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TOPICS

- **Patient blood management: Focus on iron therapy Recommendations for practice**
- **Calcium in women's health**

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Dear FOGSIANs,

Greetings!!

FOGSI's topmost priority is the health of every STREE of India. Hence the FOGSI campaign #WeforStree has the mission to empower every STREE -a SAFER STRONGER & SMARTER life. Embarking on this mission, FOGSI has taken up many such initiatives that give the STREE, wings to fly high.

This book focuses on one of the most challenging health issues faced by a STREE in India - Iron and Calcium deficiency. It covers all aspects of PATIENT BLOOD MANAGEMENT and ROLE OF CALCIUM.

Select FOGSIANs across India came together to deliberate and create these protocols. I urge all fellow FOGSIANs to put to use these Conventional & Functional Protocols.

Happy Reading.

Best wishes!

Dr. Nandita Palshetkar

MD, FCPS, FICOG
President 2019 - Federation of Obstetrics & Gynecological Societies of India (FOGSI)

Standing from left to right: Dr. Dilip Walke, Dr. Manish Machave, Dr. Basab Mukherjee, Dr. Sheeetal Sawankar, Dr. Unnati Mamtora, Dr. Rajendra Nagarkatti, Dr. Rohan Palshetkar, Dr. Dibyendu Bhattacharya, Dr. Arun Madhab Borua, Dr. Bela Bhatt, Dr. Ameya Purandare, Dr. Pratik Tambe, Dr. Priti Kumar, Dr. Kawita Bapat, Dr. Kiranmai, Dr. Aruna Suman, Dr. Archana Singh
Sitting from left to right: Dr. Tushar Kar, Dr. Asha Dalal, Dr. Shanthakumari, Dr. Rishma Pai, Dr. Nandita Palshetkar, Dr. Meera Agnihotri, Dr. Hrishikesh Pai, Dr. Archana Verma, Dr. Krishnakumari

CFP CONVENTIONAL & FUNCTIONAL PROTOCOLS

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PATIENT BLOOD MANAGEMENT:
FOCUS ON IRON THERAPY
RECOMMENDATIONS FOR PRACTICE

FOGSI President	: Dr. Nandita Palshetkar
Moderators	: Dr. Rishma Pai, Dr. Pratik Tambe
Panelists	: Dr.Bela Bhatt, Dr. Asha Dalal, Dr. Meera Agnihotri, Dr. Tushar Kar, Dr. Krishnakumari, Dr. Arun Madhab Boruah, Dr. Rohan Palshetkar, Dr. Dibyendu Banerjee, Dr. Saswati Sanyal, Dr. D. Kiranmai, Dr. Manish Machave, Dr. Unnati Mamtora

Iron deficiency (ID) and Iron deficiency Anemia (IDA) in general population

Iron deficiency (ID) is defined as the decrease of the total content of iron in the body. Iron deficiency anemia (IDA) occurs when ID is sufficiently severe due to excessive loss of iron or decreased iron absorption, which decreases plasma iron to limit or reduce erythropoiesis. This type of anemia is the most frequent chronic anemia. ID may be the result of either excessive loss or, less frequently, decreased absorption. In general, the iron absorbed daily equals the amount needed to compensate its loss, so that the overall iron pool remains stable. This fine balance is easily broken, because the capability to absorb iron orally is limited.[1]

- **Iron deficiency (ID) is defined as the decrease of the total content of iron in the body. ID may be the result of either excessive loss or, less frequently, decreased absorption.**
- **Iron deficiency anemia (IDA) occurs when ID is sufficiently severe due to excessive loss of iron or decreased iron absorption, which decreases plasma iron, ultimately limiting or reducing erythropoiesis.**

Global and Indian burden of Anemia

- The World Health Organization (WHO) has estimated that 25% of the population (around 1.62 billion people globally) are affected with anemia.[2]
- Analysis of several reports on the burden of disease between 1990 and 2010 and a survey on the burden of anemia in high risk population such as preschool children and young women has confirmed iron-deficiency anemia (IDA) to remain as the top cause of anemia.[3]
- In the Global Burden of Diseases, Injuries and Risk Factors 2010 Study, anemia caused around 68.3 million years lived with disability in 2010 (8.8% of global total), which was observed to be more than major depression (63.2 million), chronic respiratory diseases (49.3 million) and total injuries (47.2 million), although its prevalence had decreased from 1990 to 2010.[4]

Prevalence and severity of anemia in Indian women[5,6]

- A high prevalence of anemia is reported among women in India; as per the latest published National Family Health Survey-4, 2015–2016, 53% of all women have anemia.
- IDA is a common problem among women, primarily due to their recurrent menstrual loss.
- High demand for iron is higher among pregnant women, and women with anemia in combination with early onset of childbearing, a high number of births, short intervals between births and poor access to antenatal care and supplementation.

The prevalence and severity of anemia in India are as presented in Table 1.[6]

Table 1. Severity of anemia in national surveys of India[6]

Survey	Anemia of pregnancy (%)			Severity of anemia (%)		
	Urban	Rural	Total	Mild	Moder-ate	Severe
DLHS-2 (2002-04)	-	-	96.2	50.7	42.5	3.1
NNMB-2003	-	-	75%	24.4	45.9	4.3
NFHS-3 (2005-06)	54.6	59.0	57.9	25.8	30.6	2.2
NFHS-4 (2015-16)	23.6-61.7	19.6-58.1	23.6-61.4	-	-	-

DLHS: District Level Household Survey; NNMB: National Nutrition Monitoring Bureau; NFHS: National Family Health Survey.

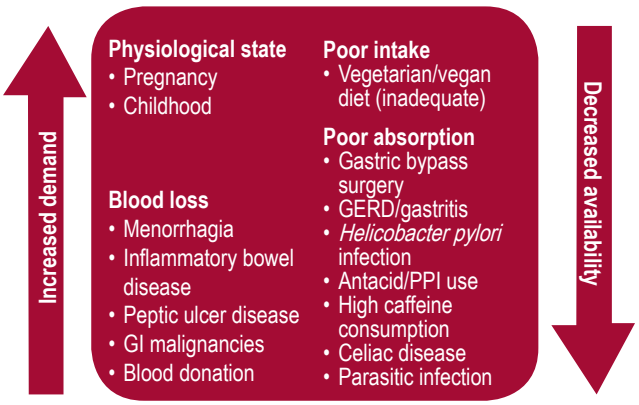
- Among the South Asian countries, India is projected to have the utmost prevalence of anemia, 57%–96.2%.
- In India, the estimated maternal deaths due to IDA is approximately 3,26,000, with an associated disability-adjusted life years (DALYs) of 12,497,000.

- Losses from IDA result in an increase in the cost of up to 4.05% of gross domestic product (GDP) in developing countries, and 1.18% of GDP in India.
- National Family Health Survey (NFHS-4, 2015-2016); the prevalence is 23.6-61.4%

- **A high prevalence of anemia is reported among women in India; 53%, as per the latest published National Family Health Survey-4, 2015–2016.**
- **In India, the estimated maternal deaths due to IDA is approximately 3,26,000, with an associated disability-adjusted life years (DALYs) of 12,497,000.**

Causes of ID & IDA

Figure 1. Causes of iron deficiency anemia.[8]



GERD = gastroesophageal reflux disease, GI = gastrointestinal, PPI = proton pump inhibitor.

IDA in pregnancy

Anemia occurs frequently during pregnancy. Anemia can be aggravated by childbirth and is associated with adverse events. In most cases, it is possible to identify and correct the situation prior to childbirth, thereby improving patient outcomes.[7]

- According to World health organization (WHO) report, about 32.4 million pregnant women suffer from anemia worldwide, of which 0.8 million women are severely anemic.
- Moreover, 50% of the cases of anemia are attributable to iron deficiency anemia (IDA).
- An estimate by WHO attributes about 591,000 perinatal deaths and 11,5000 maternal deaths globally to IDA, directly or indirectly. Anemic women are reported to have a 4 fold higher risk of preterm birth; 2.2 fold, LBW; and 1.8 fold, low Apgar score as compared to non-anemic women.[9]

Causes of ID during pregnancy

- Insufficient iron stores fail to meet the increasing demands of pregnancy due to the increase in RBC mass, foetal growth, placental development and blood losses during normal vaginal delivery or a cesarean section delivery.[7]
- Nutritional deficiencies of folate and vitamin B12, phytate rich Indian diets, inflammatory or infectious diseases, parasitic infections, and hemoglobinopathies are additional and often neglected causes of anemia.[6]

Requirement of extra iron during normal pregnancy - equivalent to 6.3 mg/day

Requirement of extra iron during lactation -1 mg/day

Consequences of ID during pregnancy[7]

Iron depletion reduces iron availability for erythropoiesis and results in decreased Hb and oxygen delivery to tissues, resulting in clinical signs and symptoms.

