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1 Anemia in Pregnancy

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Anemia is the most common medical disorder encountered during pregnancy. 40–90% of pregnant women in India are suffering from anemia. As per NFHS-4 (2015–2016)[1] incidence in pregnant women on an average is 50.4%.

Anemia is defined as decrease in the oxygen carrying capacity of the blood due to decrease in amount of RBCs or hemoglobin (Hb) or both. In adult female <12 g Hb% in peripheral blood is called anemia.

Causes of Anemia during Pregnancy

- Physiological
- Nutritional: Iron deficiency folate and/or vitamin B_{12} deficiency dimorphic
- Hemorrhagic: Acute or chronic
- Hemoglobinopathies
- Hemolytic: Congenital or acquired
- Aplastic anemia.

Physiological

Due to physiological hemodilution during pregnancy fall in Hb occurs. There is 2.5–3 times increase in plasma volume as compared to RBC mass. Maximum increase occurs in 2nd trimester. Blood volume changes during pregnancy are shown in **Figure 1.1.**

Due to this, anemia in pregnancy is considered as per center for disease control (CDC) modified WHO definition as follows:

Hb%: <11.0 g% in 1st and 3rd trimester
<10.5 g% in 2nd trimester

Degrees of anemia

	ICMR	WHO
Mild	10–10.9 g%	9–10.9 g%
Moderate	7–9.9 g%	7–8.9 g%
Severe	4–6.9 g%	<7 g%
Very serve	<4 g%	—
Postpartum	—	<10 g%

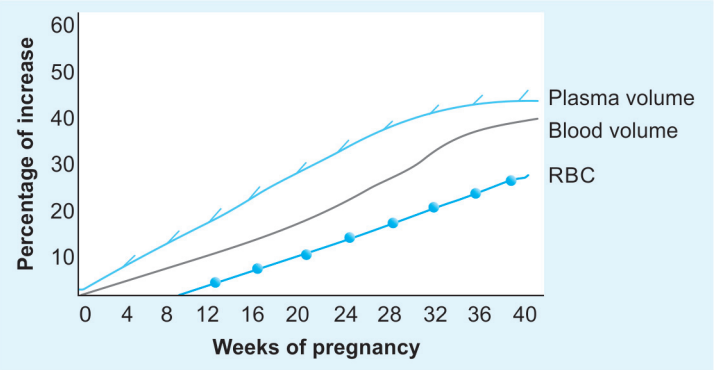

Fig. 1.1: Blood volume changes during pregnancy.

Nutritional Anemia

In India 90% of anemia in pregnancy are of nutritional origin. Iron deficiency is by far the most common cause of nutritional anemia.

Iron Deficiency Anemia

Iron is the essential element of heme pigment of the Hb. Deficiency of iron during pregnancy in our country is due to following reasons:

- **Low iron intake:** As iron cannot be produced in the body, it is essential to eat food that contains iron. Dietary sources rich in iron are mentioned in **Table 1.1**. Cooking in iron utensils is helpful.
- **Increased nutrient demand:** There is increased demand of iron during pregnancy. Each pregnancy needs approximately 1 g (1,000 mg) of extra iron as shown in **Table 1.2.**

  Most of this is required in second half of pregnancy. Although iron absorption increases during pregnancy (20–30% from normal 10%) the average vegetarian diet does not contain enough iron (10 mg average) to fulfil this demand.

  So, if woman has depleted iron stores, she requires 6–7 mg iron/day during second half of pregnancy, while woman with good iron stores 3–4 mg/day is sufficient. Thus iron supplement during pregnancy is must for an Indian mother.

  Saving of iron due to amenorrhea during pregnancy (25 × 8 = 200 mg) compensates for blood loss at delivery (150–200 mg).
- **Poor absorption and utilization:** The Indian diet which is predominantly vegetarian contains many substances which inhibit iron absorption. The factors influencing iron absorption are mentioned in **Table 1.3**.

