Contents

CHAPTER 1

Iron-deficiency Anemia in Pregnancy

Suyajna Joshi D

INTRODUCTION

Anemia is the most common hematological disorder in pregnancy which has significant maternal as well as perinatal morbidity and mortality. Anemia among pregnant women is a serious global health concern. According to the World Health Organization (WHO) report, about million pregnant women suffer from anemia worldwide, of which 0.8 million women are severely anemic. An estimate by the WHO attributes about 591,000 maternal deaths globally to iron-deficiency anemia (IDA), directly or indirectly. Majority of the cases of anemia in pregnancy are due to nutritional deficiency of which >50% cases are attributable to IDA followed by folate and vitamin B_{12} deficiency. Other causes such as hemoglobinopathies, autoimmune hemolytic anemia, aplastic anemia, chronic infections, rheumatoid arthritis, and chronic renal disease, though less commonly found, should arouse suspicion in the clinician based on symptomatology for the better management of the case.

DEFINITION

Anemia is defined as a decrease in the oxygen-carrying capacity of the blood due to a decrease in the hemoglobin concentration or due to a reduced number of red blood cells (RBCs).

CLASSIFICATION OF ANEMIA

Anemia is classified based on etiology **(Box 1)**, severity **(Table 1)**, and trimester **(Table 2)**.

IRON METABOLISM

Iron is an essential component of every cell in the body. Although best known for its critical role in the transport and storage of oxygen (in hemoglobin and myoglobin, respectively), within a large variety of enzymes, iron also acts as a carrier for electrons, a catalyst for oxygenation and hydroxylation, and is necessary for cellular growth and proliferation. Iron supplements are widely administered to treat IDA, particularly in chronic diseases such as kidney disease, heart failure, or inflammatory bowel disease. Without a sufficient supply of iron, hemoglobin cannot be synthesized and the number of erythrocytes in the blood cannot be maintained at an adequate level.

Iron usually exists in the ferrous (Fe^{2+}) or ferric (Fe^{3+}) state, but since Fe^{2+} is readily oxidized to Fe^{3+}, which in

BOX 1: Classification of anemia based on etiology.

- Anemia with nutritional deficiency
  - Iron-deficiency
  - Folic acid deficiency
  - Vitamin B_{12} deficiency
  - Combined deficiency
- Anemia associated with decreased production of RBC
  - Bone marrow disorders
  - Hypothyroidism
  - Chronic renal pathology
  - Bone marrow suppression
- Anemia associated with increased RBCs' destruction
  - Hemolytic anemias
    - Inherited and acquired
    - Sickle cell anemia
    - Thalassemia
  - Hereditary spherocytosis
    - Autoimmune hemolytic anemia
  - Hemolytic uremic syndrome
    - Thrombotic thrombocytopenic purpura
    - Malaria
- Anemia due to blood loss
  - Abnormal uterine bleeding
  - GIT bleeding
  - Obstetric hemorrhage

TABLE 1: Classification of anemia according to severity.

Category of anemia	*WHO (Hb in g/dL)*	*ICMR (Hb in g/d)*
Mild	9–10.9	10–11
Moderate	7–8.9	7–10
Severe	4–6.9	4–7
Very severe	<4	<4

(Hb: hemoglobin; ICMR: Indian Council of Medical Research; WHO: World Health Organization)

TABLE 2: Classification of anemia according to trimester.

Pregnancy state	*Hemoglobin (g/dL)*
First trimester	<11
Second trimester	<10.5
Third trimester	<11

neutral aqueous solutions rapidly hydrolyzes to insoluble iron(III)—hydroxides, iron is transported and stored bound to proteins. Effective binding of iron is essential not only to ensure that it is available where and when required, but also because Fe^{2+} can catalyze the formation of reactive oxygen species, which cause oxidative stress, damaging cellular constituents.

Total body Fe in man is 4–5 g. Daily losses, e.g., in epithelial desquamation from the gastrointestinal tract or skin, are small. Excretion in urine, bile, and sweat is negligible. The normal daily Fe requirement is thus only 1 mg, increasing with physiological need, as in growth, pregnancy, and blood loss. An additional 1,000 mg Fe is required in pregnancy and 0.5 mg Fe/mL in case of blood loss.

