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MESSAGE FROM FOGSI PRESIDENT

Narendra Malhotra
Agra

This FOGSI FOCUS on anaemia in women comes to you today as our endeavor to make a new Indian woman literate and healthier.

Anaemia is a dreaded problem in our country. Almost 60% women have a hemoglobin of less than 10 gm/dl.

Anaemia is mostly a simple disease, easy to recognize, diagnose and treat, yet our country suffers. Anaemia is the root cause of several complications which may occur and cause a high maternal mortality.

The problem of treating anaemia, again like most problems with Indian women is social. Women of India need to be educated and empowered enough to be self aware so that problems like anaemia do not come in their lives.

The motto of FOGSI this year has been to educate about, prevent & eradicate anaemia.

To eradicate anaemia we have launched the FOGSI – EMCURE anaemia eradication program and to educate, we bring you this FOGSI FOCUS with a special emphasis on clinical practice of anaemia management.

Happy reading. Do give us your feed backs on the FOGSI year 2008

Remember for women welfare, only you can make a difference.

Dr. Narendra C. Malhotra
President – FOGSI

EDITORIAL – A CALL TO ACTION

D. K. Dutta, Shirish Patwardhan and Jaydeep Tank
Kolkatta Pune Mumbai

"Never doubt that a small group of thoughtful committed citizens can change the world. Indeed, it is the only thing that ever has."

- Margaret Mead

Even in this age of "India Shining" it is tragic that a preventable disease like Iron deficiency anemia takes such a heavy toll on our women. Illiteracy of Health i.e. awareness of basic parameters, namely Height – Weight – Hb – Blood Group, is to the tune of 80% across all social classes. The relationship between Hemoglobin and intellect is not appreciated and recognized.

One of the editors (SP) has long been advocating for Universalization of basic health parameters as a novel tool to handle Illiteracy of Health. The awareness and responsibility for basic health parameters must rest with the family and the society at large. Schools and colleges are the areas where 'Health Literacy' should begin. Schools in Leh (Jammu and Kashmir) have made Immunization status cards issued by Government agencies as a part of the admission procedure. Adding Hb and Blood Group to Immunization status card would be the next logical step. This is a low cost intervention yielding maximum benefit. The social and economic costs of illiteracy of health are phenomenal.

FOGSI can play a lead role in raising knowledge about Non pharmacological and pharmacological management and conducting awareness camps / events. We are confident that no FOGSI member would refuse to support the movement to make illiteracy of health a thing of the past.

This FOGSI focus on Anemia is one effort to reach out and spread awareness about this problem. The Editors would like to record their appreciation for the President of FOGSI, Narendra Malhotra and the office bearers for assigning them this task. The contributors have been very kind and responsive in fulfilling the deadlines and we are very thankful to them. Emcure has carried the burden of putting out this Focus on its worthy shoulders and we would like to underscore the fact this issue of the FOGSI focus would simply not have been possible without them.

We hope you will find this publication useful.

ANAEMIA DEFINITIONS AND TYPES

Anupam Gupta
Agra

anaîmia (GK) = without blood.

Anaemia is defined as a qualitative or quantitative deficiency of hemoglobin. Since hemoglobin normally carries oxygen from the lungs to the tissues, anaemia leads to hypoxia (lack of oxygen) in organs. All human cells depend on oxygen for survival and therefore varying degrees of anaemia can have a wide range of clinical consequences. Anaemia is in a large majority of cases caused by lack of iron in the body.

Classification

Anaemia can be classified in a variety of ways, based on the morphology of RBCs, underlying etiologic mechanisms, and discernible clinical spectra, to mention a few.

The three main classes of anemia include excessive blood loss (acutely such as a hemorrhage or chronically through low-volume loss), excessive blood cell destruction (hemolysis) or deficient red blood cell production (ineffective hematopoiesis).

There are two major approaches of classifying anaemia's, the "kinetic" approach which involves evaluating production, destruction and loss, and the "morphologic" approach which groups anaemia by red blood cell size. The morphologic approach uses a widely available and cheap laboratory test as its starting point (the MCV). The kinetic approach focuses on the production and allows the clinician to diagnose multiple etiologies of anemia rapidly.

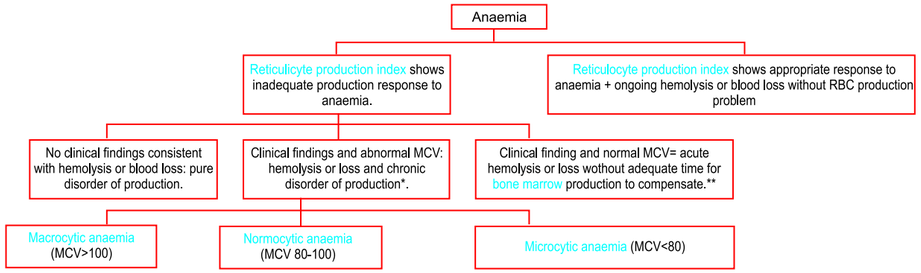
A. Production vs. destruction or loss

The "kinetic" approach to anaemia yields what many argue is the most clinically relevant classification of anaemia. This classification depends on evaluation of several hematological parameters, particularly the blood reticulocyte (precursor of mature RBCs) count. This then yields the classification of defects by decreased RBC production versus increased RBC destruction and/or loss. Clinical signs of loss or destruction include abnormal peripheral blood smear with signs of hemolysis; elevated LDH suggesting cell destruction; or clinical signs of bleeding, such as positive stool, radiographic findings, or frank bleeding.

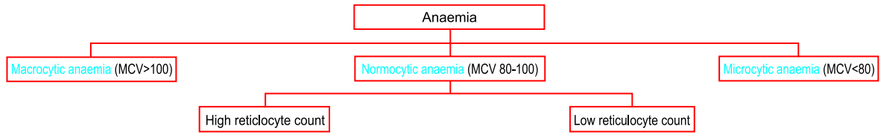
B. Red blood cell size

In the morphological approach, anaemia is classified by the size of red blood cells; this is either done automatically or on microscopic examination of a peripheral blood smear. The size is reflected in the mean corpuscular volume (MCV). If the cells are smaller than normal (under 80 fl), the anaemia is said to be microcytic; if they are normal size (80-100 fl), normocytic; and if they are larger than normal (over 100 fl), the anaemia is classified as macrocytic. This scheme quickly exposes some of the most common causes of anaemia; for instance, a microcytic anaemia is often the result of iron deficiency. In clinical work up, the MCV will be one of the first pieces of information available; so even among clinicians who consider the "kinetic" approach more useful philosophically, morphology will remain an important element of classification and diagnosis.

A schematic approach is as follows:



A schematic representation of how to consider anaemia with MCV as the starting point is as follows:



Other characteristics visible on the peripheral smear may provide valuable clues about a more specific diagnosis; for example, abnormal white blood cells may point to a cause in the bone marrow.

Microcytic anaemia

Microcytic anaemia is primarily a result of hemoglobin synthesis failure or insufficiency, which could be caused by several etiologies:

- Heme synthesis defect
  - Iron deficiency anaemia
  - Anaemia of chronic disease (more commonly presenting as normocytic anaemia)
- Globin synthesis defect
  - alpha-, and beta-thalassemia
  - HbE syndrome
  - HbC syndrome

  and various other unstable hemoglobin diseases
- Sideroblastic defect
  - Hereditary sideroblastic anaemia
  - Acquired sideroblastic anaemia, including lead toxicity
  - Reversible sideroblastic anaemia

Macrocytic Anaemia

- Megaloblastic anaemia, the most common cause of macrocytic anaemia, is due to a deficiency of either vitamin B_{12}, folic acid (or both). Deficiency in folate and/or vitamin B_{12} can be due either to inadequate intake or insufficient absorption. Folate deficiency normally does not produce neurological symptoms, while B_{12} deficiency does.

❏ Pernicious anaemia is caused by a lack of intrinsic factor. Intrinsic factor is required to absorb vitamin B_{12} from food. A lack of intrinsic factor may arise from an autoimmune condition targeting the parietal cells (atrophic gastritis) that produce intrinsic factor or against intrinsic factor itself. These lead to poor absorption of vitamin B_{12}.

❏ Macrocytic anaemia can also be caused by removal of the functional portion of the stomach, such as during gastric bypass surgery, leading to reduced vit B_{12}/folate absorption. Therefore one must always be aware of anaemia following this procedure.

- Alcoholism commonly causes a macrocytosis, although not specifically anaemia. Other types of Liver Disease can also cause macrocytosis.

- Methotrexate, zidovudine, and other drugs that inhibit DNA replication.

Macrocytic anaemia can be further divided into "megaloblastic anaemia" or "non-megaloblastic macrocytic anaemia. The cause of megaloblastic anaemia is primarily a failure of DNA synthesis with preserved RNA synthesis, which result in restricted cell division of the progenitor cells. The megaloblastic anaemias often present with neutrophil hypersegmentation (6-10 lobes). The non-megaloblastic macrocytic anemias have different etiologies (i.e. there is unimpaired DNA globin synthesis,) which occur, for example in alcoholism.

Normocytic Anaemia

Normocytic anaemia occurs when the overall hemoglobin levels are always decreased, but the red blood cell size (Mean corpuscular volume) remains normal. Causes include:

- Acute blood loss
- Anaemia of chronic disease
- Aplastic anaemia (bone marrow failure)
- Hemolytic anaemia

Dimorphic Anaemia

When two causes of anaemia act simultaneously, e.g., macrocytic hypochromic, due to hookworm infestation leading to deficiency of both iron and vitamin B_{12} or folic acid or following a blood transfusion more than one abnormality of red cell indices may be seen.

Heinz body anaemia

Heinz bodies are an abnormality that form on the cells in this condition. This form of anaemia may be brought on by taking certain medications; it is also triggered in cats by eating onions or acetaminophen (Tylenol). It can be triggered in dogs by ingesting onions or zinc, and in horses by ingesting dry red maple leaves.

Specific anaemias

- Anaemia of prematurity occurs in premature infants at 2 to 6 weeks of age and results from diminished

erythropoietin response to declining hematocrit levels.

- Aplastic anaemia is a condition generally unresponsive to anti-anaemia therapies where bone marrow fails to produc enough red blood cells.
- Fanconi anaemia is an hereditary disorder or defect featuring aplastic anaemia and various other abnormalities.
- Hemolytic anaemia causes a separate constellation of symptoms (also featuring jaundice and elevated LDH levels) with numerous potential causes. It can be autoimmune, immune, hereditary or mechanical (e.g. heart surgery). It can result (because of cell fragmentation) in a microcytic anaemia, a normochromic anaemia, or (because of premature release of immature red blood cells from the bone marrow), a macrocytic anaemia.
- Hereditary spherocytosis is a hereditary defect that results in defects in the RBC cell membrane, causing the erythrocytes to be sequestered and destroyed by the spleen. This leads to a decrease in the number of circulating RBCs and, hence, anaemia.
- Sickle-cell anaemia, a hereditary disorder, is due to homozygous hemoglobin S genes.
- Warm autoimmune hemolytic anaemia is an anaemia caused by autoimmune attack against red blood cells, primarily by IgG.
- Cold agglutinin hemolytic anaemia is primarily mediated by IgM.
- Myelophthisic anaemia or Myelophthisis is a severe type of anaemia resulting from the replacement of bone marrow by other materials, such as malignant tumors or granulomas.

Further Reading:

- eMedicine - Anaemia, Chronic : Article by Fredrick M Abrahamian, DO, FACEP
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IRON DEFICIENCY ANAEMIA IN INDIA

Jaideep Malhotra
Agra

Anaemia is a major public health problem throughout the world. Prevalence of anaemia among pregnant women in India averages 57.9%, ranging 33 to 100%.

Anemia and Maternal Health

In India anaemia is the second most common cause of maternal mortality (20% of total maternal mortality). Women in child bearing age group, adolescent girls and young children are most affected. Anaemia is associated with ante-partum hemorrhage, post-partum hemorrhage, puerperal sepsis and maternal mortality, increased incidence of low birth weight babies, premature births and high perinatal mortality. Bleeding from piles and fibroid of uterus are also responsible for anaemia in women.