- Reduced exercise tolerance, tiredness, and fatigue, impaired cognitive performance tests, decreased mental concentration ability, irritability, tendency of depression, palpitations, headaches, pallor,

glossitis, angular cheilitis, nail ridging, koilonychias, reduced immunity, increased frequency of infections and pica cravings.

Anemia is the most common indirect cause of adverse maternal outcomes, including maternal mortality.

- Moderate or severe anemia during pregnancy have been associated with an increased risk of premature delivery and child mortality and infectious diseases.

- **According to World health organization (WHO) report, about 32.4 million pregnant women suffer from anemia worldwide, of which 0.8 million women are severely anemic.**
- **Anemic women are at a higher risk of preterm birth; LBW; and low Apgar score as compared to non-anemic women.**
- **Causes of ID during pregnancy**
  - » Physiological anemia owing to hemodilution
  - » Insufficient iron stores fail to meet the increasing demands of pregnancy
  - » Neglected nutritional deficiencies, infections and hemoglobinopathies
- **Consequences**
  - » Increased maternal mortality and morbidity
  - » Perinatal morbidity and mortality - an increased risk of premature delivery fetal growth restriction and increased susceptibility to neonatal infections
  - » Infant & long term : Affects growth and development of the foetus in utero and of the newborn child in the long term during infancy

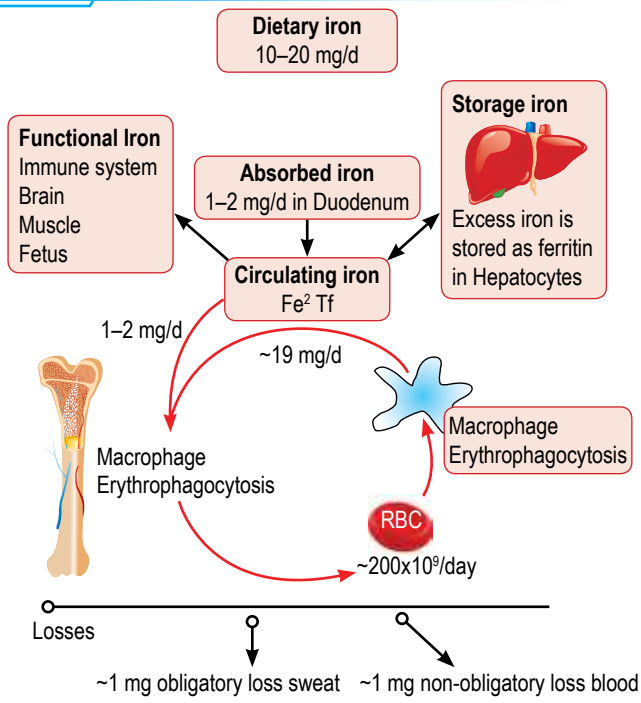
- IDA may affect growth and development, both of the foetus in utero and of the newborn child in the long term.

Iron balance in the body and stages of iron deficiency

A delicate balance of iron has to be maintained in the body, so that sufficient iron is obtained from the diet to sustain life, and ensure that excess iron is not available to generate reactive oxygen species which damage macromolecules or support the growth of pathogens. The acquisition and transport of iron by the body reflects the evolutionary mechanisms that protect the body from free iron while promoting highly efficient mechanisms for recycling and conservation of iron.[10]

- Most iron in the body (Figure 2), is present in hemoproteins and iron-containing enzymes involved in cellular respiration.

Figure 2. Iron balance in the body[10]



- Iron is also present in the plasma bound to transferrin, stored in intracellular ferritin depots and as a component of cytochromes and catalase.

- A proportion of iron is held within macrophages, the spleen and liver and in the bone marrow.
- Excess iron is stored in ferritin in hepatocytes.
- Only 1 to 2 mg of iron is absorbed from the iron consumed in meals. Iron is required for erythropoiesis, the immune system, brain requirements and for transfer across the placenta in pregnancy.
- Iron in excess of requirements may bestored in the bone marrow and liver.
- Iron required for erythropoiesis comes predominantly from the breakdown of red blood cells (RBC) by macrophages; however about 5% of iron required for RBC formation comes from the newly absorbed iron.
- The variable component of iron status is that lost in blood such as menstrual loss, blood donation, nose bleeds, and gastrointestinal bleeding.

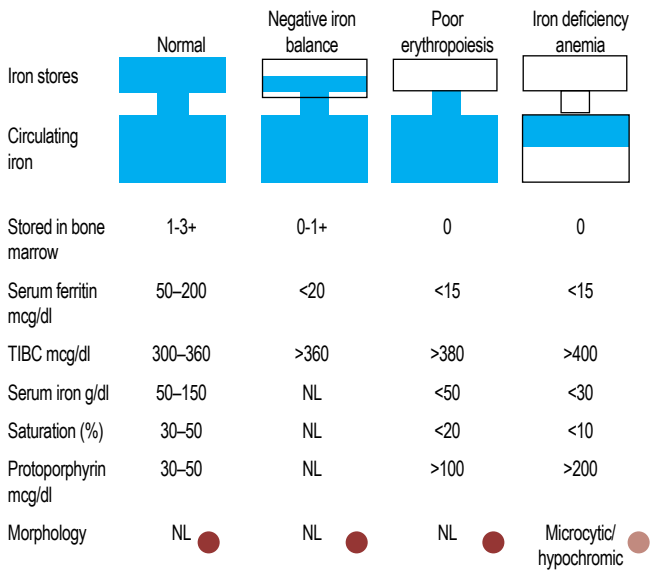
A delicate balance of iron has to be maintained in the body. Only 1–2 mg of iron is absorbed from diet. Excess of iron is stored in the bone marrow and liver. Breakdown of RBCs by macrophages provides the iron required for erythropoiesis. A variable component of iron is also lost in blood through menstrual loss, blood donation, nose bleeds, and gastrointestinal bleeding.

Stages of iron deficiency[11]

Iron deficiency can be characterized as three distinct stages.

Stage 1. Negative iron balance	Stage 2. Iron deficient erythropoiesis	Stage 3: Iron deficiency anemia
• Demand for (or loss of) iron exceeds the body's capacity to absorb dietary iron • Results due to physiological mechanisms that can include blood loss, pregnancy, growth spurts in adolescence, or an iron-poor diet • Serum ferritin levels or bone marrow iron content indicate the body iron stores • Serum iron levels, TIBC, and red blood cell protoporphyrin levels will remain within normal range since body iron stores can be circulated • Normal red blood cell morphology and indexes	• Depleted body iron stores • Increased TIBC and red blood cell protoporphyrin levels • Serum ferritin levels fall below <15 µg/l which indicates absence of bone marrow iron stores • Hemoglobin synthesis is not affected, and serum iron remains within normal ranges despite depletion of body iron stores • Hemoglobin synthesis deteriorates, when transferrin saturation falls below 15%–20%	• Hemoglobin and hematocrit levels start to fall • Transferrin saturation at this point is 10%–15% • Blood smear tests will show the first signs of circulating microcytic cells and hypochromic reticulocytes

Figure 3. Stages of iron deficiency and laboratory values[11]



	Normal	Negative iron balance	Poor erythropoiesis	Iron deficiency anemia
Stored in bone marrow	1-3+	0-1+	0	0
Serum ferritin mcg/dl	50–200	<20	<15	<15
TIBC mcg/dl	300–360	>360	>380	>400
Serum iron g/dl	50–150	NL	<50	<30
Saturation (%)	30–50	NL	<20	<10
Protoporphyrin mcg/dl	30–50	NL	>100	>200
Morphology	NL	NL	NL	Microcytic/ hypochromic

Signs and symptoms of ID & IDA[1]

ID	IDA
Less marked symptoms because physiological adaption, particularly cardiovascular and respiratory, is more effective.	Clinical symptoms become evident, including pallor and fatigue, reflecting diminished delivery of oxygen to tissues.
High impact of ID on the quality of life of the subject, but patients often get used to their symptoms and these are assumed as normal.	
Pagophagia (irresistible desire to lick or eat ice) is considered quite specific to ID and it responds quickly to treatment.	
The patient becomes aware of an improvement only when the symptoms disappear.	
Common symptoms include general weakness, fatigue, irritability, poor concentration, headache, and intolerance to exercise. These symptoms appear even in the figures for ID with normal hemoglobin levels.	