Three key proteins regulate the transport and storage of iron **(Fig. 1)**. Transferrin transports iron in the plasma and the extracellular fluid. The transferrin receptor, expressed by cells that require iron and present in their membranes, binds the transferrin di-iron complex and internalizes it into the cell. Ferritin is an iron-storage protein that sequesters iron keeping it in a readily available form. About 60% of iron is found in the erythrocytes within hemoglobin, the oxygen transport protein. The remainder is found in myoglobin in the muscles, in a variety of different enzymes ("heme" and "non-heme"), and in storage form. Most stored iron is in the form of ferritin, found in the liver, bone marrow, spleen, and muscles. Serum iron (i.e., iron bound to transferrin) represents only a very small proportion of the total body iron (<0.2%). Moreover, the relationship between physiological iron compartments is highly dynamic: Erythrocytes are broken down in the liver and the spleen and new red blood cells are produced in the bone marrow. The total serum iron pool is approximately 4 mg, but the normal daily turnover is not >30 mg, such that minor changes in the serum level due to exogenous iron administration are clinically meaningless. In this setting, conventional measurements of serum iron concentration provide no relevant information about the availability of functional iron for physiological processes, and other evaluation strategies must be pursued. A schematic representation of iron metabolism is shown in **Figure 1**.

IRON-DEFICIENCY ANEMIA

Iron is essential for normal hemoglobin (Hb) synthesis to maintain oxygen transport as well as necessary for metabolism and synthesis of DNA and enzymatic processes. Iron stores may be measured using several indices, although serum ferritin and transferrin saturation are the most common.

Iron-deficiency anemia is defined as a low Hb concentration in combination with iron-deficiency and is characterized by a defect in Hb synthesis, resulting in abnormally small (microcytic) red blood cells with a decreased Hb content (hypochromic), resulting in reduced capacity of the blood to deliver oxygen. The prevalence of Fe deficiency is much higher. Without adequate Fe supplementation, ferritin falls to subnormal levels toward the end of pregnancy, even in the industrialized nations.

Iron-deficiency anemia evolves through three distinct stages **(Table 3)**. Depletion of storage iron occurs in the first phase (stage I), where total body iron is decreased but red cell indices and hemoglobin (Hb) synthesis remain unchanged. Both these indices change when the supply of

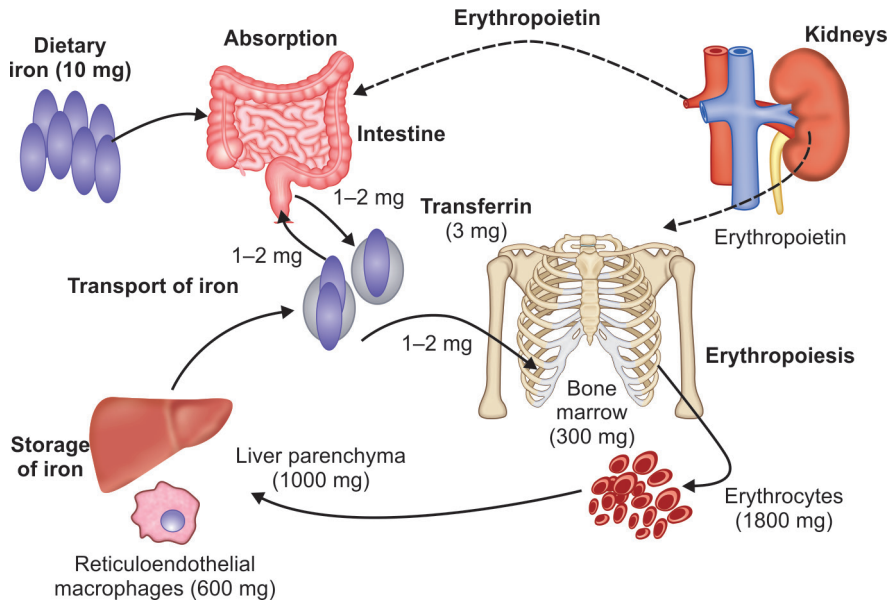

Fig. 1: Transport and storage of iron.

TABLE 3: Stages in the development of iron-deficiency.