Among pregnant woman at least half of all anaemia cases are attributed to iron deficiency which more often than not to malnutrition. Infections can also contribute to iron deficiency, causing chronic blood loss such as parasitic infestation with hookworm. Viral and bacterial infections may interfere with good intake, absorption and storage of many nutrients including iron.

Lack of proper nutrition, poverty, lack of support from families and a rise in higher order births are the major reasons for high prevalence of anaemia. Low hemoglobin level in blood causes complications during ante-natal, natal an post-natal periods.

While anaemia is common throughout India, the prevalence is highest in all states in the East region, specially Jharkhand and Bihar where more than 2/3rd of women are anaemic. Severe anaemia is most prevalent in Assam.

In India anaemia is primarily due to poor nutrition or under nutrition which is substantially higher in rural areas. Even in urban areas 33% of children are under weight.

Malnutrition and anaemia in young children are substantial problems in India. It causes higher risk of experiencing health problems such as stunted growth, mental retardation and increased susceptibility to injections diseases. Overall, only 21% of breast feeding and non-breast feeding children are fed according to the entire recommended infant and young child feeding practices. Prevalence of anaemia among children of 6 to 35 months is 79.2% according to rational family health survey 2005-2006, Govt. of India.

Prevalence of anaemia in pre-school children is 56%. The prevalence of under-5 malnutrition and low birth weight is higher in Bangladesh and India than in Pakistan and Srilanka (Comparison among major countries of South Asia).

A comparison among three Indian states-Andhra Pradesh, Maharashtra and Kerala-shows that women and children in Kerala have higher nutrition status than the other two states. This can be attributed to the higher degree of social development in Kerala as judged by the level of female literacy and perhaps better healthcare out reach.

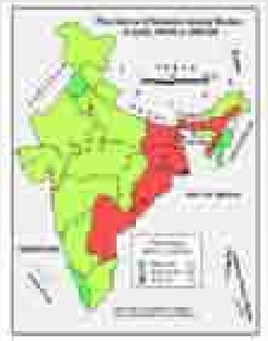
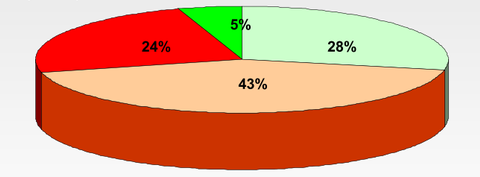


Fig: Prevalence of anaemia among women in India
Source: National Family Health Survey 2005-2006

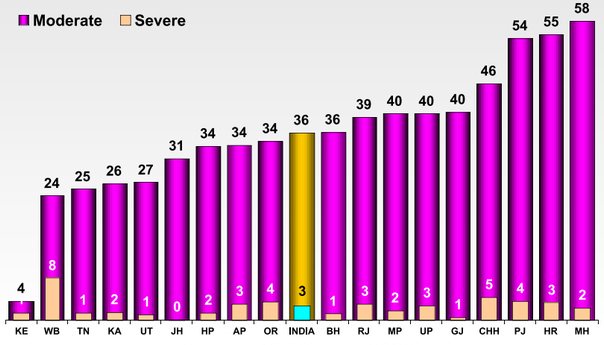
Anaemia Among Adolescent Girls

(1,71,645 girls aged 10 - 19 years)



Source: RCH Survey, 2002

Anaemia Among Pregnant Women by State



Source: RCH Survey, 2002

Balanced strategy of development ensuring food, nutrition, health and environmental security can help eliminate the burden of malnutrition in women and children.

Table 1 :Anaemia among children and adults

S.No.		NFHS-2 (2005-2006)	Residence		Education				NFHS-2 (1998-99	NFHS (1992-93)
			Urban	Rural	No. education	< 8 years completed	8-9 years completed	10 years completed and above		
1.	Children age 6-35 months who are anaemic (%)	79.2	72.7	81.2	84.1	78.8	74.5		74.2	N.A.
2.	Ever-married women age 15-49 months who are anaemic (%)	56.2	51.5	58.2	60.2	56.7	52.6	46.6	51.8	N. A.
3.	Pregnant women age 15-49 who are anaemic (%)	57.9	54.6	59.0	63.0	57.3	55.6	47.4	49.7	N.A.
4.	Ever-married men age 15-49 who are anaemic (%)	24.3	17.2	27.7	233.4	25.5	22.3	16.9	N.A.	N.A.

Source: National Family Health Survey 2005-2006

PHYSIOLOGY AND METABOLISM OF IRON IN ANAEMIA

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Introduction :

Iron is an essential trace metal a cofactor for proteins involved in oxygen transport, electron exchange, and the control of toxic free radicals. It plays numerous biochemical roles, including oxygen binding in hemoglobin and as an important catalytic center in many enzymes, for example the cytochromes.

The commonest nutritional deficiency disorder present throughout the world is iron deficiency with the prevalence being higher in the developing countries. The factors responsible for iron deficiency are best understood in the context of normal iron metabolism.

Iron need:

In normal healthy adults, approximately 0.5 - 2 mg of iron is lost each day due to blood loss and the constant exfoliation of iron-containing epithelial cells that line the gastrointestinal and urinary tracts, skin and hair. In a menstruating woman there is an additional loss of 2 mg daily. Therefore, the same amount of iron from dietary sources is required each day to replace the lost iron and maintain body iron homeostasis. Even though iron is an essential metal in human metabolism, it is highly toxic to cells and tissues if present in elevated levels. Humans do not possess the necessary machinery to rid the body of excess iron and, therefore, the absorptive process must be tightly regulated within defined physiological limits to avoid pathologies associated with both iron deficiency and overload.

Iron sources available for human consumption:

Dietary iron is found in two basic forms:

1. Haem-found in meat and meat products

2. Non-haem iron-present in cereals, vegetables, pulses, beans, fruits etc

It is present in a number of forms ranging from simple iron oxides and salts to more complex organic chelates. Non-haem iron predominates in all diets comprising some 90%-95% of total daily iron intake.

The recycled iron from the senescent cells also is an important source of iron for erythropoiesis.

Absorption of iron: The absorption of both haem and non-haem iron takes place almost exclusively in the duodenum and the bioavailability of iron from these sources is influenced by a number of variables, e.g.

1. The iron content of foods,
2. The type of iron present, i.e. haem or non-haem,
3. Other dietary constituents.

Importantly, absorption is also regulated in line with metabolic demands that reflect the amount of iron stored in the body, and the requirements for red blood cell production.

Despite accounting for only 5% -10% of dietary iron, haem is the most bioavailable source of iron amounting to some 20%-30%. In contrast, the bioavailability of non-haem iron is low. Only 1%-10% of the dietary load is absorbed and is profoundly influenced by other dietary components that can enhance or inhibit non-haem iron bioavailability. The most potent enhancer is ascorbic acid (vitamin C), which acts by reducing ferric iron to the more soluble and absorbable ferrous form. Phytates found in cereal products and polyphenolic compounds found in all plant products are the most potent dietary inhibitors of nonhaem iron absorption. However, it is important to note that on an equimolar basis the pro-absorptive action of dietary ascorbic acid can counteract the inhibitory effect of phytates and polyphenols. Calcium supplementation are also postulated to be inhibitors of iron absorption.

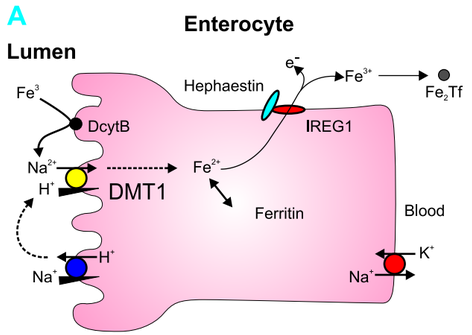
Intestinal uptake of Iron: what is new?

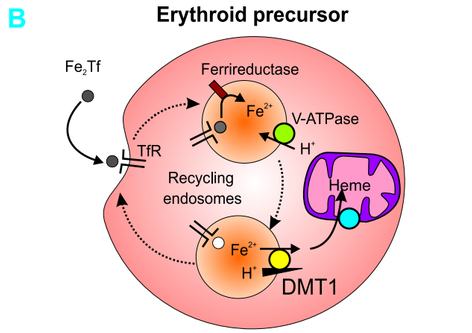
Iron absorption takes place largely in the proximal small intestine and is a carefully regulated process. For absorption iron must be taken up by the luminal cell. That process is facilitated by the acidic contents of the stomach, which maintains the iron in solution. At the brush border of the absorptive cell, the ferric iron is converted to the ferrous form by a ferrireductase. Transport across the membrane is accomplished by bivalent metal transporter1 (DMT-1, also known as Nramp- 2 or DCT-1). DMT-1 is a general cation transporter. Once inside the gut cell, iron may be stored as ferritin or transported through the cell to be released at the basolateral surface to plasma transferrin through the membrane embedded iron exporter, ferroportin. The function of ferroportin is negatively regulated by hepcidin, the principle iron regulatory hormone. In the process of release, iron interacts with another feroxidase , hephaestin, which oxidizes the iron to the ferric form for transferrin binding. Hephaestin is similar to ceruloplasmin, the copper carrying protein.

Iron absorption is influenced by a number of physiologic states. Erythroid hyperplasia, e.g. stimulates iron absorption, even in the face of normal or increased iron stores, and hepcidin levels are in approximately low. The molecular mechanism underlying this relationship is not known. Thus patients with anaemias associated with high levels of ineffective erythropoiesis absorb excess amount of dietary iron. Over time, this may lead to iron overload and tissue damage. In iron deficiency, hepcidin levels are low and iron is much more efficiently absorbed from a given diet, the contrary is true in states of secondary iron overload. The normal individual can reduce iron absorption in situations of excessive intake on medicinal iron intake; however, while the percentage of iron absorbed goes down, the absolute amount goes up. This accounts for the acute iron toxicity occasionally seen when children ingest large numbers of iron tablets. Under these circumstances, the amount of iron absorbed exceeds the transferrin- binding capacity of the plasma, resulting in free iron that affects critical organs such as cardiac muscle cells.

Transport of iron after absorption:

Iron absorbed from diet or released from stores circulates in the plasma bound to transferrin, the iron transport protein. Transferrin is a bilobed glycoprotein with two iron-binding sites. Transferrin that carries iron exists in two forms – monoferric (1 iron atom) or diferric (2 iron atoms). The turnover (half clearance time) of transferrin bound iron is very rapid, typically 60 – 90 minutes. Because almost all of the iron transported by transferrin is delivered to the erythroid marrow – the clearance time of transferrin-bound iron from the circulation is affected most by the plasma iron level and the erythroid marrow activity. When erythropoiesis is markedly





stimulated, the pool of erythroid cells requiring iron increases and the clearance time of iron from the circulation decreases. The half clearance time of iron in the presence of iron deficiency is as short as 10 – 15 minutes. With suppression of erythropoesis, the plasma iron level typically increases and the half clearance time may be prolonged to several hours. Normally, the iron bound to transferrin turns over 10 – 20 times per day. Assuming a normal plasma iron level of 80 – 100 mcg/dL , the amount of iron passing through the transferrin pool is 20 – 24 mg / dL.

The iron – transferrin complex circulates in the plasma until it interacts with specific transferrin receptors on the surface of marrow erythroid cells. Transferrin receptors are found on the cells in many tissues within the body – and all cells at sometime during development will display transferrin receptors-.The cell having the greatest number of receptors (3,00,000-4,00,000 per cell) is the developing erythroblast.