ID: iron deficiency; IDA: Iron deficiency anemia.

Absorption, utilization, and storage of iron

Absorption[10]

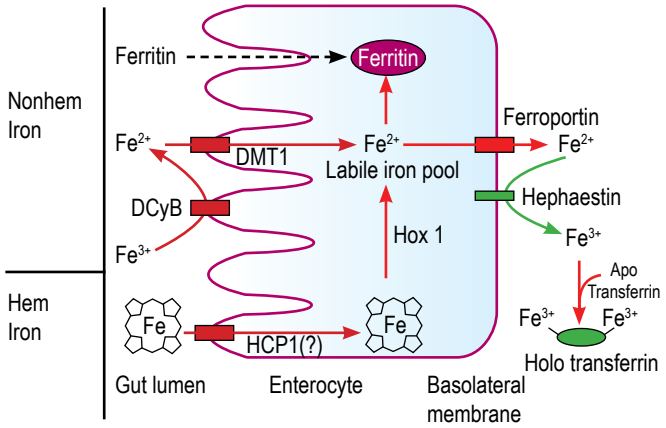
- Dietary iron is absorbed across the gut wall (Figure 4) as both heme and non-heme iron. The absorption of heme iron is more efficient and is highly bioavailable than non-heme iron.

The bioavailability of non-heme iron is affected significantly by other dietary components. Non-heme iron exists predominantly in the environment and the diet as the insoluble ferric (Fe^{+3}) form of iron but is transported across the gut wall in the ferrous (Fe^{+2}) form. Ferric iron is reduced to ferrous iron by duodenal ferric reductases such as the membrane-bound duodenal cytochrome B (DcytB).

Reducing agents in the diet such as ascorbic acid, lactic acid, citric acid, and other organic acids, or foods stimulate endogenous gastric acid production, and also reduce Fe^{+3} to Fe^{+2} and promote iron absorption.

Ferritin proteins may be absorbed intact, contributing to the acquisition of non-heme iron.

Figure 4. Dietary iron is absorbed across the gut wall as heme iron (from animal food sources) and non-heme iron (from animal and plant food sources).[10]



DMT1 – Divalent metal transporter 1; DCytB – Duodenal cytochrome B; Hox1 – heme oxygenase-1; HCP1 – Heme carrier protein 1.

Storage[10]

Within the duodenal enterocyte, the absorbed iron is either stored intracellularly as ferritin or transported across the basolateral membrane of the enterocyte. Ferritin can sequester up to 4500 atoms of iron per molecule as ferrihydrite, thus restricting the availability of intracellular free iron. This sequestration of iron in ferritin means that the duodenal enterocytes act as a short-term store of iron, buffering iron absorption in excess of requirement. Small quantities of ferritin subunits (without iron) are present in the serum so can indicate iron stores and iron status before hemoglobin concentration falls.

Fe^{+2} transported out of the enterocyte is immediately oxidized to Fe^{+3} by membrane-bound ferroxidases, and then bound to transferrin (Tf), which are transported in the circulation to cells expressing transferrin receptors (TfR1). Tf has a high binding affinity for iron and is 25%–30% saturated under physiological conditions in healthy humans so there is negligible non-transferrin-bound iron in the plasma.[10]

Holo-Tf (transferrin with iron) binds to the TfR1 on the membrane of target cells. The receptor-ligand complex is endocytosed and a proton pump causes acidification of the endocytotic vesicle; the lower pH reduces the affinity of Tf for iron so iron dissociates and is released into the cytosol.[10]

There is no route of excretion of excess iron; iron balance is regulated solely by iron absorption. Hepcidin produced by the liver, is the primary regulator of iron levels.[10]

- **The absorption of dietary heme iron is more efficient and is highly bioavailable than non-heme iron. Ferritin proteins are absorbed intact, contributing to the acquisition of non-heme iron.**
- **The absorbed iron is either stored intracellularly as ferritin or transported across the basolateral membrane of the enterocyte. Ferritin can sequester up to 4500 atoms of iron per molecule as ferrihydrite, thus restricting the availability of intracellular free iron.**
- **Iron binds to transferrin (Tf), the high binding affinity makes Tf 25%–30% saturated under physiological conditions in healthy humans, so there is negligible non-transferrin-bound iron in the plasma.**
- **Holo-Tf (transferrin with iron) binds to the transferrin receptors on the membrane of target cells, and acidification of which leads to dissociation of iron into the cytosol.**

Hepcidin: A central regulator of systemic iron homeostasis

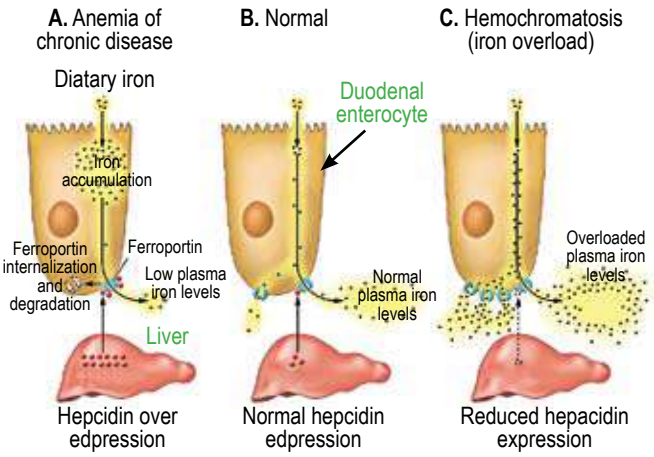
Hepcidin is an antimicrobial peptide that has emerged as the key hormone regulator of iron homeostasis involved in causing anemia.[12] Hepcidin is synthesized in the liver and secreted into the circulation.[13]

During normal iron homeostasis, hepcidin production increases with an increase in plasma iron.[14, 15]

Hepcidin down-regulates the expression of ferroportin on macrophages, hepatocytes, and enterocytes thereby controlling iron release into the plasma.[15] As the iron is consumed for synthesis of hemoglobin, the plasma iron levels decrease and hepcidin production is lowered thereby completing the homeostatic loop.[14, 15]

Figure 5 shows the role of hepcidin during normal iron homeostasis.

Figure 5. Role of hepcidin during normal iron homeostasis, in anemia of inflammation and iron overload

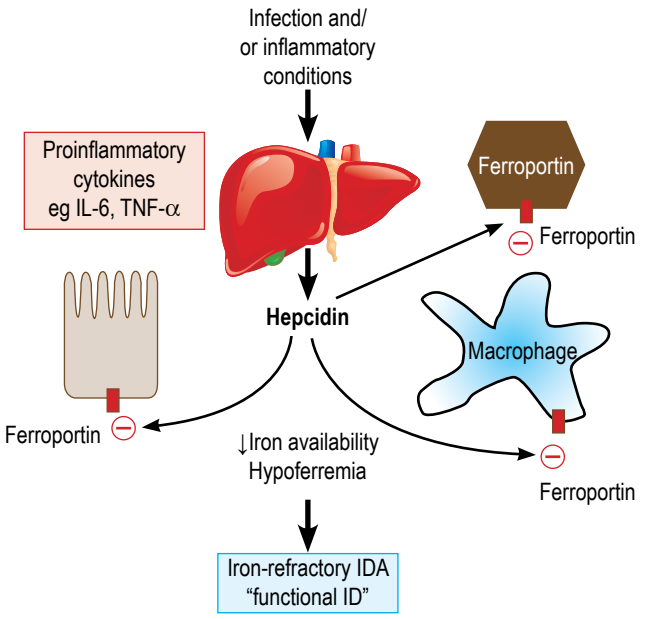


Role of hepcidin in anemia of inflammation

Clinical situations involving overproduction of hepcidin are commonly associated with anemia of inflammation. During anemia of inflammation, IL-6 and other inflammatory cytokines are released, which stimulate the synthesis of hepcidin. Increase in hepcidin binds to ferroportin and degrades it. This results in loss of

ferroportin and decrease in cellular iron export. Major iron flows into the plasma are blocked. Thus, plasma iron is decreased thereby limiting erythropoiesis. Figure 6 demonstrates the role of hepcidin in anemia of inflammation.[16]

Figure 6. Increased hepatic hepcidin production and functional ID during increased infection[10]



- Hepcidin is synthesized in the liver and secreted into the circulation. It is a key hormone regulator of iron homeostasis involved in causing anemia.
- Hepcidin controls iron release into the plasma during normal iron homeostasis.
- During inflammation, hepcidin is increased which degrades ferroportin and blocks the iron flow into the plasma, thereby limiting erythropoiesis, and ultimately causing iron deficiency.