  Also the bioavailability of nonheme iron (vegetarian diet) is poor and is slowly absorbed as compared to heme iron (5–10% vs 35–40%).
- **Poor reserve:** Normal iron store in adult female is 300–500 mg. An average Indian woman enters her first pregnancy with inadequate or poor iron stores. This is due to inadequate nutrition during adolescent period because of gender bias, poverty, and less education.

  In parous women repeated pregnancies at short intervals (<2 years) and prolonged lactation (without iron supplement) also leads to depletion of iron stores.
- **Increased loss:** The increased loss is due to high incidence of malaria and hookworm infestation. In rural areas hookworm infestation is common. This leads to average blood loss from 0.03 (*Necator americans*) to 0.2 mL (*Ankylostoma duodenale)* per parasite/day. In heavy infestation daily loss of iron can be up to 5 mg. Excessive menstrual loss (before pregnancy) and sweating are also responsible.

Table 1.1: Dietary sources rich in iron.

Vegetarian	Green leafy vegetables, spinach, mustard, fenugreek
Cereals	Whole wheat, bajra, jowar
Pulses	Green peas, beans, groundnuts, lentils
Fruits	Apple, banana are medium sources
Others	Jaggery, dates
Nonvegetarian	Liver, meat (fish and egg are medium sources)

Table 1.2: Iron requirement during pregnancy.

Expansion of RBC	400–500 mg
Fetus (80 mg/kg)	200–250 mg
Placenta and cord	80–100 mg
Basal losses	220–250 mg
Total	900–1,100 mg
	Average 1,000 mg (1 g)

Table 1.3: Food factors influencing the absorption of iron.

Inhibitors	Enhancers
❖ Phytates in cereals ❖ Tannins in tea. Polyphenols in coffee ❖ Oxalates in vegetables ❖ Phosphates in egg yolk ❖ Proteins	❖ Ascorbic acid—vitamin C ❖ Organic acids, such as citric acid, lactic acid ❖ Sprouted and fermented food ❖ Meat, fish

IRON METABOLISM

Total body iron depends upon age, sex (more in male) and body weight of the person. In an adult female it is 2.0–2.5 g (35–40 mg/kg). It is distributed in the body as shown in **Table 1.4**.

Absorption

- Exact mechanism of absorption is still not known.
- Iron is mainly absorbed from duodenum.
- Nonheme iron (vegetarian diet) is mostly in ferric (Fe^{+++}) form. It has to be reduced to ferrous (Fe^{++}) form for absorption.
- Due to acidic pH of the stomach and other reducing agents Fe^{+++} is reduced to Fe^{++}.
- A transporter protein called divalent metal transporter 1 (DMT 1) of enterocytes transports Fe^{++} iron from duodenal lumen to inside the enterocyte. With the enzyme peroxidase it is converted to ferric (Fe^{+++}) iron.
- Ferric iron can have one of the two fates: (1) Iron combines with apoferritin to form ferritin which is deposited in the intestinal cells and eventually excreted on their desquamation. (2) Iron which is not combined with apoferritin is absorbed and circulated in the plasma as ferric form combined with transferrin.
- Heme iron is in Fe^{++} form so its absorption is 2–3 times more than nonheme iron. Heme iron is present in hemoglobin and myoglobin (i.e., nonveg diet).
- Absorption of heme iron is not decreased by other foods simultaneously ingested.

Table 1.4: Distribution of body iron.

	Percentage of total body iron
Hb	65–70%
Stores (ferritin, hemosiderin)	20–25%
Myoglobin + enzymes (catalase, cytochromes, peroxidase)	5–10%
Plasma iron (bound to transferrin)	0.1–0.2%

Transport

- Fe^{+++} is taken up by transferrin (siderophilin), an iron-binding protein present in the blood for transportation to various parts of the body.
- Transferrin receptors present in the various cells of the body including RBCs (erythropoiesis) recognize transferrin leading to the entry of complex into the cell. Iron is released intracellularly. While transferrin is released back into the circulation to carry fresh load of iron.
- Iron from the breakdown of senescent RBCs in the reticuloendothelial system (RES) is also transported by transferrin for recycling in erythropoiesis.