Once the iron bearing transferrin interacts with its receptor, the complex is internalized via clathrin coated pits and transported to an acidic endosome , where the iron is released at the low pH. The iron is then made available for heme synthesis while the transferrin receptor complex is recycled to the surface of the cell, where the bulk of the transferrin is released back into circulation and the transferrin receptor re-anchors into the cell membrane. At this point a certain amount of transferrin receptor protein may be released into circulation and can be measured as soluble transferrin receptor protein. Within the erythroid cell, iron in excess of amount needed for hemoglobin synthesis binds to a storage protein, apoferritin, forming ferritin. This mechanism of iron exchange also takes place in other cells of the body expressing transferrin receptors, especially liver parenchymal cells where the iron can be incorporated into heme containing enzymes or stored. The iron incorporated into hemoglobin subsequently

enters the circulation as new red cells are released from the bone marrow. The iron is then part of the red cell mass and will not become available for reutilization until the red cell dies.

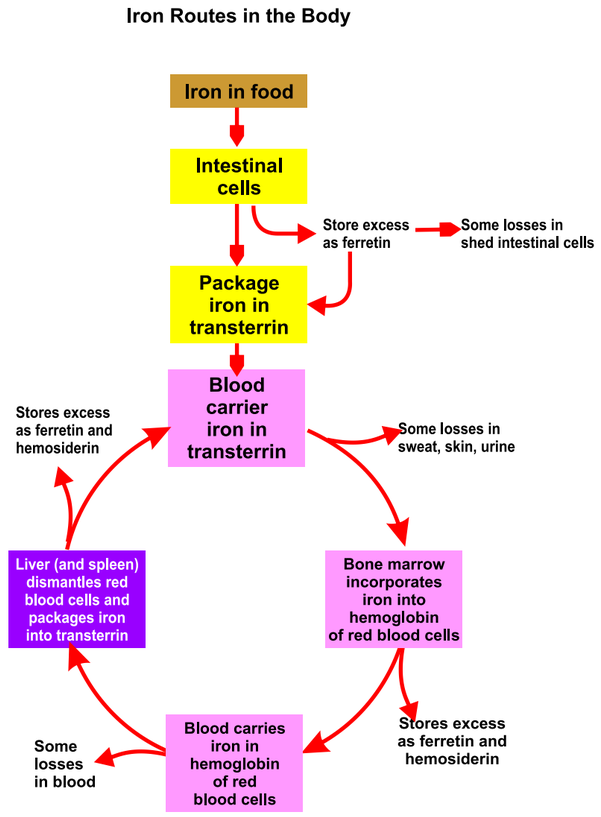
In a normal individual, the average red cell life span is 120 days. Thus, 0.8 – 1 % of red cells turn over each day. At the end of its lifespan, the red cell is recognized as senescent by the cells of the Reticulo-endothelial system, and the cell undergoes phagocytosis. Once within the RE cell, the hemoglobin from the ingested red cell is broken down, the globin and other proteins are returned to the amino acid pool, the iron is shuttled back to the surface of RE cell ,where it is presented to circulating transferrin. It is the efficient and highly conserved recycling of iron from senescent red cell that supports steady state (and even mildly accelerated) erythropoesis.

Since each milliliter of red cells contains 1 mg of elemental iron, the amount of iron needed to replace those red cells lost through senescence amounts to 16- 20 mg /dL (assuming an adult with a red cell mass of 2 L). Any additional iron required for daily red cell production comes from the diet. Normally, an adult male will need to absorb at least 1 mg of elemental iron daily to meet needs, while females in the childbearing years will need to absorb an average 1.5 mg /dL. However to achieve a maximum proliferative erythroid marrow response to anaemia, additional iron must be available. With markedly stimulated erythropoesis demands for iron are increased by as much as 6- 8 fold. With extra vascular hemolytic anaemia the rate of red cell destruction is increased, but the iron recovered from the red cell is efficiently reutilized for hemoglobin synthesis. In contrast, with intra vascular hemolysis or blood loss anaemia, the rate of red cell production is limited by the amount of iron that can be mobilized from stores. Typically, the rate of mobilization under these circumstances will not support red cell production more than 2.5 times normal. If the delivery of iron to the simulated marrow is suboptimal the marrow's proliferative response is blunted, and hemoglobin synthesis is impaired. The result is a hypo-proliferative marrow accompanied by microcytic hypochromic anaemia.

The iron balance:

The balance of iron in humans is tightly controlled and designed to conserve iron for reutilization. There is no regulated excretory pathway for iron, and the only mechanisms by which iron is lost from the body are blood loss (via GI bleeding, menses or other form of bleeding) and the loss of epithelial cells from the skin, gut and genitourinary tract. Normally, the only route by which iron comes into the body is via absorption from food or from medicinal iron taken orally. Iron may also enter the body through red cell transfusion or injection of iron complexes. The margin between the amount of iron available for absorption and the requirement for iron in growing infants and the adult female is narrow, this accounts for the great prevalence of iron deficiency worldwide - currently estimated at one half billion people.

The amount of iron required from the diet to replace losses averages about 10% of body iron content a year in man and 15% in woman of childbearing age. Dietary iron content is closely related to total caloric intake (approximately 6 mg of elemental iron / 1000 calories). Iron bioavailabilty is affected by the nature of food stuff, with heme iron (e.g. red meat) being most readily absorbed. An individual with iron deficiency can increase iron absorption to about 20% of the iron present in a meat containing diet but only 5- 10% of the iron in a vegetarian diet. Vegetarians are at an additional disadvantage because certain food stuffs that include phytates and phosphates reduce iron absorption by about 50%.when ionisable iron salts are given together with food, the amount of iron absorbed is reduced. When the percentage of iron absorbed from individual food items is compared with the percentage for an equivalent amount of ferrous salt, iron in vegetables is only about 1/20 th as available , egg iron 1 / 8th, liver iron ½, and heme iron 1/ 2 to 2/3 rd.



Infants' children and adolescents may be unable to maintain normal iron balance because of the demands of body growth and lower dietary intake of iron. During the last two trimesters of pregnancy, daily iron requirements increase to 5- 6 mg. That is the reason why iron supplements are strongly recommended for pregnant women in developed countries. Enthusiasm for supplementing food such as bread and cereals with iron has waned in the face of concerns that the very prevalent hemochromatosis gene would result in an unacceptable risk of iron overload.

The stages of iron deficiency:

Iron deficiency anaemia is the condition in which there is anaemia and clear evidence of iron lack. The progression to iron deficiency can be divided into three stages:

1. The first stage: negative iron balance

In this the demands for (or losses of) iron exceed the body's ability to absorb iron from the diet. This stage results from a number of physiologic mechanisms:

- Blood loss
- Pregnancy (in which the demands for red cell production by the fetus over strip the mother's ability to provide iron)
- Rapid growth spurts in the adolescent
- Inadequate dietary iron intake.

Blood loss in excess of 10 – 20 ml of red cells per day is greater than the amount of iron that the gut can absorb from an abnormal diet. Under these circumstances the iron deficit must be made up by mobilization of iron from RE storage sites. During this period, iron stores- reflected by Serum ferritin level or the appearance of stainable iron on bone marrow aspirations- decrease. As long as iron stores are present and can be mobilized, the serum iron, total iron binding capacity (TIBC), and red cell protoporphyrin levels remain within normal limit.

At this stage red cell morphology and indices are normal.

2. The second stage: iron deficient erythropoiesis

When iron stores become depleted, the serum iron begins to fall. Gradually, the TIBC increases, as do red cell protoporphrin levels. By definition,the marrow iron stores are absent when the serum ferritin level is less than 15 mcg /L. As long as the serum iron remains within the normal range, hemoglobin synthesis is unaffected despite the dwindling iron stores. Once the transferrin saturation falls to 15 – 20 % , hemoglobin synthesis becomes impaired. This is a period of iron deficient erythropoiesis. Careful evaluation of the peripheral blood smear reveals the first appearance of microcytic cells and if the laboratory technology is available, one finds hypochromic reticulocytes in circulation. Gradually, the Hemoglobin and hamatocrit begin to fall reflecting iron deficiency anaemia. The transferrin saturation at this is point 10- 15 %.

3. The third stage :Iron deficiency anaemia

When moderate anaemia is present (Hb : 10 – 13 g/dL), the bone marrow remains hypoproliferative. With the more severe anaemia (Hb : 7- 8 g/dL) , hypochromia and microcytosis become more prominent, target cells and misshapen cells (poikilocytes) appear on the blood smear as cigar or pencil shaped forms, and the erythroid marrow becomes increasingly ineffective. Consequently with severe prolonged iron deficiency anaemia erythroid hyperplasia of the marrow developes, rather than hypoproliferation.

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- 17th edition Harrison's Principles of Internal Medicine
- Understanding Heme Transport : Nancy C. Andrews : New England Journal of Medicine. January 2006
- Molecular mechanisms involved in Intestinal Iron Absorption : Paul Sharp et al : World Journal of Gastroenterology September 2007

CLINICAL SIGNS AND SYMPTOMS OF IDA

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"No country sends its soldiers to war to protect their country without seeing that they will return safely and yet mankind for centuries has been sending women to renew human resources without protecting them".

(Fred Sai, Former president of IPPF)

Anaemia is the most frequently observed nutritional deficiency diseases in the world today. It has been major problem for the obstetricians both with regard to maternal as well as fetal health.

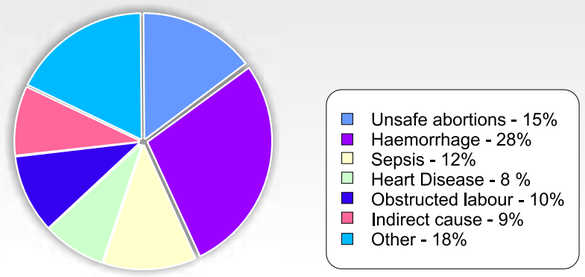
WHO definition: Anaemia in pregnancy is defined as haemoglobin concentration of 11 gm/100 ml or less in the peripheral blood. During pregnancy plasma volume expands resulting in haemoglobin dilution. For this reason, haemoglobin level below 10 gm/ dl at any time during pregnancy is considered anaemia (WHO – 1993, CDC 1990).

Anaemia accounts for 20-30% of maternal deaths and in another 20% it is a contributing factor. It is also associated with three times greater risk of premature delivery and low birth weight babies and nine times higher risk of perinatal mortality.

Clinical stages of iron deficiency :

Iron deficiency is the **commonest form of anaemia** during pregnancy. It occurs in varying degrees of severity that merge imperceptibly into one another. Iron depletion is the earliest stage of iron deficiency, in which storage iron is decreased or absent but serum iron concentration and blood hemoglobin levels are normal. Iron deficiency without anaemia is the next stage of iron deficiency, characterized by decreased or absent storage iron, usually low serum iron concentration and transferring saturation, without overt anaemia. Iron

Causes of Maternal Death in developing countries



deficiency anaemia is the overt manifestation of iron deficiency. It is characterized by decreased or absent iron stores, low serum iron concentration. Low transferring saturation, and low haemoglobin concentration or hematocrit value.

Clinical Features of anaemia :

Symptoms: There may be no symptoms, especially in mild and moderate anaemia. Fatigue, irritability, and headache are common and the earliest complaints of patients specially those with iron deficiency. Patients may complain of weakness, exhaustion and lassitude, indigestion and loss of appetite. Palpitation, dyspnoea, giddness, oedema feet and rarely generalized anasarca and even congestive cardiac failure can occur in severe cases.

Headache, paresthesias, and a burning sensation of the tongue are symptoms of iron deficiency, probably caused by deficiency of iron within tissue cells. Pica, the craving to eat unusual substances such as dirt, clay, and ice is a classic manifestation of iron deficiency and is usually cured promptly by iron therapy.

Folate deficiency is the commonest form of megaloblastic anaemia. Symptoms due to folic acid deficiency are usually insidious and first revealed in the last trimester or early puerperium. Gastrointestinal symptoms like anorexia or protracted vomiting are commonly seen in megaloblastic anaemia. An occasional patient may have diarrhoea.

Megaloblastic anaemia is commonly associated with systemic symptoms like fever. Anaemia due to haemoglobinopathies like Sickle-cell anaemia and Thalassemias syndrome commonly show symptoms of associated complications like infections, cerebrovascular accidents, pulmonary infarction and embolism.