Iron deficiency with increased hepcidin refractory to oral iron therapy

Iron sequestration in intracellular ferritin leads to hypoferremia and decreased availability of iron for pathogens (Figure). It is this pathway that is responsible for anemia in conditions such as infection and inflammatory conditions; this anemia is refractory to oral iron therapy because the raised hepcidin levels result in iron being trapped in the enterocyte and not being exported into the blood.[10]

In a study, in iron-depleted young women, oral iron doses of 60, 80, 160, and 240 mg Fe given in the morning acutely increased plasma Hepcidin on the

- Iron supplements at doses of 60 mg Fe as $FeSO_4$ or higher increases hepcidin for up to 24 hours and are associated with lower iron absorption from the second dose on the following day.
- The soluble transferrin receptor/ferritin ratio and hepcidin are equivalent predictors of iron absorption from supplements.
- In pregnant women, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) recommend 30 to 60 mg Fe per day.*
- The WHO recommends 30 to 60 mg of elemental iron and 400 µg of folic acid for pregnant women to prevent maternal anemia.#
- The CDC recommends that all pregnant women should take a 30 mg/day iron supplement, unless they have hemochromatosis.@

*Moretti D, et al. Blood. 2015; 126(17):1981–9.
#WHO. Daily iron and folic acid supplementation during pregnancy. https://www.who.int/elena/titles/guidance_summaries/daily_iron_pregnancy/en/
@Schantz-Dunn J et al. OBG Management. 2017; 29(12): 9–16

same day and 24 hours later. This increase was strongly associated with decreased absorption from the second iron dose, given 24 hours after the first. Providing 60 mg of iron twice daily amplified the plasma hepcidin increase and decreased the fractional absorption of both the afternoon dose and the next morning dose, so that total iron absorbed from the 3 doses (2 mornings and afternoon) was not different from that of the two morning doses. These short-term effects observed on hepcidin suggest that oral iron at doses ≥60 mg greater will result in higher fractional absorption when dosages are spaced by 48 hours. Therefore, it was concluded that fractional absorption in iron-depleted women was highest at low iron doses (40–80 mg) and that acute, consecutive-day dosing results in decreased iron bioavailability.[17]

Role of iron, deleterious effects of ID and prevention of IDA[10]

Iron use in the body follows a hierarchy. Before erythropoiesis is compromised, ID in the body deleteriously affects other iron-dependent functions, such as those involved in the central nervous system and immune functions. Therefore, IDA becomes apparent in such situations.

The prevalence of ID is significantly higher than IDA, particularly in women. ID is associated with a range of clinical outcomes including depression, reduced endurance and work performance, and compromised intellectual and cognitive functions.

Iron therapy in intervention studies frequently results in improved cognitive function and iron therapy in pregnancy has been demonstrated to have effects on the offspring ' s cognition. In adult ID, iron therapy restores brain function, whereas ID in children may have irreversible detrimental consequences for the developing brain.

Iron overload and toxicity[10]

Free iron in the presence of H_2O_2 and O_2 forms highly reactive and destructive hydroxyl radicals, which can lead to oxidative burst in neutrophils and can cause oxidative damage to essential macromolecules such as DNA, lipids, proteins and antioxidants. Therefore, iron overload can damage the body. Iron overload leads to genetic instability and altered risk of infection and disease; excess iron is associated with diabetes, cardiomyopathy, liver damage, neurodegenerative diseases and various types of cancer.

Ganjoni's formula to calculate the dose of iron[18]

The cumulative dose for repletion of iron is based on the patient's Hb and body weight and should not be exceeded. The cumulative dose can be calculated by the Ganzoni formula.

Ganzoni formula:

Total body iron deficit/cumulative iron dose (mg) = body weight* (kg) x (target Hb – actual Hb in g/L) x 0.24** + iron depot (mg)***

* Use ideal body weight in overweight patients. If underweight, use actual body weight

** The factor 0.24= 0.0034 x 0.07 x 1,000: For this calculation the iron content of hemoglobin = 0.34%, blood volume = 7% of the bodyweight, and 1,000 is the conversion from grams to milligrams

*** Iron depot: <35 kg body weight: iron depot = 15 mg/kg body weight ≥35 kg body weight: iron depot = 500 mg

For example a 70 kg female with Hb 80 g/L has an iron deficit of: 70 x (150–80) x 0.24 + 500 = 1676 mg i.e. approx. 1700 mg

Note that the target Hb may vary according to patient population.

Assessment of iron status

Importance of identifying ID before occurrence of IDA

It is important to identify ID before IDA occurs, so that the individuals at risk can be assessed or timely

treatment can be offered. Assessing markers of iron in transport and indicators of increased demand by cells such as a fall in transferrin saturation and/or an increase in sTfR can help in detection of ID.[10]

Suggested Laboratory tests

- Serum ferritin is the most sensitive and preferred initial diagnostic test.[19]
- Total iron binding capacity (TIBC) is often measured at the same time as serum iron. This measurement indicates the potential capacity of transferrin molecules to bind with serum iron.[19]
- Measuring hemoglobin status[10]
  - » The hemoglobin status identifies late stage iron deficiency affecting erythropoiesis. But, hemoglobin concentration lacks specificity as a marker of ID, since production of red blood cells requires several other nutrients in addition to iron.
  - » Measurement of hemoglobin concentration also has low sensitivity since hemoglobin synthesis is preserved at the expense of other iron-requirements.
  - » Other markers of impaired production of red blood cells such as mean cell hemoglobin concentration (MCHC), mean cell volume (MCV), red cell distribution width (RDW) and erythrocyte/zinc protoporphyrin also indicate late stage ID when there is not adequate iron for normal erythropoiesis.

Serum Ferritin: The most important marker to detect iron stores[10,20]

- Iron stores in the body exist primarily in the form of ferritin. It is an intracellular hollow protein shell composed of 24 subunits surrounding an iron core that may contain as many as 4000-4500 iron atoms.
- When a small amount of ferritin is secreted into the plasma, its plasma concentration is positively correlated with the size of the total body iron stores in the absence of inflammation.
- In contrast to hemoglobin, the body ferritin levels are not affected by residential elevation above sea level or smoking behaviour.
- Mild ID can be diagnosed by fall in serum ferritin levels.
- Presence of inflammation increases hepcidin production which causes iron to be sequestered in cells, so serum ferritin concentrations increase independently of iron status, which suggests sufficient iron stores, but is actually a deficiency of iron. Hence, measuring an inflammatory marker such as C-reactive protein concurrently with serum ferritin is essential.[10]
- In the absence of inflammation or liver disease, high serum ferritin concentrations indicate iron overload.
- Table 1 presents serum ferritin concentrations reflective of depleted iron stores.

Table 1. Serum ferritin concentrations reflective of depleted iron stores

	Serum ferritin (µg/l)			
	Less than 5 years of age		**5 years of age or older**	
	Male	**Female**	**Male**	**Female**
Depleted iron stores	< 12	< 12	< 15	< 15
Depleted iron stores in the presence of infection	< 30	< 30	–	–
Severe risk of iron overload (adults)	–	–	>200	>150

Detection of iron status in areas where inflammation is not prevalent[20]

Serum ferritin, along with soluble transferrin receptor, provides an approach to measuring the iron status of populations in areas where inflammation is not prevalent, as transferrin receptor does not rise in response to inflammation. The interpretation of low serum ferritin and high transferrin receptor concentrations is presented in Table 2.

Table 2. The interpretation of low serum ferritin and high transferrin receptor concentrations

Percentage of serum ferritin values below cut-offs[a]	Percentage of transferrin receptor values above cut-offs[b]	Interpretation
Lower than 20%[c]	Lower than 10%	Iron deficiency is not prevalent
Lower than 20%[c]	10% or higher	Iron deficiency is prevalent; Inflammation is prevalent
20% or higher[d]	10% or higher	Iron deficiency is prevalent
20% or higher[d]	Lower than 10%	Iron depletion is prevalent

[a] Apply cut-offs by age group
[b] Apply cut-offs recommended by manufacturer of assay until an international reference standard is available.
[c] Lower than 30% for pregnant women
[d] 30% or higher for pregnant women

sTfR-ferritin Index: Valuable in identifying ID before IDA

Serum sTfR is a useful marker of ID; it is not an acute phase reactant like ferritin so it is not affected by inflammation and it increases with ID before the manifestation of IDA. Combinations of biomarkers such as the sTfR-ferritin index are valuable in identifying ID before IDA, particularly where inflammation may coexist.[10]

Advantage of using serum ferritin as a measure of iron status[20]

- Serum ferritin is an indicator of the size of iron stores, reflects the iron status and responds to iron interventions.