Storage

- Some iron is stored in the RE cells in the liver, spleen and bone marrow as ferritin (major portion) and hemosiderin.
  Fe^{+++} + Apoferritin = Ferritin
  Aggregate of ferritin = Hemosiderin
- Ferritin can accommodate up to 4,500 of iron atoms. Ferritin is water-soluble while hemosiderin is not. Stores are mobilized to provide iron as and when need arises. In iron deficiency first the stores are depleted.

Excretion

- About 0.8–1.0 mg of lost iron is daily through exfoliated gastrointestinal (GI) mucosal cells, skin and in stool, urine, and sweating. In female approximately 1.0 mg/day should be added for menstrual loss during reproductive age group.

Iron cycle is mentioned in **Figure 1.2**. As there is no physiological mechanism for

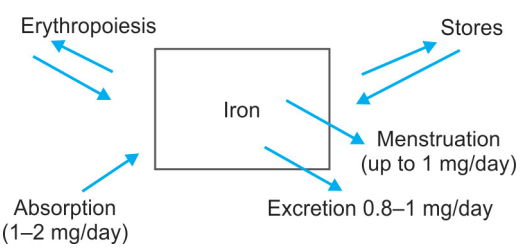

Fig. 1.2: Iron cycle.

Table 1.5: Factors affecting iron absorption.

Factors favoring	Factors reducing absorption
Iron deficiency	Iron excess
↑↑ Erythropoiesis	↓↓ Erythropoiesis
Inorganic iron	Organic iron (diet)
Ferrous iron (iron salts, heme iron)	Ferric iron (nonheme iron)
Acids: HCl, ascorbic acid, citric acid	Alkalies—antacids
Calcium citrate, calcium carbonate	Other calcium salts
Pregnancy	Infections

iron excretion, which is almost constant; iron content of the body is regulated by absorption alone. The amount of iron absorbed from the diet depends upon iron stores and requirement for erythropoiesis. Factors affecting iron absorption are mentioned in **Table 1.5** (food factors affecting the absorption of iron are already mentioned in **Table 1.3**).

- **Drugs**, such as Alphadopa, Levodopa, Ciprofloxacin, and Cimetidine interfere with iron absorption.

Iron deficiency occurs in three stages

First stage: Depleted iron stores.

Second stage: Decrease in serum iron and increase in total iron-binding capacity (TIBC). There is deficient erythropoiesis.

Third stage: Iron deficiency anemia.

Thus decrease in Hb represents very late stage of iron deficiency.

Erythropoiesis

RBCs are formed in the red bone marrow situated in the ends of long bones, from nucleated cells known as stem cells or hemocytoblasts.

Stem cells → Proerythroblast → Basophilic erythroblast (early normoblast) → Polychromatophilic erythroblast (intermediate normoblast) → Acidophilic erythroblast (late normoblast) → Reticulocyte → Erythrocyte (RBC)

From proerythroblast to reticulocyte it takes 7 days. From reticulocyte to mature RBC it takes 2 days. Erythropoiesis is stimulated by the hormone erythropoietin secreted from the kidney. Erythropoiesis is stimulated if there is tissue anoxia or if the red cell count goes down.

Clinical Features

Symptoms

- Fatigue, weakness, lassitude, impaired work capacity
- Dizziness, giddiness, headache, insomnia
- Dyspnea on exertion, palpitation
- Anorexia, dyspepsia
- Edema of ankles.

Signs

- Pallor of skin and mucous membrane. In severe anemia there is even loss of color in the palmar creases.
- There may be glossitis, stomatitis and dysphagia.
- Koilonychia (changes in nails: Initially brittleness and dryness, later there is flattening and finally concavity, i.e., spoon-shaped nails).
- Tachycardia.

Effects of Anemia in Pregnancy

Mother

- Increased susceptibility to infection.
- Cardiac failure at 30–34 weeks of pregnancy if severe anemia.
- Pre-eclampsia may be related to malnutrition.
- Preterm labor (3 times greater risk).