Two types of Sickle-cell crisis can occur in the third trimester. Common being hemolytic crisis associated with rapidly developing anaemia, jaundice, fever and leucocytosis. Sickle cell crisis is due to vascular occlusion of capillaries in various organs leading to infarction and congestive cardiac failure.

Associated symptoms of malabsorption, excessive blood loss through various routes and passage of worms are commonly seen.

Signs : The physical findings in iron deficiency anaemia include, in approximate order of frequency : pallor, glossitis (smooth, red tongue), stomatitis and angular cheilitis. Koilonychia, once a common finding, is now encountered rarely. Icterus of varying severity is generally seen in hemolytic anaemia associated with haemoglobinopathies like sickle-cell and thalassemia syndrome.

Anemic patients have pedal edema which is mainly due to hypoprotenaemia and associated pre-eclampsia.

Pre-eclampsia is more commonly associated with megaloblastic anaemia. Retinal hemorrhages and exudates may be seen in severely anemic patients. The palpable spleen and liver is seen in a small proportion of patients with iron deficiency anemia , megaloblastic anemia and also in patients of severe anaemia with cardiac failure.

A soft systolic murmur can be heard in the mitral areas due to hyperdynamic circulation. It must be differentiated from pathological murmur of heart diseases. There can be fine crepitations at bases of lungs due to congestion.

Clinical signs and symptoms due to some of the important complications should be looked for like

- Intercurrent infections.
- Congestive cardiac failure.
- Deep venous thrombosis.
- Pulmonary embolism.

Early diagnosis facilitates treatment of anemia but the urge to over investigate must be resisted. To be truly effective the diagnosis should take into account the cost effectiveness and impact on the management of the investigations undertaken

INVESTIGATING IDA

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This is perhaps one of the most controversial areas in the management of anemia. The controversy is not so much about the investigations themselves but rather their application particularly in resource poor settings.

The threshold for investigations is always being redefined particularly from a obstetricians or a policy maker or a hematologist's point of view.

There is consensus that a Patient having hemoglobin level below 10 gm% should be considered for further hematological investigation. This becomes all the more necessary when the hemoglobin fails to rise despite empiric treatment. The Primary objectives of this investigation are to determine the degree, type and cause of anaemia.

Hemoglobin Estimation:

The cyanmethemoglobin method for determining hemoglobin concentration is the best laboratory method for the quantitative determination of hemoglobin. It serves as a reference for comparison and standardization of other methods.

Arbitrary grading of pathological anaemia is done according to the level of Hb i.e. Mild anemia 8 – 10 gm%, Moderate anemia 6.5 – 8 gm% and severe less than 6.5 gm%

Hematological Indices :

Hematocrit measurement is an acceptable and recommended method for anaemia determination, but has no advantage compared to hemoglobin measurement. Among all the red cell indices measured by electronic blood counters, mean corpuscular volume and mean corpuscular hemoglobin are the two most sensitive indices of iron deficiency. Reduction in mean corpuscular volume occurring in parallel with anaemia is a late phenomenon in the development of iron deficiency.

Bone Marrow Examination :

This is a specialized test and should be done only when the other tests are inconclusive. A bone marrow stain for iron has been regarded as the reference against which to evaluate other iron tests. Absence of stainable iron reflects absent iron stores. The other features seen are

- Erythroid Hyperplasia,
- Increase in more mature forms,
- Polychromatic normoblasts as the predominant cells,
- Micronormoblastic erythropoiesis
- Reticulo endothelial iron is absent,
- Sideroblasts greatly diminished.

5. Biochemical Findings

Iron status can be determined by several well-established tests in addition to measurement of haemoglobin or haematocrit. Unfortunately, however, there is no single standard test to assess iron deficiency without anaemia. The use of multiple tests only partially overcomes the limitation of a single test and is not an option in resource-poor settings.

Moreover, iron-related tests do not all correlate closely with one another because each reflects a different aspect of iron metabolism (98). In anaemic individuals, such tests are used to confirm or help clarify the type or cause of anaemia.

Although these tests are utilized for special surveys in populations, they are not routinely conducted on a large scale because of their relatively high cost. This cost usually limits their use to settings with adequate resources. Even where feasible, most iron biochemical tests are of limited use in resource-poor settings. In such situations, other nutrient deficiencies and high rates of infections can interfere with the interpretation of such tests relative to iron status.)

- **S Ferritin**
  - A low serum ferritin level reflects depleted iron stores and hence is a precondition for iron deficiency in the absence of infection.
- **Serum iron, transferrin, and transferrin saturation**
  - Iron deficiency results in a reduction in serum iron (SI) levels, an elevation in transferrin (total iron-binding capacity [TIBC]) levels, and hence a net reduction in transferrin saturation (i.e. SI/TIBC)
- **Serum transferrin receptors**
  - Serum transferrin receptor levels increase progressively as the supply of iron to the tissues becomes progressively more deficient
- **Erythrocyte protoporphyrin**
  - An elevated erythrocyte protoporphyrin level correlates well with low serum ferritin, and can serve to screen for moderate iron deficiency without anaemia in the absence of infection or inflammation, lead poisoning, and haemolytic anaemia

Adjunct investigations can be performed as needed to further outline the cause of the anemia e.g. Stool examination to look for Helminthasis (hookworm) infestation or presence of occult blood, urine examination to look for hematuria and X Ray Chest (with abdominal shield in case of pregnancy).

Further Reading:

- Iron Deficiency Anaemia Assessment, Prevention and Control A guide for programme managers WHO, 2001

LIFESTYLE MANAGEMENT FOR COMBATING ANAEMIA

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Any kind of Medicine is a 'trick.'
The problem is solved permanently only through life style changes.

Epidemic of Nutritional Anaemia has its roots in life style changes that have occurred over the past 30-40 odd years. Iron supplementation is a short term solution, while life style change is the long term solution.

From jaggery to sugar: In good old days jaggery was the rule and sugar was an exception. Jaggery contains 11 mg iron per 100 g of edible portion. This permanent source of iron has been done away with by using sugar. So the message is to switch back to Jaggery.

Iron Utensils: Using iron 'tawa, kadhai and ladle' for cooking gives 4 mg of elemental iron daily and life long for the whole family. This traditional cookware has been replaced by german/hindalium/aluminium or non-stick cookware. Use of iron utensils is considered backward. In Vidarbha(Maharashtra), it is customary to give boiled water with iron ladle kept in it for 30 min or more, to recently delivered lady. The life style change is to switch back to iron 'tawa, kadhai and ladle.'

Take lot of fruits: Addition of citrus fruits to diet allows ascorbic acid to protect ferrous iron from competitive binding to tannins/ phytates and polyphenols.

Tea and coffee: Iron absorption is reduced by 80 - 100% with consumption of tea and / or coffee one hour before or after food. Switching back to milk would be the ideal change. However, if it is difficult, avoid tea and / or coffee one hour before / after food.

Eating when not hungry: Hydrochloric acid present in the stomach is essential for break down of iron from the vegetarian food. When one is not hungry, there is no acid in the stomach. This is the reason why so many from the affluent class too are afflicted by Nutritional anaemia. Since they keep on eating without being hungry, iron is not absorbed. The message is – 'Eat only when you are really hungry.'

Illiteracy of Health: While we lead in mobile telephony, computer and other forms of literacy, what about health literacy? Illiteracy of Health essentially means lack of knowledge of basic health parameters. These are Height – Weight – Hb – Blood Group. Over 90% of Indian population is not aware their basic health parameters. Hb levels of doctors and paramedics are equally poor. Medical professionals must lead by example. Just preaching will not help. While we propagate use of Medicines, let us not forget life style changes. After all any kind of Medicine is a 'trick.' A trick cannot solve the problem. The problem is solved only through changes which change the environment leading to Nutritional Anaemia.

Life style change: Daily and Life long

Use Jaggery (Gud)

Use iron utensils for cooking (tawa, kadhai and ladle)

No tea and / or coffee one hour before and after food

Eat when really hungry

Know your Basic Health Parameters

Iron content in Vegetarian food
Per 100 g of edible portion

600 mg	Bael phul
100 mg	Garden cress seeds (Aliv-Haliv)
70 mg	Coconut meal – deoiled, Turmeric (Halad)
60 mg	Lotus stem – dry (kamal gatta), Niger seeds (Karale), Pipalli
20 – 40 mg	Amaranth (Math), Bengal gram leaves (Harbhara pane), Cow peas leaves (chavli pane), Garden cress leaves (aliv pane),Shepu

* from Karodpati Passbook

AN OVERVIEW OF TREATMENT

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Introduction

Anaemia is a global problem which was under-recognized and under-diagnosed globally and in India. Things are changing today, and concerted efforts by FOGSI over the past decade have highlighted this issue. However once we have identified the problem, quick and decisive steps need to be taken to address it.

Prevention

The National Nutritional Anaemia Prophylaxis Program recommended 100 tablets of iron (Ferrous sulfate 200 mg with 63 mg elemental iron) with folic acid (0.5 mg) to all pregnant women in the third trimester of pregnancy, lactating women, acceptors of family planning and children 1-11 years. Despite the National Nutritional Anaemia prophylaxis program being initiated in 1972, even today only 58% receive iron, folate tablets or syrup (UNICEF 2004). Presently, the recommendation is to increase the elemental iron to 100 mg per day, by giving 2 tablets daily instead of one.
WHO – recommends supplements of 30-60 mg elemental iron to those with normal iron stores, and 120-240 mg to those with none.

Suggestions for better prophylaxis

1. Dietary modifications to add iron rich foods :
   (Dark green leafy vegetables, Ragi, methi, Jaggery, Meats, Citrus fruits).
2. Community based distribution of tablets.
3. Fortification of common foodstuffs may be more effective e.g. wheat and salt.
4. Educating adolescent girls about diet.
5. Hookworm infestation should be treated.
   Chemoprophylaxis for malaria, in endemic or high-risk cases, especially in pregnancy.

Treatment of iron-deficiency anemia

Choice of therapy depends upon 3 FACTORS:

- Severity of anaemia,
- Gestational age of pregnancy
- Tolerance of therapy chosen.

Parenteral therapy :

Traditional indications include

- Intolerance to oral iron
- Poor compliance to oral iron
- Gastrointestinal disorders
- Malabsorption syndromes
- Rapid blood loss
- Inability to maintain iron balance (haemodialysis)
- Patient donating large amount of blood for auto-transfusion programme?
- Pregnant women with severe IDA, presenting late in pregnancy

Intramuscular Iron Preparations:

- Iron dextran complex (Imferon)
- Iron sorbitol complex (Jectofer)

Usage :100mg of elemental iron given daily (after first test dose)deep I.M. by Z-technique

- Side effects : Fever, muscular pain, joint pains, discoloration of skin.

Intravenous Iron

- Haldane's Formula 0.3 x weight in pounds x (100 – Hb%) gives the total elemental iron required
- Additional 50% to replenish the body stores
- Side effects : Anaphylactic reactions, other side-effects can occur.
- Addition of hydrocortisone reduces the risk for venous thrombosis

Newer iron preparations

- Iron sucrose (Orofer-S, Encifer)
- Iron gluconate (Globac)
- Fractionated Iron dextran

Iron sucrose : Iron (III) - hydroxide sucrose complex

- Excellent tolerance
- Almost no complications
- 5 ml vial contains 20 mg/ml of elemental iron, only for intravenous use
- Slow I.V. over 5 minutes or short infusion over 15 minutes (in NS)
- Cannot be given as single dose, total infusion is 1-3 doses per week
- Available in Europe for several decades, Approved in US in 2000
- Approved in India in 2005

Which method???

In a comparison of intravenous versus oral iron, women who received 600 mg intravenous iron sucrose followed by standard oral iron after four weeks, replenished their iron stores more rapidly and had a more favorable development of the fatigue score indicating improved quality of life.

A large meta-analysis from the Cochrane review came to the following conclusion: Despite the high incidence and burden of disease associated with this condition, there is a paucity of good quality trials assessing clinical

maternal and neonatal effects of iron administration in women with anaemia. Daily oral iron treatment improves hematological indices but causes frequent gastrointestinal adverse effects. Parenteral (intramuscular and intravenous) iron enhances hematological response, compared with oral iron, but there are concerns about possible important adverse effects. Large, good quality trials, assessing clinical outcomes (including adverse effects) are required.