- Identification of ID is suggested before the occurrence of IDA, so that timely treatment can be offered and IDA can be prevented.
- We recommend that a full blood count (FBC) be obtained to screen for anemia at booking and at 28 weeks, as well as at any time during pregnancy if symptoms of anemia are present (1A).
- In a woman with microcytic or normocytic anemia, iron deficiency (ID) should be confirmed by a trial of oral iron (unless she is known to have a hemoglobinopathy) or a serum ferritin measurement (1B).
- In the absence of an hemoglobin (Hb) increment in response to a trial of oral iron conducted correctly, it is recommended to further evaluate iron status by checking serum ferritin and considering whether additional laboratory testing is needed (1C).
- In anaemic women of Indian origin, it is recommended to confirm the presence or absence of a hemoglobinopathy either by selective (based on a family of origin questionnaire) or universal screening for hemoglobinopathies.
- Anemic women with a known hemoglobinopathy should have their serum ferritin checked and should only be offered oral iron therapy if their serum ferritin level is <30 ngmL–1 (1B)
- Serum ferritin is the most sensitive and preferred initial diagnostic test. Iron stores in the body exist primarily in the form of ferritin. Mild ID can be diagnosed by fall in serum ferritin levels. High serum ferritin concentrations indicate iron overload in the absence of inflammation or liver disease.
- Ferritin measurements and corresponding cut-offs facilitate an indicator of the size of iron stores, reflects the iron status and responds to iron interventions.
- Serum sTfR is a useful marker of ID; it is not an acute phase reactant like ferritin so it is not affected by inflammation and it increases with ID before the manifestation of IDA. sTfR-ferritin index are valuable in identifying ID before IDA, particularly where inflammation may coexist.

Interpretation of laboratory tests to assess iron status[21]

Table 3. Interpreting laboratory blood test results to assess iron status*

Diagnosis	Hemoglobin	Mean cell volume and mean cell hemoglobin	Serum ferritin mcg/L	Transferrin or total iron binding capacity	Transferrin saturation†	Soluble transferrin receptor	Serum iron‡
Tissue iron deficiency without anemia	Normal	Normal or low	< 15–30	Normal or high	Low-normal or low	High-normal or high	Low
Iron deficiency anemia (IDA)	Low	Low (or normal in early IDA)	< 15–30 adult < 10–12 child	High	Low	High	Low
Anemia of chronic disease or inflammation	Low	Normal (may be mildly low)	Normal or elevated (elevated ferritin does not imply elevated iron stores)	Normal	Low	Normal	Low
IDA with coexistent chronic disease or inflammation	Low	Low	Low or normal, but usually < 60–100mcg/L	Normal or high	Low	High	Low
Thalassaemia minor§	Low (or normal)	Low (or normal)	Normal or elevated	Normal	Normal or elevated	Normal or elevated	Normal
Iron overload	Normal	Normal	Elevated (correlates with body iron stores)	Normal to low	High	Normal	Normal to elevated

*Compared with laboratory reference range for age, sex and gestation if applicable. † Ideally performed on fasting morning sample. ‡ Serum iron is markedly labile with a significant diurnal variation, is low in both iron deficiency and inflammation, and should not be used to diagnose iron deficiency. § Includes α-thalassaemia minor and single or two alpha gene deletion thalassaemia minor. A thalassaemic condition and iron deficiency may coexist, particularly in pregnancy.

Patient blood management

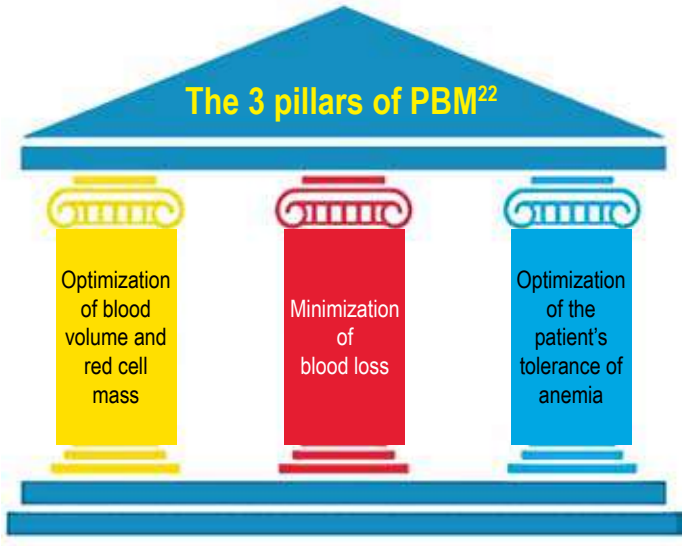
Patient blood management (PBM) is the timely application of evidence-informed medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcomes.[7]

Focus of PBM

PBM aims to escape unnecessary exposure to blood components and improves clinical outcomes.

The goal of PBM focuses in improving and conserving the patient's own blood, wherein transfusions can be avoided or reduced to prevent related-complications.

The core focus of PBM is to ensure improving and conserving the patient's own blood. Therefore, this strategy can help in avoiding or involving fewer transfusions of donated blood components, thereby preventing transfusion-associated complications.[22]



Blood transfusion: Is it necessary?

During the presence of major hemorrhage, or when disabling anemia is associated with cancer chemotherapy, or when bleeding is associated with profound thrombocytopenia, absence of rigorous data to guide the appropriate approach of treatment leads to a straight forward decision of transfusion. Even today, in many operating rooms, transfusions are often the first intervention when Hb falls below 10 g/dL.[23]

Denton Cooley and his associates have demonstrated that transfusions may not always be necessary and that tolerance to anemia may be higher than often believed. They illustrated this fact by performing an open heart surgery successfully without an allogeneic blood transfusion. This encouraged others to create bloodless surgery centres which used alternative management strategies to manage these patients. The strategies during surgical procedures to minimize transfusion requirements included use of intravenous (IV) iron and exogenous erythropoietin stimulating agents (ESAs). Evidence of the negative impact of blood transfusions is increasing, despite it having life-saving benefits in major hemorrhage.[23]

- **Blood transfusions may not always be necessary and that tolerance to anemia has shown to be higher than often believed.**
- **Alternative management strategies such as use of IV iron along with ESAs have shown to be beneficial in managing patients in the operating rooms.**

Avoiding unnecessary blood transfusions in women with profound anemia

Anemia during pregnancy is a risk factor for transfusion, and is linked to adverse maternal and perinatal outcomes.[22]

A study was conducted to describe the management practices and outcomes in women with profound anemia who refused blood transfusion. A retrospective analysis over a 10-year of severely anaemic women (Hb <5 g/dL) with benign conditions who had requested not to receive a blood transfusion was conducted. Anemia management involved initially addressed the underlying etiology and was followed by intravenous iron (all cases) plus erythropoiesis stimulating agents, hemocoagulase and/or fluids. The mean length of hospital stay was 10.5 ± 4.4 and 13.7 ± 4.1 days for the obstetric and gynecologic groups. The Hb increased in all women by the time of hospital discharge. No deaths or other serious complications were reported. Therefore, conservative management without blood transfusions is a feasible option for women with 'profound anemia', even with concentrations below 5 g/dL, in young and otherwise healthy obstetric and gynecologic cases.[23]

Conservative management with intravenous iron can be considered as an effective and a feasible option without blood transfusions for women with profound anemia having very low hemoglobin levels.

Factors to be considered before indicating blood transfusion

- Blood transfusion should not be a default decision if blood components are likely to be indicated. [22]
- The clinician should carefully consider the decision on whether transfusion is required by taking into account the full range of available therapies. [22]
- Blood transfusions should only be prescribed when the clinician is satisfied that it is likely to offer a worthwhile benefit or that the risk of not transfusing is likely to be greater than the risk of transfusing.[23]

- A clinician should also allow the patient to make a choice, provide sufficient time to ask questions, and should answer the queries in the process of obtaining informed consent for transfusion.[22]

Moreover, the WHO also defines PBM as "the transfusion of safe blood products to treat a condition leading to significant morbidity or mortality that cannot be prevented or managed effectively by other means."[7]

Before indicating blood transfusion, the clinician should:

- **Carefully consider the decision on whether transfusion is required by taking into account the full range of available therapies.**
- **Be prescribed only when it is likely to offer a worthwhile benefit or that the risk of not transfusing is likely to be greater than the risk of transfusing.**
- **Allow the patient to make a choice between blood transfusion or non-transfusion interventions such as oral or IV iron.**

Non-transfusion interventions to reduce transfusion requirements[24]

Postoperative anemia, which may be present in up to 90% of patients undergoing major surgery, is mainly caused by perioperative blood loss. Iron deficiency, being the leading cause of perioperative anemia, is a frequent condition among surgical patients, and has been linked to increased postoperative morbidity and mortality, and decreased quality of life.