Labor

- Uterine inertia.
- Postpartum hemorrhage—even moderate blood loss can lead to collapse.
- Cardiac failure
- Shock

Puerperium

- Cardiac failure
- Puerperal sepsis
- Subinvolution
- Failing lactation
- Chronic ill health, backache.

Fetus and Neonate

- Prematurity
- Intrauterine growth restriction (IUGR) (3 times increased risk).
- Increased perinatal deaths.
- Decreased iron stores in neonate (Hb level in the fetus or neonate is not affected in anemic mother but soon infant can develop anemia due to deficient iron store).

Diagnosis

Although clinical history and examination (pallor) are suggestive, following investigations are done. Investigations are carried out for:

- **Diagnosis and degree of anemia:** Clinical estimation can be erroneous. Hb estimation is used for diagnosis. Hb below 11.0 g% suggests pathological anemia. Value of mild, moderate and severe degrees are already mentioned before.

  RBC count <3.2 million and packed cell volume (PCV) <30% suggest anemia.
- Type of anemia:
  - *Peripheral smear (PS):* To study the morphology of RBCs. It shows microcytic hypochromic picture in iron deficiency anemia. RBCs are smaller in size with central pallor. Also there is anisocytosis (variation in size) and poikilocytosis (variation in shape). PS may also help in diagnosing malarial parasites. Reticulocyte count may be slightly raised. Occasionally target cells are present.
  - *Hematological indices:* These are mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Their values in iron deficiency anemia as compared to normal are mentioned in **Table 1.6.**
  - Specific investigations for iron deficiency include serum iron, TIBC, percentage saturation (serum iron/TIBC), serum ferritin level **(Table 1.6)**. In fact decreased ferritin level is the first feature of iron deficiency.

Table 1.6: Hematological values.

	Normal values in female	Iron deficiency anemia in pregnancy
Hb	12.0–16.0 g%	<11.0 g%
RBC count	4–5 million/mm^3	<3.2 million/mm^3
PCV	32–36%	<30%
MCV	75–100 cubic micron	<75 μ^3
MCH	25–33 pg	<25 pg
MCHC	30–36%	<30%
Serum iron	60–120 µg/dL	<60 µg/dL
TIBC	300–350 µg/dL	>400 µg/dL
Percentage saturation	20–45% (1/3rd average)	<16%
Serum ferritin	15–200 µg/L (ng/mL)	<12 µg/L
Transferrin receptors	2–4 mg/L	Increased
FEP	0–35 µg/dL	Increased
Stainable bone marrow	Present	Absent

Free erythrocyte protoporphyrin (FEP) and transferrin receptor levels are not routinely carried out. They increase early in case of iron deficiency and are more sensitive than even ferritin.

Bone marrow examination: This is not routinely done. It is only indicated in—(1) refractory anemia and (2) aplastic/hypoplastic anemia. In iron deficiency anemia iron stores are absent. The absence of stainable iron is 'gold standard' for IDA.

- **Cause of anemia:** For diagnosing the cause, detailed history is also important, e.g., food habits, obstetric history (multipara, short intervals), gynecologic history (menorrhagia), history of malaria or worms.
  - *Urine examination:* Routine and microscopy (culture studies if indicated) are done for diagnosing urinary tract infection (UTI), asymptomatic bacteriuria, hematuria, etc.
  - *Stool examination:* Ova (eggs), cysts and for occult blood. Eggs of hookworm are segmented (4 blastomeres) and float in saturated solutions of common salt.
  - *Serum proteins:* Hypoproteinemia.

Special tests may be carried out in megaloblastic and other rare anemias.

Serum folate, RBC folate—megaloblastic anemia

Serum vitamin B_{12}

Serum bilirubin—hemolytic anemia.

Coomb's tests—autoimmune hemolytic anemia

Sickle test—sickle cell syndromes

Hb electrophoresis—hemoglobinopathies.