Post-partum anaemia

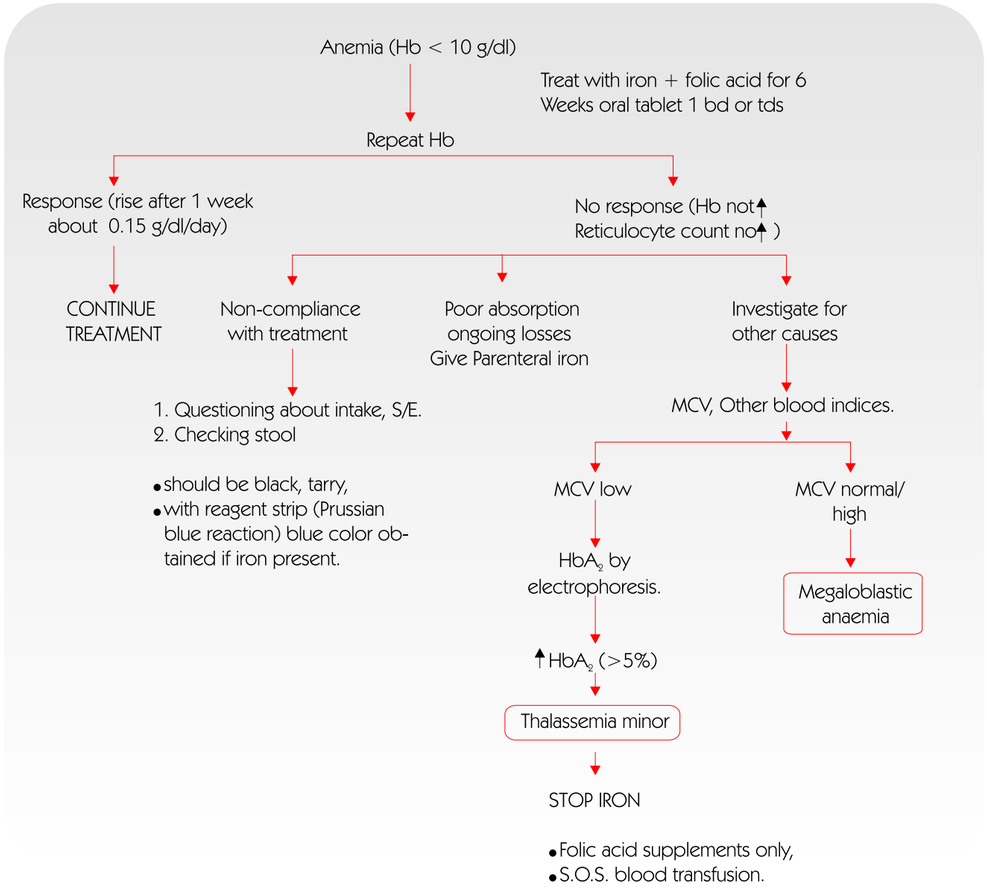
Postpartum anaemia is associated with breathlessness, tiredness, palpitations and maternal infections. Blood transfusions or iron supplementation have been used in the treatment of iron deficiency anaemia. Recently other anaemia treatments, in particular erythropoietin therapy, have also been used.

One study suggested that intravenous iron sucrose increases the Hb level more rapidly than oral ferrous sulphate in women with postpartum IDA. It also appears to replenish iron stores more rapidly. However, this study was not large enough to address the safety of this strategy.

To assess the clinical effects of treatments for postpartum anaemia, including oral, intravenous or subcutaneous iron/folate supplementation and erythropoietin administration, and blood transfusion a large meta-analysis was carried out. There is some limited evidence of favorable outcomes for treatment of postpartum anaemia with erythropoietin. However, most of the available literature focuses on laboratory hematological indices, rather than clinical outcomes. Further high-quality trials assessing the treatment of postpartum anaemia with iron supplementation and blood transfusions are required. Future trials may also examine the significance of the severity of anaemia in relation to treatment, and an iron-rich diet as an intervention.

Anaemia non – responsive to iron therapy

In clinical practice : Anaemia is assumed to be nutritional, and a therapeutic trial with iron folate supplements is given in the flow chart :



Role of erythropoietin in iron deficiency anaemia

Blunted EPO production is seen in certain conditions such as

- Anaemia of systemic disease
- Anaemia of malignancy
- Anaemia secondary to chemotherapy
- Anaemia of AIDS / HAART therapy
- Anaemia of prematurity

These may be considered for erythropoietin usage.

Blood Transfusion

WHO has stated that 'transfusion should be prescribed ONLY for conditions for which there is NO OTHER TREATMENT.'
It has also been said that if you feel you need to give only ONE unit of blood, please reconsider as you probably DO NOT need to give it at all.

Limitations of Blood Transfusions:

- Transfusion-transmissible infections e.g. HIV, Hepatitis B&C, CMV infections etc.
- Effectiveness of procedures ,
- Availability, Cost,
- Reaction to constituents

Efficiency of blood cold chain for storage & transportation is an important factor.

SUMMARY :

- Anaemia prevention should be a priority for all women's health care providers
- Treatment options have evolved over the years
- Choice of treatment should be based on type of anaemia, compliance and severity
  Blood transfusion should be a last resort

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THE PHARMACOLOGY OF IRON AND ITS VARIOUS PREPARATIONS

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Almost all cases of iron deficiency anaemia respond readily to treatment with iron supplementation.

Iron can be supplemented by

- Food fortification,
- Oral route, and
- Parenteral route.

This article focuses on the first two options

Food fortification

Food fortification with iron has increased significantly in the last three decades. The utilization of reduced iron for that purpose in the United States has increased from 72 tons in 1970 to 10,124 tons in 1987. Reduced iron constituted 13.2% and 96.7% of the total amount of iron used in fortification, respectively A variety of iron products are used for food fortification purposes, including ferrous sulfate, ferrous lactate, ferrous gluconate, ferric ammonium citrate, ferrous fumarate, ferrous succinate, ferric saccharate, ferric orthophosphate, ferric ammonium orthophosphate, ferric pyrophosphate, EDTA iron, haemoglobin, and elemental iron (electrolytic and carbonyl iron).

Paradoxically enough, iron supplementation has a larger impact on population health than fortification Iron fortification has the lowest cost-effectiveness ratio and is from the economic point of view most attractive. However, one of the key processes in developing a fortification program is choosing a suitable food vehicle. This can be a challenge, especially in countries with large rural populations like India with a small food industry with limited technology, and with limited access to and low consumption of processed foods. Moreover, consumption of fortified foods is generally limited to the middle- and high-income groups who are not always at greatest risk of nutritional deficiencies.

ORAL THERAPY

Various salts and various formulations and various forms of oral therapy are available, like tablets, capsules, drops, syrups, slow release tablets and chewable tablets.
The selection of formulation depends upon

Bioavailability,
Side effects,
Cost effectiveness and patients tolerance to a given preparation.

Ferrous salts

All dietary iron has to be reduced to ferrous form to enter the mucosal cells. Hence bivalent iron salts like ferrous sulfate, fumarate, gluconate, succinate, glutamate and lactate have been preferred over ferric salt

preparations. In addition these salts are amongst the cheapest preparations of iron available for medicinal use.

Ferrous sulfate (FS) (20 % elemental iron) is commonly used for tablet preparations. Liquid formulations of the salt are available as elixirs in sorbitol base as syrup preparations are poorly stable (the salt is easily oxidizable in moist environment) which negates the cost advantage.

These salts have uniformly good bioavailability. However, the bioavailability decreases markedly in the presence of dietary inhibitors like phytates, tannic acid etc. They cannot be added to other foods/milk/fortified formulas for the same reason.
The problems with ferrous salts are that there is a

- High incidence of gastrointestinal side effects (~23 %),
- Teeth are known to be stained with liquid preparations if the drops are not placed carefully at the back of the tongue and
- Ferrous sulphate has a salty astringent taste which is not palatable for most children.

Ferrous Fumarate (FF) (33% elemental iron) has a similar efficacy and GI tolerance to ferrous sulphate, is moderately soluble in water, environmentally more stable and is almost tasteless. Ferrous fumarate is less soluble than ferrous sulfate in water but is soluble in dilute acid such as gastric juice. It does not precipitate proteins and does not interfere with the proteolytic or diastatic activities of the digestive system.

Ferrous ascorbate It is believed that:

- Administration of iron in the form of ferrous ascorbate delivers maximum amount of ferrous iron to the duodenal brush border and at the same time produces minimum GI adverse effects. Further,
- Ascorbic acid has been shown to inhibit the effect of phytates, phosphates and oxalates on iron absorption, besides
- It also inhibits the conversion of ferrous to ferric iron; this leads to increased absorption of iron.
- Ascorbic acid also facilitates iron absorption by the formation of soluble iron ascorbate complexes and by inhibiting the formation of insoluble iron complexes.
- Inhibition of conversion of ferrous to ferric iron reduces the amount of free radicals generated, thereby minimizing the GI adverse effects.
- Moreover ascorbic acid mobilizes iron from the core of ferritin to the sites of erythropoiesis and at the same time inhibits conversion of ferritin to hemosiderin which can not be utilized.
- Thus ascorbic acid improves iron utilization and prevents iron overload. Ferrous ascorbate allows maximum (40%) amount of iron absorption by inhibiting the formation of insoluble iron complexes with dietary phosphates, tannates and polyphenols. Ferrous ascorbate thus allows rapid correction of hemoglobin. Different study show absorption of 40% iron from ferrous ascorbate.

There is evidence to indicate that the above theoretical advantages translate into clinical reality. When compared with carbonyl iron in a study, it was found that 100 mg of Ferrous ascorbate produces greater increase in

haemoglobin (5.03 ± 1.08g/dL)as compared to carbonyl iron(2.82 ± 1.43g/dL. More patients became nonanaemic- 93.33% as compared with 46.66 % with carbonyl iron. Ferrrous ascorbate replenished stores to a greater extent than with carbonyl iron.

Similarly in the HERS study which was prospective open label study done on 1461 patients shows that ferrous ascorbate tablet was effective in treating anaemia, with rapid increase in hemoglobin within 45 days, and was well tolerated.

Ferric salts

- Ferric salts have traditionally not been preferred over ferrous salts as the ferric ion first requires reduction to ferrous form in the intestinal lumen and usually this reducing capacity is not enough to reduce doses of iron therapeutically administered.
- The bio-availability of iron from ferric salts is 3 to 4 times less than that of ferrous sulphate.
- Other properties are essentially similar to ferrous salts.Ferric ammonium citrate (18% elemental iron) is the most commonly used of these salts.
- Another Ferric iron used is Carbonyl iron. Its size of 5 micrometer is well absorbed. It has a very low toxicity. It is cost effective and side effects are tolerable. it is also useful as a food additive.

Iron Amino-acid chelates

Iron amino-acid chelates are conjugates of the ferrous or ferric ion with amino-acids. Although numerous conjugates have been formulated the most studied of these are ferrous bis-glycinate (20% elemental iron content), ferric trisglycinate and ferrous glycine sulphate. They have no effect on the color or taste of food products.
They have relatively high bioavailability in the presence of dietary inhibitors. It is theorized that the chelates prevent iron from binding to inhibitors in food or precipitating as insoluble ferric hydroxide in the pH of the small intestine.

Iron-polymaltose complex (IPC)

A combination of ferric iron with maltol (a food additive), was developed as a molecule that is soluble at neutral pH and is not chelated by other substances.[9] A study was carried out to compare efficacy of FS with IPC(Iron Polymaltose Complex) and results show that IPC can be considered as a useful alternative formulation for the treatment of IDA during pregnancy for those patients who cannot tolerate other iron preparations (ferrous form); this is an important finding, as compliance is a significant concern during pregnancy.