The greatest number of allogeneic blood transfusion (ABT) occurs at the time of abdominal radical hysterectomy in gynecological practice. Surgical blood loss in patients prompts the need of ABT. Therefore, preoperative correction of anemia emerges as a possible alternative to ABT, as many of these patients presented with IDA or ID, due to chronic blood loss.

Evidence has shown that use of preoperative IV iron (iron sucrose or ferric carboxymaltose) in patients with IDA or ID undergoing abdominal hysterectomy led to higher Hb levels both immediately before surgery and after discharge, which prevented the need of ABT. Therefore, rapid recovery of Hb levels makes IV iron a safe, effective option for treating perioperative anemia in patients undergoing gynecological surgery. This also is useful to correct persistent fatigue which is the most common complaint of patients following hysterectomy.

Perioperative IV iron therapy (iron sucrose or FCM) is an effective and safe alternative to blood transfusion for treating perioperative anemia in patients undergoing gynecological surgery.

Recommendations for blood transfusion

The National Blood Authority (NBA) has put forth the following recommendations for red blood cell transfusion in the management of maternity and non-maternity patients.[22]

Recommendations for red blood cell transfusion in maternity and non-maternity patients[22]

- Close monitoring of all women, and early recognition and rapid response, are critical, as major blood loss can occur rapidly in the absence of hemodynamic compromise around the time of giving birth.
- In maternity patients who are not actively bleeding, Hb concentration alone should not be considered too dictate RBC transfusion, but should also be based on assessment of the patient's clinical status (the risk of further hemorrhage).
- Most maternity patients can generally tolerate moderate degrees of anemia while medical therapies take effect.
- In maternity patients who are not actively bleeding, non-transfusion therapies, including iron, should be considered as part of the treatment of anemia.
- In maternity patients, the risk of RBC alloimmunization and potential clinical impact should be considered when balancing the risks and benefits of RBC transfusion.
- Moreover, RBC transfusion is usually considered inappropriate in patients with Hb concentration of >9 g/dL.
- In non-maternity patients, transfusion of RBC and other blood components is independently associated with increased morbidity and mortality.
- The requirement for packed red cell transfusion for severe anemia in pregnancy should be determined based on the hemodynamic status, gestational age and ongoing hemorrhage.
- In pregnant women at less than 34 weeks of gestation, blood transfusion is recommended when Hb is less than 5 g/dL irrespective of signs of cardiac failure or hypoxia. In cases of impending heart failure at less than 34 weeks with Hb between 5-7 g/dL, transfusion should be considered.
- In women at more than 34 weeks of pregnancy, blood transfusion is recommended irrespective of the signs of cardiac failure or hypoxia when Hb less than 7 g/dL. (Grade B, level 3).

Recommendations for non-transfusion interventions

A universal advice is to actively screen for anemia in pregnancy, and to treat iron deficiency anemia with iron. Iron is required for expansion of maternal red cell mass, and the red cell mass of the fetal and placental circulation during pregnancy.[22]

Recommendations for non-transfusion interventions in maternity and non-maternity patients[22]

- In maternity patients with ID without anemia, a low dose of elemental iron (e.g. 30–60 mg daily) may be considered, and may be better tolerated than higher doses.
- Parenteral iron is also recommended for pregnant women with severe anemia who are hemodynamically stable and require rapid restoration of iron stores in the second and early 3rd trimester of pregnancy.
- In maternity patients requiring iron, IV iron is preferred when oral iron is poorly tolerated (affecting compliance), or absorption is likely to be impaired.
- When IV iron is prescribed, calculation of the dose should take into consideration the iron deficit.
- In maternity patients, a therapeutic dose of 30-60 mg of ferrous iron daily should be prescribed.*
- Iron supplements of 60 mg ferrous iron daily appear sufficient to produce maximal hemoglobin response and appear to be adequate to prevent IDA in pregnant women.*
- The WHO guidelines have recommended that iron is provided to pregnant women during antenatal visits at a daily supplementation of 60 mg elemental iron, for 6 months during pregnancy and 3 months postpartum.*
- When IV iron is prescribed, calculation of the dose should take into consideration the iron deficit.
- Parenteral iron should be administered in a healthcare set up with basic facilities for resuscitation including an emergency tray to manage anaphylactic reactions. (Grade A, Level 4)

*Milman N. J Pregnancy. 2012;2012:514345. doi: 10.1155/2012/514345.

IV FCM as a first line of management in pregnant women: The Ministry of Health & Family Welfare, Anemia management protocol[25]

Anemia management protocol for pregnant women as per the Ministry of Health & Family Welfare, Government of India		
Hemoglobin is 10–10.9 g/dl (mild anemia)	**Hemoglobin is 7–9.9 g/dl (moderate anemia)**	**Hemoglobin cut-off is 5.0–6.9 g/dl (severe anemia)**
Parental iron [IV Iron sucrose or sucrose or Ferric Carboxy Maltose (FCM) may be considered as the first line of management in pregnant women who are detected to be anemic late in pregnancy or in whom compliance is likely to be low (high chance of lost to follow-up].		First dose of treatment is suggested to be done using IV Iron Sucrose/ FCM

- The Ministry of Health & Family Welfare, Government of India operational guideline, 2018, recommends IV Ferric Carboxy Maltose as a first line of management in pregnant women under different Hb levels from mild to severe anemia.

- In areas with a high prevalence of anemia in pregnancy, it is recommended that daily oral iron (30–60mg) and folic acid (400 mcg) supplementation as part of routine antenatal care to reduce the risk of maternal anemia and ID and infant low birthweight (1B).
- It is recommended that for preventing maternal anemia in pregnant women, 30 to 60 mg of elemental iron and 400 µg of folic acid is recommended.#
- Once the Hb concentration is in the normal range, it is recommended that iron supplementation be continued for at least 3months to replenish iron stores (1A)

Evidences showing the benefits of Oral and IV iron in management of ID and IDA

Oral iron therapy in maternity and non-maternity patients

Oral iron replacement therapy is the frontline of treatment for IDA.[26] The main goal of oral iron supplements is to supply sufficient iron to restore normal iron stores and replenish hemoglobin deficits.[27]

For treating ID, iron preparations are available with iron salts, complexes, and combinations. Oral iron preparations are available in both ferrous and ferric states. Ferrous sulfate, ferrous gluconate, and ferrous fumarate are the most commonly available oral preparations.[27] They are similar in regards to pharmacodynamic and pharmacokinetic properties as well as to the rate of adverse events. But the ferrous salts are associated with high rate of gastrointestinal adverse effects (35% to 59%)[28] such as constipation, nausea, and bloating. Therefore, to overcome the disadvantages of ferrous salts, iron amino acid chelate are used.[29]

Oral iron therapy supplies sufficient iron to restore normal iron stores and replenish hemoglobin deficits, are convenient for administration and are cost effective.

Iron amino acid chelate preparation

The advantages of iron amino acid chelate include:

- Amino acids are ideal, good chelators or ligands from both chemical and nutritional points of view.[29]
- Are readily absorbed.
- Body is efficient at absorbing amino acids and dipeptide.
- The chelation protects the iron from absorption inhibitors: In the gastric medium of the stomach, the chelate successfully passes the test of stability. Past duodenum, the ligands break in the alkaline medium. Near the absorption windows in small intestine, on coming in contact with the enzymes present in the mucosal lining, it then gets cleaved.[30]
- These preparations are programmed for maximum absorption on demand: A maximum absorption of 75% is observed.[30]
- Less likely to cause intestinal side effects: The ability of maximum absorptions of iron leads to minimum residue in the GI tract causing minimum gastric irritation.[30]
- As compared to inorganic sources of iron, iron amino acid chelate has been shown to have an increased bioavailability and reduced irritability.[29]

Iron amino acid chelates protects the iron from absorption inhibitors, are programmed for maximum absorption on demand and are less likely to cause gastrointestinal side effects.

