B_{12} and/ or folate.

Investigations in deficiency of vitamin B_{12}

- MCV raised: vitamins B_{12} and or FA deficiency; Pernicious anemia, hypothyroidism, aplastic anemia, erythroleukemia & paroxysmal noctural hemoglobinuria (Detailed investigations needed).
- Neutrophil hypersegmentation -neutrophil's nuclei have six or more lobes or the presence of more than 3% of neutrophils with at least five nuclear lobes.
- BM: large erythrocyte and leucocyte series; megaloblasts have sieve like chromatin- dissociation between nucleus and cytoplasm maturity They are typically seen in megaloblastic anemia due to vitamin B_{12} or folic acid deficiency, but may also be present in myelodysplastic syndromes and rare congenital conditions..
- Blood-Vitamin B_{12} and folate levels to differentiate. If low folate, estimate erythrocyte folate level. B_{12} deficiency (serum cobalamin level of <200 pg/mL) is diagnostic. The measurements of serum homocysteine (Hcy) and methylmalonic acid (MMA) and holotranscobalamin (holoTC) are diagnostic. Research suggests that MMA and Holotranscobalamin may be more accurate at reading low B_{12} levels because they represent active B_{12}.
- **Control of Nutritional Anemia in Countries like INDIA**

a) Overpopulation, b) undernutrition/ hidden hunger c) low wages, d) infections/ infestations, e) non availability of clean water/ hand washing detergent/ sanitizer and f) finally low education level at all levels.

National programs to control and prevent anemia have not been successful. Experiences from other countries in controlling moderately severe anemia guide to adopt long-term measures i.e. fortification of food items like milk, cereal, sugar, salt with iron. Use of iron utensils in boiling milk, cooking vegetables etc may contribute significant amount of dietary iron. Nutrition education to improve dietary intakes in family for receiving needed macro/micronutrients as protein, iron and vitamins like folic acid, **B_{12}**, A and C etc. for hemoglobin synthesis remain important. As an immediate measure medicinal iron is necessary to control anemia. Addition of folate with iron controls anemia and is neuroprotective (6). Evidence in early childhood suggests high prevalence of associated vitamin **B_{12}** deficiency, thus may also be added along with iron and folate (10-15).

Control and treatment of nutritional anemia:

Anemia during adolescence, pregnancy, and lactation should be treated to ensure that infants are born with sufficient iron stores at birth.

Baby should be breast fed colostrums and mature milk; even anemic mothers transfer sufficient iron in milk (18). 49% absorbable iron in breast milk is sufficient with available fetal stores till baby doubles the birth weight. Weaning foods from 5-6 months onwards should have one iron rich dietary item and iron supplementation be given, if recommended.

Almost one-fourth of iron intake in the **United States of America,** comes from fortified sources, mainly flour products.

Iron EDTA has been highly effective in fortification trials with- Egyptian flat breads, curry powder in South Africa, fish sauce in Thailand and sugar in Guatemala.

In *Grenada*, *flour* used in commercial baking is enriched with iron and B vitamins.

Fortified foods in India

- DFS (Double Fortified Salt (19), provides 100% of daily

dietary iodine (15ppm) requirement, and ~30 to 60% of daily dietary iron requirement (Tata- 0,8-1.1 mg Fe/ g of salt). In Bihar rural studies did not find improvement in Hb (PEM and/ or Infection) Possibly associated malnutrition and infection inhibited response?)

- Tata-Pepsico – Lehar Iron chusti puff and drink.

- Britania Tiger bisscuit-a high fortified variant with 5 mg of elemental iron per biscuit for supervised consumption of 4 biscuits per child a week; and also a low fortified variant with 0.3 mg of elemental iron per biscuit for the wider market pac, daily one biscuit (Mid-day meal program).

- **Commercial Fortification** of **wheat flour** with iron (20), folic acid and vitamin B_{12} offers one of the most feasible and cost-effective strategy to combat anemia and other micronutrient deficiencies. "**Fortification** of staple foods, including **wheat flour** is gaining momentum, in India, FSSAI (Food Safety and Standard Authority of INDIA) said. ...Apr 10, 2017

Fortification of staple foods, including wheat flour is gaining momentum," the FSSAI said. "It is strongly backed by the scientific panel on fortification, medical experts and the academia. Fortification of wheat flour with iron, folic acid and vitamin B_{12} offers one of the most feasible and cost-effective strategy to combat anemia and other micronutrient deficiencies that impact more than 50% of India's population across the population groups and geographies, affecting all socio-economic classes equally. India has a fairly high consumption of wheat flour with an average per person consumption of about 200-250 grams per day, equaling to an overall annual consumption of 63.3 million tonnes."

Hand washing, Chlorinated water and control of infestations and infections remain essential.

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