The Road ahead

Several other iron preparations are in various stages of development or being gradually phased out. Prominent in the latter group are heme based preparations. Hemoglobin as a source of iron was promoted on the basis of the high bioavailability of heme iron. However the iron content of hemoglobin is 0.34 %. As a result 300 mg of hemoglobin is required to deliver 1 mg of elemental iron which leads to large volumes and

inhibitory costs.

Newer preparations include

Ferrous oxalate, microencapsulated ferrous sulphate and microencapsulated ferrous fumarate. Ferrous oxalate has been recently found to have good efficacy and low toxicity in studies conducted on piglets. Recently, a supplement containing microencapsulated ferrous fumarate (plus ascorbic acid) has been developed which can be sprinkled on any complementary food at the table given by the caregiver. Iron being encapsulated does not change the color and taste of the food and has been found to be equally bioavailable to FS. Similarly, a ferrous sulphate preparation microencapsulated with phospholipids was found to have equivalent bioavailability to $FeSO_4$.

Good Practice Points

- Iron usually should be given in dose of about 200 mg of elemental iron per day in single or divided doses.
- It is preferably given on empty stomach or between meals to facilitate absorption, but if the patient complains of GI side effects it is better to administer it after meals, although this approach would also reduce the absorption of iron.
- Doses higher than 200 mg per day are not recommended as it would not be more effective but only give rise to more side effects.
- Once the patient is started on oral iron therapy, it takes about 6 - 10 weeks for hemoglobin to return to normal level. However in IDA, iron stores are exhausted and need to be replenished.
- Replenishment of iron stores begins only after hemoglobin returns to normal. Hence stopping iron soon after hemoglobin is normal means inadequate therapy and predisposes patient to recurrence.
- Absorption of iron diminishes after hemoglobin returns to normal and hence replenishing iron stores is a very slow process and takes about 3 - 4 months. Thus iron therapy should be continued for 5 - 6 months

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PARENTERAL IRON THERAPY
When & How ?

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Anemia is a major global problem affecting between 20-70% of the population in various countries. The commonest is iron deficiency anemia.(IDA)

Decades of oral iron therapy – Is there a decline in prevalence ?

Oral iron provided to most women – both in urban and rural India has failed to improve the levels of anaemia in India and is fraught with poor absorption and compliance. Twenty years ago the prevalence of mild and moderate IDA in pregnancy was estimated at 49.7% , and ten years ago it was 59.4%. We have conducted a study to estimate the current prevalence and found it to be 66.5% in urban and rural populations in India.
The oral iron-folic acid (IFA) programs have by these measures not been success, and the prevalence of IDA appears to be rising. The funds that continue to be poured into the IFA programs should be rationalized and novel strategies need to be enforced.

Traditional indications of Parenteral Iron

Parenteral iron therapy was considered occasionally necessary for patients intolerant or unresponsive to oral iron therapy, Non compliance of the patient, or patient near term with severe anaemia.

We agree that Oral iron supplementation is the ideal way to replace iron stores as it uses the body's normal mechanisms. The shortcoming is the gastrointestinal tract's limited capacity for iron absorption. Only about 2-3 mg of elemental iron is absorbed, even when 50 or 100 mg are presented to the gut lumen. Most orally consumed iron flows untouched through the elementary tract. Replenishing a 1000 mg iron deficit may take most of a year.

Many, if not most, patients fail to comply with such a prolonged oral iron replacement therapy. and replacement of stores with oral iron becomes a nearly impossible task. Also, there are conditions where dietary iron intake is adequate, however, iron absorption, recycling and distribution from iron stores are insufficient to meet the needs of hemoglobin synthesis in the marrow. This “iron refractory anaemia” may represent anaemia of inflammation as well as those not responding to oral iron supplementation. For these patients, intravenous (I.V.) iron therapy is the preferred treatment.

It is not yet determined for how long one should treated with oral iron supplementation before being defined non-compliant or resistant and switched to I.V. therapy. There are no reliable diagnostic tests to discriminate between absorber and non-absorber. In fact, there are only a few reports on the value of iron absorption test.1, 2 It is suggested that a flat absorption curve indicates an abnormal and decreased absorption capacity, necessitating I.V. supplementation.

Mechanism of action of Parenteral preparations

Following parenteral administration of iron, the iron carbohydrate complex is separated by reticulo-endothelial system. Iron is gradually released into the circulation where it combines with transferrin for transport to

the liver, spleen and bone marrow. Iron then binds to bone marrow receptors sites for Hb synthesis. The clearance of iron from the body is dependent on the body's need for iron, iron storage status and the demand for body metabolic processes. A small amount of iron is eliminated in the urine. Ferric gluconate and iron sucrose are more readily available for erythropoietin than iron dextran. Increase in Hb is noted after one week of Iron sucrose administration.

Newer parenteral preparations- Options and advantages

Three parentaral iron preparations are available : Iron dextran, sodium ferric gluconate and iron sucrose. Each has been widely used. Iron dextran has the longest history. However, immediate life-threatening anaphylactic reactions constitute the most serious risk associated with its use. This occurs in 0.5% to 1.2% of patients. From the affected number many succumb to this reaction. During the period of 20 years (from 1976 to 1996), 31 deaths were reported[4]. Delayed but severe serum sickness-like reaction may develop in a substantial proportion of patients. This is characterized by fever, urticaria, myalgia, arthralgia and adenopathy.

Iron dextran is usually given by deep intramuscular route. This is the painful therapy. In view of anaphylactic reaction, test dose is a must. It can also be given as a total dose intravenous therapy in a single day. However, the risk of anaphylaxis remains. Availability of iron sucrose has made iron dextran almost obsolete.

Over last one decade, the efficacy and safety of intravenous iron sucrose therapy has been well-studied. The tolerance is excellent, adverse reactions are infrequent and, most important, it leads to a rapid rise in hemoglobin concentration . There are concerns about the release of free iron during I.V iron infusions because the capacity of available apotransferrin to bind the free iron can be exceeded. Free iron is known to increase the toxicity of free radicals and other reactive oxygen products that are normally found in the body. Thus it contributes to oxidative stress. Trace amounts of free iron can catalyze production of a highly toxic hydroxyl radical via Fenton / Haber-Weiss reaction cycle.

The risk of inducing the release of free iron appears to depend on

- The dose of I.V iron,
- The rate of iron infusion
- The available apotransferrin / transferrin to bind the iron.

Many of the adverse events attributed to sodium ferric gluconate - including flushing, hypotension, nausea, vomiting and diarrhoea - have been linked with the release of free iron. Van Wyck et al reported that regardless

Side Effects	Iron Dextran	Ferric Gluconate	Iron sucrose
Serious life threatening anaphylaxis	0.6-0.7 %	0.04 %	0.002 %
Hypersensitivity reactions	0.2 - 3 %	0.4%	0.005%
Mild adverse reactions	Up to 50 %	Up to 36 %	Up to 35 %

of the increasing use of intravenous iron, the availability of iron sucrose has eliminated most of the side-effects and more importantly, no intravenous iron sucrose compound generated detectable free iron.

Practical aspects : Sodium ferric gluconate and iron sucrose both have been used for decades in Europe, but only recently have been approved in US and subsequently in India. Extensive studies have shown that the prevalence of adverse events following iron sucrose is the least and substantially lower than that for iron dextran. Prospective, randomized and controlled comparisons among the there agents are, however, lacking.
Iron sucrose cannot be given by intramuscular route. Also, it cannot be given as a total-dose single day infusion. It can be either administered as slow intravenous bolus of 50-100 mg 2 or 3 times in a week or even as a short infusion of 100-200 mg over 2-3 hours once or twice a week. The total dose administered can be calculated by the usual formula, however, usually 1 gm is adequate. No test dose is indicated and hence there is no black box warning.

Fresh thinking – Practical strategies making I.V Iron usage work :

Oral iron supplementation during pregnancy as a public health strategy clearly should not be the only strategy being implemented with vigor. There is a need for fresh thinking if the problem is to be overcome. Intravenous iron sucrose has the potential for eradicating iron deficiency anaemia because it overcomes the problems of compliance and absorption and has an excellent safety record. Through a single total dose infusion of iron sucrose it is possible to eradicate the commonest medical disorder of pregnancy there by dramatically reducing maternal morbidity and mortality, while improving the quality of life of women in the developing world.

With regards to cost, definitive cost effective studies need to be done at the appropriate time, but it is difficult to cost the morbidity and mortality suffered by women in the developing world as a result of iron deficiency anaemia, never mind the impact on the next generation.

The case for realistic pricing of this life saving treatment will be overwhelming and both providers (the relevant pharmaceutical industry) and health care providers (government) will be compelled to come to an accommodation where this treatment will be affordable for one and all women who need it.

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ROLE OF ERYTHROPOIETIN IN THE TREATMENT OF IRON DEFICIENCY ANAEMIA DURING PREGNANCY

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Erythropoietin

What is it?

- Erythropoietin (EPO) is a hormone produced by the kidney that promotes the formation of red blood cells in the bone marrow.
- EPO is a glycoprotein. Human EPO has a molecular weight of 34,000.

Production of Erythropoietin

- EPO is produced mainly by peritubular fibroblasts of the renal cortex. It is synthesized by renal peritubular cells in adults, with a small amount being produced in the liver.
- The EPO gene has been found on human chromosome 7 (in band 7q21). Different DNA sequences flanking the EPO gene act to control kidney versus liver production of EPO.

Roles of Erythropoietin

1. Erythropoietin and RBCs

Erythropoietin is known to stimulate the production of red blood cells (RBCs) and increase the hematocrit i.e. the ratio of the volume occupied by packed red blood cells to the volume of the whole blood or the percentage of blood by volume composed of erythrocytes, as measured by a hematocrit instrument. A good example of erythropoietin in action is the effect of increased altitude on the blood oxygen concentration. As the altitude progressively increases, the atmospheric pressure decreases causing a resultant decrease in the available oxygen needed for respiration.

2. Neuro-protective Action of Erythropoietin

Various studies that have been conducted to evaluate the anti-apoptotic mechanisms to account for the neuro-protective actions of erythropoietin suggest its short latency protective effects by inhibition of neuronal apoptosis after cerebral ischemia & other brain injuries. The neurotrophic actions suggest that there may be longer-latency effects or erythropoietin as well.

3. Wound Healing and Erythropoietin

Some studies have investigated the role of the hematopoietic cytokine erythropoietin (EPO) during wound healing, the physiological response to tissue injury, and found that the local, exogenous recombinant erythropoietin administration into the fibrin matrix significantly increases the granulation tissue formation in a dose-dependent manner.

Function of Erythropoietin in RBC synthesis

- EPO is the prime regulator of red blood cell production. Its major functions are to promote the differentiation and development of red blood cells and to initiate the production of hemoglobin, the molecule within red cells that transports oxygen.
- Endogenous erythropoietin increases the number of developing proerythroblasts and enhances the release of reticulocytes from bone marrow. It is required for the viability, multiplication and differentiation of erythrocytes and their precursors.
- Human recombinant erythropoietin increases the reticulocyte production rate in a dose-dependent manner.

Regulation of Erythropoietin

- The kidney cells that make EPO are specialized and are sensitive to low oxygen levels in the blood. These cells release EPO when the oxygen level is low in the kidney. EPO then stimulates the bone marrow to produce more red cells and thereby increase the oxygen-carrying capacity of the blood.

Measurement of Erythropoietin levels

- The measurement of EPO in the blood is useful in the study of bone marrow disorders and kidney disease. Normal levels of EPO are 0 to 19 mU/ml. Elevated levels of EPO can be seen in polycythemia. Lower than normal levels of EPO are seen in chronic renal failure.

Uses

- Using recombinant DNA technology, EPO has been synthetically produced (**Recombinant human erythropoietin--rHuEPO**) for use in certain types of anemia -such as anemia due to renal failure, anemia secondary to anti-retroviral therapy, and anemia associated with malignancies.

Recommended dose of erythropoietin

The usually recommended dose of erythropoietin is 50 -150 IU/kg to be given subcutaneously twice or thrice weekly till the course of parenteral iron is over.