Efficacy and safety in maternity patients

Iron amino acid chelate vs. iron sulfate and iron gluconate

In a study, researchers compared the efficacy and safety of iron chelated amino acid therapy (15 mg daily) vs. traditional oral iron therapy (iron sulfate and iron gluconate) in the treatment of IDA during pregnancy (n=450). The patients in iron chelated amino acid therapy group showed significantly lower incidence of nausea ($p<0.001$), vomiting ($p<0.001$), constipation ($p<0.001$), abdominal cramping ($p<0.001$), and diarrhea ($p<0.001$) vs. the other oral therapy. In the iron chelated amino acid therapy group, the rates of increase of reticulocytes, hemoglobin % and mean corpuscular hemoglobin concentration were faster ($p<0.001$ for all).[31]

In a study, researchers compared the effects of oral ferrous bisglycinate (25 mg iron/day) vs. ferrous sulfate (50 mg iron/day) in the prevention of iron deficiency and IDA in pregnant women (n=80). The result of the study revealed that with respect to hematological status and iron status, no difference was observed between the two groups. In the bisglycinate group, the frequency of gastrointestinal complaints was lower vs. sulfate group ($p=0.001$). As compared to the sulfate group, in the bisglycinate group, the weight of newborns was slightly higher (3395±426 g vs. 3601±517 g, $p=0.09$).[32]

Iron amino acid chelate vs.ferrous fumarate

In a recent study, researchers compared the efficacy and tolerability of iron amino acid chelate (15 mg of elemental iron) and ferrous fumarate in the treatment of IDA with pregnancy (n=150). After 4, 8, and 12 weeks of treatment, the rise in hemoglobin level was significantly faster in the iron amino acid chelate group vs. ferrous fumarate ($p=<0.001$). As compared to

- **In pregnant women, iron amino acid chelates are recommended as efficacious and safe oral iron therapy for the treatment of IDA.**
- **As compared to iron salts, iron amino acid chelates are associated with less gastrointestinal side effects, most effective and increases the rate of absorption of iron.**

the iron amino acid chelate group, in ferrous fumarate group, the significantly common adverse effects were constipation (p=0.022) and colicky pain (p=0.031).[33]

Efficacy in non-maternity patients

Iron amino acid chelate vs. ferrous sulfate

In a study, researchers compared the efficacy of ferrous iron (120 mg, 60 mg, or 30 mg) chelated to amino acids and ferrous sulphate (120 mg) in treating in treating IDA in adolescent (n=100). A significant increase in the ferritin level was observed from both 120 mg iron sources and the 60 mg of iron chelate. The complaint of gastric distress was reported in 9.5% of the patients in 60 mg group vs. 0% in the 30 mg group. Based on hemoglobin levels, as compared to the 120 mg doses, 30 mg of iron per day from the chelate were absorbed four times more efficiently. By increasing the treatment duration of the 30 mg dose to 6 to 8 weeks, an effect similar to that of the 60 mg/day dose could be obtained.[34]

In a study, researcher compared the safety and tolerability of an iron amino acid chelate 10% preparation in premenopausal women vs. ferrous sulfate during a 7-day period. As compared to the ferrous sulphate preparation, the iron amino acid chelate was found to have significantly lower (p<0.05) adverse effects.[35]

In another study, researchers evaluated the safety and tolerability of a novel iron multi-amino acid chelate (IMAAC) preparation in premenopausal women. The patients were administered IMAAC or ferrous sulphate as a single dose for 7-days. Between the groups, no significant difference was found in any of the hematological outcomes. As compared to IMAAC, a significantly (p=.044) higher number of patients reported adverse events when taking the ferrous sulfate supplement. Subjects in IMAAC group reported a significantly lower number of adverse effects (p=.008).[36]

- **In non-maternity patients, iron amino acid chelates 30 mg can be recommended, since it is efficacious and safe oral iron therapy for the treatment of IDA.**
- **Iron amino acid chelates has comparable efficacy and lower side effect vs. ferrous sulphate**

Dosing

- **In pregnant women and menstruating adult women and adolescent girls (non-pregnant females in the reproductive age of group, in setting where the prevalence of anemia is 40% or higher) daily oral iron therapy with 30 mg to 60 mg of elemental iron is recommended (WHO recommendation)**

Guidelines for iron supplementation to pregnant women		
Prevalence of anemia in pregnancy	**Dose**	**Duration**
<40%	60 mg iron + 400 µg folic acid daily	6 months in pregnancy
≥40%	60 mg iron + 400 µg folic acid daily	6 months in pregnancy, and continuing to 3 months postpartum
INACG: International Nutritional Anemia Consultative Group		

Injectable iron therapy with ferric carboxymaltose

IV iron administration is usually recommended for IDA treatment under following conditions patients:[37]

- Pre-existing anemia (moderate to severe)
- Refusal of blood transfusion

- Limited time until delivery or planned operation
- Coexisting risks (eg, placenta praevia, Jehovah's witness)
- Pre-, postoperative phase

- **It is recommended that the administration of intravenous (IV) iron be considered in women with severe IDA (Hb<8 g/dL) or newly diagnosed IDA beyond 34 weeks of gestation (1B).**
- **It is recommended that the administration of IV iron be considered in women with confirmed IDA who fail to respond to the correct administration of oral iron (Hb concentration increase <10 or 20 g L–1 in 2 or 4 weeks, respectively) or are intolerant to oral iron treatment, if the gestational age is >14weeks (1B).**
- **For anemia treatment, IV iron is recommended for moderate to severe pre-existing anemia, missing compliance with oral iron, to overcome the side effects associated with oral iron and in case of refusal for blood transfusion.**

Ferric carboxymaltose (FCM) as parenteral iron[28]

- FCM is a new parenteral dextran-free iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell.
- The design of the complex allows controlled delivery of iron to the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins, ferritin and transferrin, with minimal risk of releasing large amounts of ionic iron into the serum. It is found to have a better safety profiles than the more traditional IV preparations.
- As FCM are non-dextran-containing, the risk of anaphylactic reactions is low.
- It can be administered in large doses (up to 1000 mg/infusion) in a single and rapid (15-minute) infusion without the requirement of a test dose.

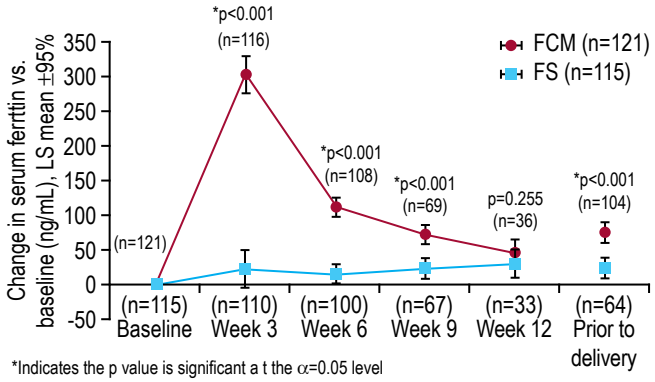
- **The design of FCM allows controlled delivery of iron to the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins, ferritin and transferrin, with minimal risk of releasing large amounts of ionic iron into the serum.**
- **A high dose of FCM is safe and can be administered in a short time frame (15 min), rapidly replenishing iron stores.**

Efficacy in maternity patients

IV FCM vs. Oral ferrous sulphate

In a recent study, researchers performed a post-hoc subgroup analysis in pregnant women with IDA, who participated in the Phase III FERASAP (FCM-Assessment of SAfety and efficacy in Pregnancy) study to compare the efficacy and safety of ferric carboxymaltose (FCM) (n=46, 1000–1500 mg iron) with oral ferrous sulfate (n=44; 200 mg iron/day). Throughout the study period, significantly higher increases in serum ferritin at each visit (vs. baseline) were observed for FCM vs. ferrous sulphate treatment (Figure 7). Prior to delivery,

Figure 7. Changes from baseline over time in a serum ferritin.[38]



*Indicates the p value is significant a t the α=0.05 level

pregnant women treated with FCM achieved significant clinically relevant improvements in all three 36-item short-form questionnaires (mental, physical, and vitality) vs. ferrous sulphate group. The total incidences of treatment-emergent adverse events (TEAEs) were similar in both groups (FCM (n=27): 83; FS (n=28):70).[38]

In a recent study, researchers compared the efficacy and safety of IV FCM (1000-1500 mg iron) with first-line oral ferrous sulfate (200 mg iron/day) in pregnant women with IDA for 12-weeks. In FCM group, a significantly more women achieved anemia correction vs. ferrous sulphate [hemoglobin≥11.0 g/dL; 84% vs.70%; odds ratio (OR): 2.06, 95% confidence interval (CI): 1.07, 3.97; p=0.031] and within shorter duration of time median (3.4 vs. 4.3 weeks). A markedly higher rates of gastrointestinal disorders reported with ferrous sulphate (16 women) vs. FCM (3 women).[32,39]