Naked eye single tube red cell osmotic fragility (NESTROF) test[2]—beta thalassemia trait. Glucose-6-phosphate dehydrogenase (G6PD) screening,

Red cell osmotic fragility test—hereditary spherocytosis.

Causes of microcytic anemia:

- Iron deficiency anemia
- Thalassemia
- Anemia of chronic disease
- Sideroblastic anemia
- Lead poisoning
- Anemia associated with copper deficiency
- Alcohol use.

Management

General preventive measures are:

- Screening of adolescent girls in school and giving iron supplements.
- Education and motivation for taking diet rich in iron **(Table 1.1).**
- Change in food habits, i.e., avoiding tea or coffee for at least 2 hours after meals.
- Prevention of hookworm and malaria. For hookworm, Albendazole 400 mg stat or Mebendazole 100 mg BID for 3 days is recommended. For malarial prophylaxis weekly 2 tablets of Chloroquine (300 mg base) are given from 2nd trimester onwards in endemic areas.
- Keeping adequate interval between pregnancies (>2 years minimum) and avoiding prolonged lactation without iron supplement.
- Fortification of food by iron, i.e., 30–36 mg iron should be added per kg of wheat flour.
- Fortification of common salt by iron.
- Cooking in iron utensils is helpful.

Govt of India (Ministry of Health and Family Welfare) has recommended 100 mg of elemental iron + 0.5 mg FA/day for 100 days to every pregnant woman in our country as prophylaxis from second trimester onwards and postpartum for 6 months. Dose is to be doubled if there is mild anemia.

Treatment

Apart from treatment of the cause, iron therapy for correction of anemia as well as to replenish the iron store is essential.

Iron Therapy

- **Oral iron therapy:** It is indicated in all mild and moderate iron deficiency cases. It is cheap, safe and effective in most of the cases. 100–200 mg elemental iron per day

is recommended. Different common iron salts with their elemental iron content is mentioned in **Table 1.7.**

- Ferrous salts are 3 times readily absorbed than ferric salts.
- Ferrous sulfate is the cheapest and well absorbed form of iron.
- Ferrous gluconate is well tolerated but it has low iron content (36 mg in 320 mg tablet).
- Ferrous fumarate is the most commonly used salt in commercial preparations.
- **Ferrous ascorbate** is a synthetic molecule of ascorbic acid, iron and as ascorbate makes stable chelate with iron there is no dissociation in GI tract, so there is no action of food inhibitors. Tablets containing 100 mg elemental iron is available for use.
- **Carbonyl iron:** Newer market preparation contain this. Carbonyl refers to manufacturing process where iron is obtained by thermal decomposition of iron pentacarbonyl which when heated to above its boiling point decomposes to give iron and carbon monoxide. Iron thus obtained has high purity (>98%), very fine spherical size (<5 μ) and uniform particle size.It is easily absorbed and less toxic than ionized forms of iron, such as iron sulfate. It has a high safety range.

Table 1.7: Oral iron preparations.

Salt	Tablet	Elemental iron
Ferrous sulfate	200 mg	60 mg (30%)
Ferrous fumarate	200 mg	66 mg (33%)
Ferrous gluconate	320 mg	36 mg (12%)
Ferrous succinate	100 mg	35 mg (35%)
-Ferric ammonium citrate	125 mg	25 mg (17–22%)
Ferrous ascorbate	—	100 mg
IPC	—	100 mg
Carbonyl iron	—	90 mg
Sodium feredetate	—	231 mg
Ferric pyrophosphate	—	30 mg

- **Sodium feredetate:** It contains ferric sodium EDTA. It contains iron in a unionized form. It is not astringent and does not discolor teeth. Its absorption is less affected by food inhibitors, such as phytates.

  Ferric pyrophosphate: It is relatively newer iron preparation with advance microsomal technology. It leads to lower GI side effects than conventional oral iron preparation.

  Faster rise of Hb is claimed by manufacturer.
- Micronization of iron and encapsulation with liposomes increases bioavailability.