Parameters	*Normal*	*Iron depletion*	*Iron-deficient erythropoiesis*	*IDA*
Hemoglobin	150 g/L (15 g%)	130 g/L (13 g%)	100 g/L (10 g%)	50 g/L (5 gm%)
MCV	N	↓	↓	↓↓
MCHC	N	N	↓	↓↓
Iron stores	Present	Reduced	Absent	Absent
Serum Fe/TIBC (µg/L)	1,000/3,000	75/3,000	500/4,500	250/6,000
Serum ferritin (µg/L)	100	20	10	<10
RBCs	Normal	Normal	Normal	Hypochromic microcytosis

(IDA: iron-deficiency anemia; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; RBC: red blood cells; TIBC: total iron-binding capacity)

iron to bone marrow is reduced (stage II or iron-deficient erythropoiesis). Stage III, eventually iron-deficiency anemia develops due to insufficient supply of iron to sustain a normal Hb concentration.

Signs and Symptoms of Iron-deficiency Anemia

Although the Hb test is recommended at the first antenatal visit, examination for signs of pallor of the palpebral conjunctiva, tongue, nail beds, and palm should be regularly done. Some iron-deficient patients, with or without clinical signs of anemia, may have alopecia, atrophy of lingual papillae, or dry mouth due to reduced salivation.

The symptoms specific to iron-deficiency anemia include the syndrome of Plummer–Vinson or Paterson–Kelly (dysphagia with esophageal membrane and atrophic glossitis), gastric atrophy, stomatitis due to rapidly turning over of epithelial cells, spoon-shaped nails (koilonychias), and pallor. These changes were caused by the reduction of iron-containing enzymes in epithelial and gastrointestinal (GI) tracts. The restless leg syndrome might be striking neurological squeal prevalent in pregnancy. Pica, the eating disorder in which there is an appealing desire to lick or eat nonfood items such as gypsum, chalk, soil, ice (pagophagia), or paper, is prevalent in pregnant women. Pagophagia (intense desire to eat ice) is quite specific to Iron-deficiency and responds quickly to treatment.

Diagnosis of Iron-deficiency Anemia

There are four groups of tests which are available for detection of IDA:

1. Hb, mean corpuscular volume (MCV), red cell distribution width (RDW), reticulocyte Hb content, % hypochromic cells, red cell size factor, and low Hb density
2. Direct measurements of iron stores through assessment of serum iron, total iron-binding capacity (TIBC), % saturation, serum ferritin, bone marrow biopsy iron
3. Assessment of iron heme form through assessment of free erythrocyte protoporphyrin (EPP)
4. Assessment of iron uptake by measuring the soluble serum transferrin receptor (sTfR), soluble transferrin receptor-log[ferritin] (sTfR-F) index, and zinc protoporphyrin (ZPP)

A primary step in the diagnosis of IDA is to consider the complete blood count, including Hb, MCV, mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), which is simple, inexpensive, rapid to perform, and help early prediction of IDA.

Changes in Hb concentration and hematocrit occur only in later stages; both these tests are indicators of Iron-deficiency. Low Hb with a reduced MCV is usually the initial finding on a routine complete blood count (CBC). The severity of anemia is based on the patient's Hb/hematocrit level.

Altitude above sea level and smoking are the known modifiers of Hb. Currently, the Hb cut-off according to trimester has not been defined by the WHO, but it should be recognized that the Hb falls about 0.5 g/dL in the second trimester. Hb concentration is the most common hematological estimation. There is a strong correlation between Hb concentration and serum ferritin levels. The generally recommended methods of Hb estimation are cyanomethemoglobin and HemoCue@ system. RDW has better sensitivity than MCV for diagnosis of IDA. Falling MCV accompanied by a rising RDW should alert the clinician to the presence of possible IDA which is then confirmed by marked RDW increase occurring early after initiation of therapy.

Peripheral smear shows the presence of microcytic hypochromic red cells and typical "photo pencil cells" being indicative of IDA. Other than IDA, the conditions which cause a microcytic blood picture are anemia of chronic disorder, beta-thalassemia, and sideroblastic anemia.

Of all the available indices, the Meltzer index (MCV/RBC) has been shown as the most reliable index with high sensitivity.