Side effects of Erythropoietin

- As with most ergogenic substances, there is usually a downside associated with the use of erythropoietin.
- As the hematocrit increases, the other main components of blood plasma decrease. It may lead to polycythemia .
- Viscosity of the blood also increases blood pressure and the risk of clotting incidents like a stroke.

Misuse of Erythropoietin in Sports

- With the recent advances in genetic engineering and recombinant DNA technology, synthetic or recombinant Erythropoietin (rEPO) has become readily available and has been utilized extensively by athletes as an ergogenic aid. The rationale behind such use of erythropoietin is that if you increase the oxygen-carrying ability of the blood above normal levels, then the muscles shall receive more oxygen and are expected to be able to perform better for a longer periods of time, thereby significantly improving performance.

Role of erythropoietin in iron deficiency anaemia during pregnancy

RhuEPO has been tested as a potential therapy in anaemia due to various maternal disorders during pregnancy:

A. End stage renal disease
B. Antepartum iron deficiency anaemia

C. Postpartum anaemia
D. Anaemia of pregnant women with chronic haematological disorders

It increases hemoglobin by stimulating erythropoiesis. Apart from the above mentioned indications, **one of the emerging uses of erythropoietin is treatment of moderate to severe iron deficiency anaemia during pregnancy**, especially as an alternative to patients refusing blood transfusion.

Studies supporting role of erythropoietin in iron deficiency anaemia during pregnancy

(A) In a prospective, randomized, open study, Breymann et al. evaluated the efficacy and safety of intravenous iron sucrose with or without rHuEPO in correcting iron deficiency anemia in pregnant patients (gestational age > 21 weeks) in whom the daily administration of oral ferrous sulfate 160 mg for at least two weeks failed to increase Hb concentration.

Twenty patients received either rHuEPO 300 IU/kg or iron sucrose 200 mg administered intravenously or iron sucrose 200 mg alone; twice weekly for 4 weeks or until the target Hb of 11 g/dL was reached.

There was an immediate reticulocyte response and progressive increase in hematocrit in both groups; however, a higher reticulocyte count and increase in Hct was observed in the group that received the combination therapy. Median duration of therapy was shorter in the combination therapy group and more patients in this group reached the target Hb by 4 weeks.

Consequently, the authors concluded that intravenous iron therapy alone should be considered first in resistant iron-deficiency anemia during pregnancy. rHuEPO may be considered in severe anemia cases requiring rapid correction of anemia or in patients who do not respond to intravenous iron therapy alone.

(B) Another prospective study evaluating the efficacy of rHuEPO combined with parenteral iron in the treatment of moderate to severe iron deficiency anaemia during pregnancy concluded that **rHuEPO combined with parenteral iron is an effective treatment for moderate to severe iron deficiency anaemia during pregnancy, with minimal adverse or side effects. It may serve as an alternative to blood transfusion, or in cases of resistant anaemia that are not effectively treated by iron supplementation alone.**

In this study, 26 pregnant women, who had been ineffectively treated with iron supplementation alone for at least 8 weeks were enrolled. They met the following criteria for inclusion in the study:

- Hb < 8.5 gm%
- Evidence of iron deficiency anaemia
- Absence of other pregnancy complications or severe systemic disease. The treatment

protocol comprised of a combination therapy with 150 IU/kg rHuEPO subcutaneously three times per week and 100 mg parenteral iron daily, for a total period of 4 weeks. 19 women (73%) showed a quick response, with Hb reaching normal levels within first 2 weeks of treatment. In 5 women (19.2%) there was no significant increase in Hb levels, while in 2 women (7.6%) a further decline in HB concentration was observed, that necessitated a blood transfusion.

Further studies are needed to investigate the poor response observed in about 25% of treated patients.

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Blood Transfusion and Blood Products in IDA in Pregnancy

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Introduction :

Access to good quality blood / ↑ blood components can reduce maternal and perinatal mortality & morbidity. In 2003 T. J. Bray et al in the national wide Indian study reported that adult recipients accounted for 87% of transfusion, and amongst the age group of 25-34, 73% of transfusions were for women. Anemia was listed as indication for 60% of transfusions, surgery for 42%, acute haemorrhage for 26% and pregnancy for 16%. Seventy four per cent of adult transfusions were inappropriate.

Whole Blood:

Whole blood is used in many clinical situations like in acute blood loss where there is also hypovolamia. When blood is stored, there is reduction in the pH, increase in plasma potassium concentration, progressive reduction in the red cell content, loss of all platelet function within 48 hrs and reduction in Factor VIII.

Advantages: It requires only simple and inexpensive single collection pack and no special equipment is needed for processing. Disadvantages: Patients are at risk of circulatory overload as whole blood contains high volume than red cell concentrate.

Blood products :

The term blood products indicate any therapeutic substance prepared from human blood. Blood can be separated into a variety of blood component for different clinical indications. But many countries have no facilities for component separation and therefore, whole blood remains the most widely used product in most developing countries. But if facilities are available, the use of blood component offers certain advantages.

1) Following are blood components separated from whole blood
   - Red cell concentrates
   - Red cell suspension
   - Plasma
   - Platelet concentrates

2) Plasma or platelets collected directly from the donor, usually by mechanical method known as Apheresia.

3) Cryoprecipitates is prepared from frozen plasma which is rich in factor VIII and fibrinogen

4) Plasma derivatives are prepared from human plasma i.e. Albumin, Coagulation factor concentrates and Immunoglobulins.

Red Cell concentrate: (packed red cells) also contains white cells .It does not cause fluid overload hence, indicated in severe chronic anaemia and incipient cardiac failure. It is simple and inexpensive to prepare . But because of high ratio of red cells to plasma there is increase in viscocity and hence increase in the time required

for transfusion .

Red Cell suspension: It has lower packed cell volume which reduces cell viscocity, has longer self life due to better preservative. But it requires special blood collection set which is cost effective .

Buffy coat depleted red cells: It contains only 10% white cells and cost effective and requires trained personnel.

Leucocyte depleted (filtered) red cells, special leucocyte filter is used to separate practically all the white cells.

Platelet concentrates: used in treatment of bleeding due to thrombocytopenia and platelets function defects.

Plasma-It is used for the treatment of coagulation disorders with bleeding due to reduce level of several clotting factors. It is frozen at –250 C to preserve its labile coagulation factors V and VIII. It also contains albumin and immunoglobulins and can be used atleast for one year. Fresh frozen plasma is indicated for replacement of multiple coagulation factor deficiencies like liver disease, Warfarin anticoagulant overdose, depletion of coagulation factors in patients receiving large volume transfusions, DIC and thrombotic thrombocytopenic purpura (TTP).

Cryoprecipitate is prepared from fresh frozen plasma. It is indicated as an alternative to factor VIII concentrate in the treatment of inheritated deficiency of Von Willebrand Factor (von Willebrand 's disease) , factor VIII (haemophilia A) ,factor XIII and as a source of fibrinogen in acquired coagulopathies like DIC.

Plasma Derivatives: Processes for heat treatment or chemical treatment of plasma derivatives to reduce the risk of transmitting viruses are currently very effective against viruses that have lipid envelopes e.g. HIV 1 and 2, Hepatitis B and C , HTLV-1 and 2.

Human Albumin Solutions: Indicated in the therapeutic plasma exchange (5%) , treatment of diuretic resistant edema in hypoproteinaemic patients (20% with diuretic) , 5% in volume replacement , burns and hypoalbuminaemia . It is not used as IV nutrition as it is expensive and has insufficient source of essential amino acids. Administration of 20% albumin may cause acute expansion of intravascular volume with risk of pulmonary edema.

No blood or blood products should be administered until all nationally required tests are negative. Each unit should be tested and labeled indicating ABO group and its Rh D groups.. Plasma usually transmit most of infections present in whole blood while factors VIII, IX and immunoglobulins rarely transmit the infections. Hence, Factors VIII, IX and immunoglobulin are preferred but are cost effective.

Blood Transfusion Reactions:
Blood transfusion involves the transplant of tissue from the donor to the recipient. Therefore, there are risks to the recipient of transfusion - transmitted infections and of immunological responses to foreign cells or plasma proteins. It also causes errors in blood transfusion which is likely to cause litigation. Hence, blood and blood products are administered only when there are clear indications. When used correctly they are life saving and

inappropriate used can endanger the life.

Acute complications of transfusion occurs due to
- Acute haemolytic transfusion reaction.
- Infective shock.
- Transfusion related Acute Lung Injury (TRALI) .
- Fluid overload.
- New haemolytic febrile reaction to transfusion of platelets and red cells.
- Severe allergic reaction or anaphylaxis.

Delayed complications of transfusion reported are
- Delayed haemolysis of transfused red cells.
- Development of antibodies to red cells in patient's plasma.
- Development of antibodies that react with antigen of white cells or platelets.
- Post transfusion purpura.
- Graft Vs host disease .
- Iron overload .
- Infection.

In 2004, SHOT report from 67% of U. K. hospitals revealed 4 transfusion related deaths, 540 serious transfusion related events and 1076 near misses.

Chronic anemia in pregnancy :

Usually results due to iron deficiency, short birth intervals, folic acid deficiency, Vit B_{12} deficiency, HIV infection, Malaria, sickle cell disease etc. When anaemia is detected, it is important to diagnose the cause and to assess the severity of anaemia clinically as well as by laboratory tests. The prevalence of anaemia and need for transfusion during pregnancy can be reduced by prevention and management of nutritional anaemia and adequate antenatal care.

Blood transfusion in an anemic patient does not treat the cause of anaemia or does not correct the non-haematological effects of iron deficiency. The decision for blood transfusion must be based on the patients clinical needs and also on hemoglobin concentration including stage of pregnancy. Local guidelines are necessary for the safety of blood and other local factors.

The indications for transfusion in chronic anemia are broadly divided into 3 groups.

1) Duration of pregnancy less than 36 weeks.
   - Hemoglobin 5.0 mg % or below,
   - Hemoglobin between 5.0 to 7.0 gm % and in the presence of established or incipient cardiac failure or clinical evidence of hypoxia, pneumonia or any other serious bacterial infection and Malaria

2) Duration of pregnancy 36 weeks or more
   - Hemoglobin 6.0 gm % or below and in the presence of established or incipient cardiac failure or clinical evidence of hypoxia, pneumonia or any other serious bacterial infection and Malaria

3) Elective LSCS

- When elective Caesarean section is planned and there is a history of Antepartum hemorrhage (APH), Postpartum hemorrhage (PPH), Previous Caesarean section with Hemoglobin between 8.0 and 10.0 gm % then one unit of blood should be cross matched. If hemoglobin less than 8.0 gm% two units of blood should be cross matched.

Above guidelines are an example to show how local guidelines can be formed. The specific indications for transfusion in chronic anemia in pregnancy should be based on national guidelines and can be modified appropriately to the local situation.

Blood Transfusion for Major Obstetric hemorrhage :

Acute blood loss in obstetric is one of main causes of maternal mortality. Acute blood loss causes hypovolaemic shock however, because of the physiological changes induced by pregnancy, the women may demonstrate few signs of hypovolaemia, even though she may have lost a considerable volume of blood. She may be then suddenly collapse unless the blood volume is promptly restored. It may result due to abortion, ruptured ectopic pregnancy, antepartum haemorrhage (APH) and postpartum haemorrhage (PPH). Primary PPH can occur due to atonicity of the uterus, trauma to genital tract, abnormally adherent placenta acute inversion of uterus. At term, blood flow to the placenta is approximately 700 ml per minute. The patient's entire blood volume can be lost in 5-10 minutes if uterus remains atonic. Secondary PPH can occur due to puerperal sepsis, retained products of conception, and breakdown of the uterine wound after cesarean section.

Disseminated intra vascular coagulation can result following missed abortion, abruptio placenta, PIH, amniotic fluid embolism, IUFD, retained products of conceptions and sepsis. In such situation, it is essential to take immediate steps to identify cause of bleeding and treatment along with resuscitative measures. Primary treatment by infusing crystalloids / colloids are necessary. Volume should be replaced 2 to 3 times more than volume lost. Care should be taken not to overload the fluid.