  Ferrous bisglycinate chelate: It is a chelated form of iron, where two molecules of amino acid glycine are bound to a molecule of iron. It does not cause gastric irritation and constipation. Absorption of bisglycinate is not affected by phytates in food.
- Iron polymaltose complex (IPC): It is ferric hydroxide polymaltose complex. It is nonionic and it does not stain the teeth. There is no metallic taste and no interaction with food or other drugs. Initially claimed high therapeutic results were not found in clinical practice, so it is less used now.
- Sustained-release (SR) or time release (TR) preparations have less GI side effects but lesser iron is released in the main absorptive area, i.e., duodenum and upper jejunum and so less is absorbed.
- Gastric delivery system (GDS) contains ferrous sulfate in a gel forming polymer matrix, so the tablet floats in the stomach for 5–12 hours releasing small amount of iron to the main absorptive area (i.e., duodenum). It is claimed that 3 times more iron is absorbed with less side effects.

Iron prescription:

- More than 2 tablets/day is not favored as it increases the side effects without therapeutic benefits.

- If there is swallowing problem or intolerance use liquid preparation (less side effects but staining of teeth may be a problem).
- Iron should be taken on empty stomach with fruit juice for better absorption, i.e., 1 hour before or 2 hours after meals. Due to stomach upset it is usually taken with the meals.
- Tea, coffee avoided for 2 hours after taking iron.
- Taking vitamin C helps in absorption.
- Calcium salts (except calcium carbonate and calcium citrate) and antacids should be avoided.

Response:

- Reticulocyte count increases by 7–10 days.
- Hb% rises at 10–14 days. About 1 g%/week rise in Hb occurs from 2nd week onwards.

Side effects of oral iron: Upper GI tract—nausea, gastric discomfort, loss of appetite and eructation. Staining of teeth particularly in liquid preparation.

Lower GI tract—constipation, diarrhea, and flatulence.

Nonresponse to oral iron: Reasons can be:

- Noncompliance due to intolerance or otherwise.
- Poor absorption
- Wrong diagnosis another etiology of anemia.
- Continued loss of iron.

◆ **Parenteral iron therapy:** It is indicated when:

- Intolerance to oral iron.
- Noncompliance to oral iron.
- Poor absorption of oral iron (malabsorption syndrome, dysentery, etc.)
- No response to oral iron after 4 weeks in a confirmed case of iron deficiency anemia.
- Some cases of moderate anemia (6–8 g Hb) very late in pregnancy.

Preparations:

- *Iron sucrose:* It is available as 20 mg/mL in 5 mL (100 mg) or 10 mL (200 mg) ampoules.
- Ferric carboxymaltose (FCM) available as 50 mg/mL in 5 mL or 10 mL vials.

Iron sucrose:

- It is category B drug.
- Dose calculation is total iron = 2.4 × weight in kg × deficit of Hb in g. 500 mg should be added for pregnancy.
- It is safer, effective and well tolerated.
- Test dose is not recommended. However, some authorities prefer to give test dose.
- It can be given undiluted IV slowly 1 mL/min OR diluted 100 mg in/100 mL of normaI saline and given IV over 15 minutes.
- Maximum 200 mg per dose is given repeated up to three times a week.
- Iron sucrose is dissociated by the reticuloendothelial (RE) system into iron and sucrose. The released iron increases Hb. 75% sucrose is excreted by kidney in 24 hours.
- It is claimed that there is rapid rise of Hb than oral iron, i.e., after 1 week and also rapid buildup of iron stores.[3]
- It cannot be given IM due to alkaline pH (>10) as it causes muscle damage.
- It is not stable in dextrose, so it cannot be diluted in dextrose.

Ferric carboxymaltose (FCM):

- It is newer parenteral iron where ferric hydroxide core is stabilized by carbohydrate shell so there is controlled release of iron leading to decreased oxidative stress.
- It was initially recommended only for postpartum use but now safety during pregnancy is established.
- Dose is calculated as per standard formula and single dose is given in not <15 minutes in 250 mL saline.
- Dose should not exceed 15 mg/kg body weight and if required 2 doses are given 7 days apart.