Management of Disseminated Intra vascular coagulation :

Primary aim is to deliver fetus & placenta and evacuate the uterus, as indicated for retained or necrotic tissue. Uterine stimulants are given to promote contraction of uterus. Blood products are given to control haemorrhage. In many cases of acute blood loss, the development of DIC can be restored with a balanced salt solution i.e. Hartmanns' solutions or Ringer's lactate. Transfusion of fresh whole blood plays important role in DIC.

One should avoid the use of cryoprecipitate and platelet concentrates unless bleeding is uncontrollable. If bleeding is not controlled and coagulation tests show very low platelets, fibrinogen, prolonged PT or APTT then replacement of coagulation factors and platelets should be done with cryoprecipitate at least 15 packs, prepared from single donor units, containing 3-4 gm fibrinogen in total. If cryoprecipitate is not available, then fresh frozen plasma (15ml / kg): 1 unit for every 4-6 units of blood is given to prevent coagulation defects resulting from use of stored red cell concentrates / suspensions. If there is thrombocytopenia, platelet concentrates is necessary to control obstetric haemorrhage due to DIC. If these blood components are not available, then fresh whole blood is transfused (ideally not more than 36 hours old).

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FAILURE OF THERAPY IN IDA

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There are various factors that are responsible for failure of iron therapy & thus persistence of anaemia. Oral iron therapy is the commonest modality of treatment of anaemia and it is the commonest route where failure of therapy is noted.

Compliance

The patient has to be compliant while treating anaemia. She has to understand the importance of proper diet & iron supplement especially during pregnancy. If nutritional requirements are not met with Hemoglobin rise will not be evident. Similarly, if iron is not taken in prescribed format, it is likely that the woman may not show improvement in Hemoglobin. The reason for poor compliance could be iron intolerance which has to be taken into consideration. Ferrous sulphate is the preparation producing intolerance most commonly.

Improper absorption of iron

If iron molecule is not absorbed properly, the hemoglobin rise will not be evident. The reason could be mal absorption syndrome like celiac disease wherein up take of iron is poor. Patient may show intolerance to oral iron therapy & thus hemoglobin fails to rise. Women consuming tea coffee after meals may exhibit poor response to iron therapy as these do interfere with absorption of iron.

B Annibel et al from Italy found that Gastrointestinal diseases that do not usually cause bleeding are frequently associated with iron deficiency anaemia in patients without gastrointestinal symptom or other potential causes of gastrointestinal bleeding.

Iron formulation offering high elemental iron absorption e.g. ferrous ascorbate, should be preferred over formulation with low absorption e.g ferric hydroxide (2.4%), carbonyl iron (7%) or ferrous sulphate (<10%)

Inadvertent blood loss

Patient may not notice but could lose blood through gastrointestinal tract in the form of bleeding piles, haematemesis or malena. This loss not reported by patient could contribute to failure of hemoglobin rise & thus correction of anaemia. The causes like undiagnosed malignancy / inflammatory disease should be kept in mind. There are patients who are regularly taking aspirin / heparin and may show evidence of occult blood loss in gastrointestinal tract. Young pubertal girls with persistent menorrhagia are the most common victims of anaemia. The women from child bearing age group may suffer from menorrhagia, many a times secondary to intra uterine device, could be non responders of oral iron therapy.
In Indian context, worm infestations especially hook worm infestation is a common cause of inadvertent blood loss; anthelminthic therapy would improve the response to iron therapy.

Dietary considerations

Indian diet is predominantly vegetarian and contains large amounts of inhibitory ligand like phytates, phosphates and polyphenols. These substances are known to inhibit iron absorption by oxidizing ferrous iron to ferric form. In the alkaline pH of small intestine, ferric iron gets converted to insoluble ferric hydroxide which is not absorbed in the body. In case of oral iron therapy, such inadequate absorption may manifest in terms of decreased efficacy and/or tolerability.

Intake of citrus fruits like oranges introduces ascorbic acid to keep ferrous iron soluble and prevent formation of ferric hydroxide, which is insoluble. Also calcium containing products like milk and calcium tablets should not be taken along with iron tablet.

Deficiency of micronutrients

Pattern of micro nutrient deficiencies can defer in different populations due to diet and other life style related factors. In vegetarian populations, studies reporting iron deficiency concomitant with other micro nutrient deficiencies are mainly on folic acid or B_{12}. There is a possibility of variable interactive effects of micro nutrients on hemoglobin status. In Indian population, where major cause of iron deficiency is poor availability of iron from their vegetarian diets, there is also a risk of other micro nutrient deficiencies

In a study conducted in Mexico, there was a lack of hemoglobin response in anemic children who received iron supplements for 12 months. Though their iron deficiency was corrected, they remained anaemic which is due to general syndrome of under nutrition, manifested by poor dietary quality and growth and possibly to vitamin B_{12} deficiency specifically. Public health interventions usually aim at delivering iron supplements or iron with folate, or fortify food supplies with iron alone, but their appears a need for supplying other nutrients for proper hematopoiesis.

An Indian study done by Chiplonkar et al from Pune evaluated the simultaneous impact of micronutrient deficiencies on hemoglobin status. Relative significance of riboflavin and copper was noted to be greater than ascorbic acid and retinol in influencing iron status.

Interaction with other molecules

Several animal studies have clearly shown that calcium interferes with dietary iron absorption and that addition of calcium to the diet may even induce iron deficiency. Epidemiologic data also suggest that calcium interferes with iron absorption. In an extensive study in France, serum ferritin and hemoglobin concentrations were negatively and significantly correlated with the intake of calcium. Women with high iron requirements (e.g., adolescents, menstruating and pregnant women) should try to restrict calcium intake with main meals, which contain most of the dietary iron.

Dietary ligands (weak binding agents) and their effect on mineral absorption

Improve absorption (minerals affected)	Improve absorption (minerals affected)
Citrate (iron, zinc, copper, manganese)	Phytate* (calcium, magnesium, iron, zinc, selenium, chromium, manganeses)
Other organic food acids (iron, copper)	Fatty acids (calcium, magnesium)
Ascorbate (iron)	Oxalate** (calcium, iron, zinc, manganese)
Cysteine-containing peptides (iron, zinc, copper)	Tannate*** (iron, zinc)
Histidine and other amino acids (zinc, copper, chromium, manganese)	
Heme (iron)	

* Found in whole grains, legumes and nuts
** Found in spinach and some other vegetables, berries, nuts, tea and chocolate
*** Found in tea and coffee

Underlying pathology

Conditions like Thalassemia (major & minor), sickle cell disease may be missed and diagnosed only after a patient is investigated for nonresponding anaemia. This phenomenon of non response is applicable to oral as well as Injectable iron.

Thus, if a woman is found to be persistently anaemic in spite of iron treatment; other factors must be taken into consideration. Such patents do respond well to non oral methods of iron delivery system. One may then consider parenteral iron most suitable for the patient. Multi factorial deficiency should also be kept in mind before treating anaemia only by iron supplement.

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CONTROVERSIES ON 'ROUTINE' IRON THERAPY IN PREGNANCY

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Introduction

Although widely accepted as a routine the seemingly simple act of prescribing Iron to a pregnant woman is in fact surrounded be several unanswered questions.

These questions in no way detract from the fact the act of iron supplementation is in fact responsible for saving lives. The intention is to point to the gaps in data which still exist and need to be urgently filled.

Prescription policy

There is some data to suggest that women who have hemoglobin above 12 to 13 gm % may not benefit from iron supplementation. In fact anecdotal data suggests that even iron if used in these circumstances may predispose to intestinal infection and also cause intolerance due to side effects. The jury is still out on this issue although common sense seems to dictate that the demands raised by pregnancy will deplete iron stores which ought to be replaced!!

Dosage of iron - for routine prophylaxis

It is common practice to prescribe the same dose of iron through the pregnancy. This is convenient to do this in clinical practice and avoids confusion in the patients mind. Physiologically though, the requirements for iron differ in each trimester with requirements increasing with increasing gestational age. The clinical application of this physiological finding has not however found favor and clinicians continue practicing giving the same dose through the pregnancy. It has to b admitted however that this seems to work well in real life settings.

Clinicians differ on when to take iron in relation to meals. The problem is that

- After meals - The absorption hampered as there may be formation of insoluble phytate, phosphate, Tanate, Oxalate etc. if taken
- Before meals - there is gastric irritation and therefore intolerance. There is no consensus on this issue and the decision will have to be individualized taking iron.

Either two hours before or two hours after the main meals may be a compromise solution although difficult to implement for the patient to remember to take the medicines on time.

It should be reiterated that all the above controversies do not take anything away from the fact that the simple act of giving iron may be in a large number of mothers life saving. These issues should spur us on to study the area in greater detail.

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LABORATORY REFERENCE RANGES FOR HAEMATOLOGICAL INVESTIGATIONS

Investigation	Reference Range	Unit
Total leucocyte count	4-10	thousand/µL
Differential Leucocyte Count		
Neutrophils	40-80	%
Lymphocytes	20-40	%
Monocytes	2-10	%
Eosinophils	1-6	%
Basophils	0-1	%
RBC count	4.5-5.5	million/µL
Haemoglobin	13-17	g/dL
Haematocrit	40-50	%
MCV	83-101	fL
MCH	27-32	pg
MCHC	31.5-34.5	g/dL
Platelet count	150-400	thousand/µL
Serum Ferritin	M: 22-322 F: 10-291	ng/mL ng/mL
Serum iron	59-148	µg/dL
TSAT	20-50	%
TIBC	260-390	µg/dL

ROLE OF CORPORATE IN PUBLIC HEALTH

Arun Khanna – Emcure (Pharma Industry)

Today 74-88% of women in child bearing age across geographical divide or community spread in India are anaemic. The modern day lifestyle and junk food only complicate the problem of anaemia in urban lifestyle. This statistic is enough to point out the magnitude of anaemia in our society especially when women and girl child form the foundation of the nation.

As a responsible organization, Emcure in association with FOGSI has undertaken FESR- FOGSI-Emcure Social Responsibility of creating awareness and management of anaemia through various programmes. This initiative is our way of contributing to the society of which we all are a part.

Having formally inaugurated the 12 × 12 initiative with FOGSI in 2007, we have imbibed this initiative into our system and adopted them as our own. Over the period of 2 years, anaemia awareness and management has been imparted in numerous schools across the country. This year, we have initiated three more programmes v.i.z. 24 × 7 × 365, Ankur and the Adolescent health care programme. 24 × 7 × 365, Anaemia eradication programme was aimed at sensitization of drs towards spreading awareness for tackling anaemia. Through Ankur, counseling and support is provided to the pregnant lady along with her family belonging to the underprivileged section of the society and through the Adolescent Health programme, the importance of correct diet is advised to today's teen to try and prevent the rise in the incidence of Anemia in our future population.

Emcure's commitment towards this cause is a long standing one and taking anemia management further ahead, we have once again partnered with FOGSI in putting together the National guidelines for Anaemia management, presented to you in the form of this book, where in a core group of doctors from all across the country have put their knowledge, their expertise into good use in laying out these guidelines.

We believe that Emcure, and FOGSI have a major role to play in building up a healthier nation and the steps we had taken are just the beginning. In the coming year too, Emcure is committed to carry forward these initiatives in 202 villages from across the country under '**Reaching out... Village adoption programme**'.

Philosophy of Corporate Social Responsibility (CSR) in Emcure first began with our initiatives for Cancer patients in partnership with Prashanti Cancer Mission Trust.

Another area where our CSR initiatives are focused is the HIV/AIDS. Caring for people infected with HIV/AIDS, Emcure has initiated TAAL, a unique care and support center run by and for the HIV positive people. TAAL means Treatment, Adherence, Advocacy and Literacy. Today the TAAL centers are located in different parts of India and provide personalized care, support and counseling to the HIV positive people.

Our energies, our responsibilities and our commitment remain undeterred towards tackling the growing menace of anaemia and other burning issue of public health as we firmly believe - A healthy nation today is a more healthy and prosperous nation tomorrow.