IV FCM in pregnant women with mild, moderate and severe anemia in the 2nd and 3rd trimester

In another study, Froessler et al, assessed the safety and efficacy of IDA correction with IV FCM in pregnant women with mild, moderate and severe anemia (n=65) in the second and third trimester. In all the women, IV FCM infusion significantly increased hemoglobin values (p<0.01) above baseline levels. Post-infusion, there was a significant increase in hemoglobin levels from 3 to 6 weeks (average increase 12 g/dl; p<0.01) and up to 8-weeks. After the infusion, a significant improvement was observed in the ferritin levels (Table 2). No drug related negative impact on the fetus was observed. After receiving infusion, no serious adverse effects were recorded in any of the women. Feeling of wellbeing was reported in 65.5% of the women.[40]

Table 2. Ferritin levels (µg/L) across the testing period for women in the study[40]

	Booking	Pre infusion	Post infusion
Ferritin µg/L	13.5 (13) n = 47	6.5 (3.9) n = 25	194 (316)* n = 24

Data are presented as means (SD). *p < 0.05 compared to pre-infusion levels.

In a retrospective study conducted by Pel et al, the safety and efficacy of IV FCM (1000 mg) was assessed in pregnant women (n=64). At the time of delivery, the median hemoglobin increased from 8.4 g/dL (interquartile range 7.7; 8.9 g/dL) (at the first FCM administration) to 10.7 g/dL (9.8; 11.5 g/dL; n=46), the level were comparable to control group (n=64) (nonanemic or had anemia but were not considered for IV iron) (10.8 g/dL [9.8; 11.8 g/dL; n = 48]). Between the two groups, no treatment-related adverse events or statistically significant differences in pregnancy outcomes were observed.[41]

IV FCM vs. IV iron sucrose in pregnant women with IDA

In another study, assess side effects and tolerance of IV FCM compared to IV iron sucrose in pregnant women with IDA. In both groups, the incidence of drug-related adverse events was low and mostly mild. Mild adverse events were reported in 7.8% of the patients in FCM group vs.10.7% in iron sucrose group. The mean rise of hemoglobin value was 15.4 g/L for FCM vs. 11.7 g/L for iron sucrose.[42]

Expert opinion

- **IV iron preparations are usually recommended in women with severe IDA (hemoglobin <9.0g/dL), or intolerability to oral iron, or insufficient hemoglobin increase after oral iron treatment.**
- **IV ferric carboxymaltose is recommended as safe and efficacious for treatment of IDA in pregnant women.**

Efficacy in non-maternity women

IV FCM vs. oral iron sulfate in abnormal uterine bleeding

In a study, Vanwyck DB et al. evaluated the efficacy and safety of rapid, large-dose IV administration of FCM vs. oral iron in correcting iron deficiency anemia due to

heavy uterine bleeding. Patients were administered IV FCM (≤1000 mg over 15 min, repeated weekly to achieve a total calculated replacement dose) or ferrous sulfate (65 mg elemental iron) prescribed orally thrice daily for 6 weeks. As compared to ferrous sulfate group, more patients in the FCM group responded with a hemoglobin increase of 2.0 g/dL or more (62% vs. 82%, 95% confidence interval fortreatment difference 12.2-28.3, p<0.001), more achieved a 3.0 g/dL or more increase (36% vs. 53%, p<0.001), and more achieved correction (Hb ≥12 g/ dL) of anemia (50% vs.73%, p<0.001).[43]

IV FCM vs. oral iron in postpartum anemia

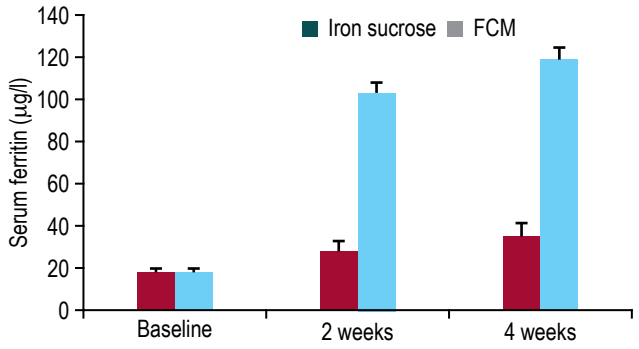
In a study, researchers compared the efficacy of rapid, large-dose IV administration of FCM (≤1000 mg over 15 minutes) vs. oral iron therapy (325 mg orally thrice daily for 6-weeks) in anemic postpartum women. As compared to the oral iron group, patients in the FCM group achieved a hemoglobin rise ≥2.0 g/dL earlier (14 vs.7 days p<0.001) and were more likely to achieve a hemoglobin rise ≥3.0 g/dL at any time (60.4% vs. 86.3%, p<0.001). They were more likely to achieve a hemoglobin >12.0 g/dL (68.6% vs. 90.5%, p<0.001). In both the groups, a similar proportion of patients achieved a hemoglobin rise ≥2.0 g/dL. No serious adverse drug reactions were reported.[44]

IV FCM in premenopausal women with ID and IDA

In a study, researchers evaluated the efficacy and tolerability of single-dose IV FCM (1000 mg iron) vs. placebo in iron-deficient, premenopausal women with symptomatic, unexplained fatigue. A reduction in fatigue was observed in 65.3% (FCM) and 52.7% (placebo) of patients (OR 1.68, 95% CI 1.05–2.70; p = 0.03). As compared to the placebo-treated patients, a 50% reduction of piper fatigue scale (PFS) score was achieved in 33.3% FCM vs. 16.4% placebo-treated patients (p<0.001). All FCM-treated patients, at Day 56, had hemoglobin levels ≥120 g/L (vs. 87% at baseline). While with placebo, the proportion decreased from 86% to 81%. The FCM group had a better improvement in mental quality-of-life (SF-12) and the cognitive function scores. Treatment-emergent adverse events were mainly mild or moderate.[45]

In a recent study, Naqash et al compared the effectiveness and safety of IV FCM to iron sucrose in women 18 years or older with IDA. As compared to iron sucrose group, at 4-week, a significantly higher laboratory values (hemoglobin, mean Corpuscular Volume, serum iron, serum ferritin (Figure 8), total iron binding capacity, and transferrin saturation% levels) was observed in FCM group vs. iron sucrose group (p<0.0001 for all comparisons).[46]

Figure 8. Comparison of serum ferritin (µg/L) levels before and after iron sucrose and FCM therapy.[46]



IV FCM vs. standard medical care

In another recent study, compared safety and efficacy of single dose IV FCM (maximum 1000 mg) (n=996) vs. standard medical care (SMC) (n=1022) for IDA in postpartum women and women with heavy menstrual bleeding. As compared to the SMC group, the increase in mean hemoglobin was greater in the FCM group vs. SMC group. At least 1 serious adverse event (AE) was reported by 0.6% patients in FCM group and by 2.2% in SMC group.[47]

IV FCM is recommended as safe and efficacious for treatment of anemia in abnormal uterine bleeding, post-partum anemia, and explained fatigue in iron-deficient women.

Dosing

The recommended dose of IV FCM in pregnant and non-pregnant women is 1000 mg.

FCM administration and dosage

FCM can be administered by the intravenous route:

- By injection or by infusion or during a hemodialysis session undiluted directly into the venous limb of the dialyzer.

As IV injection	As IV infusion
IV injection using undiluted solution.	IV infusion and it must be diluted with sterile 0.9% m/V sodium chloride solution as shown in Table 2.
The maximum single dose is 15 mg iron/kg body weight but should not exceed 1,000 mg iron.	The maximum single dose is 20 mg iron/kg body weight, but should not exceed 1,000 mg iron.
The administration rates are as shown in Table 1.	

Table 1. Administration rates for intravenous injection of FCM

Volume of Ferinject required			Equivalent iron dose			Administration rate/Minimum administration time
2	to	4 mL	100	to	200 mg	No minimal prescribed time
>4	to	10 mL	>200	to	500 mg	100 mg iron / min
>10	to	20 mL	>500	to	1,000 mg	15 minutes

Table 2. Dilution plan of FCM for intravenous infusion

Volume of Ferinject required			Equivalent iron dose			Maximum amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
2	to	4 mL	100	to	200 mg	50 mL	-
>4	to	10 mL	>200	to	500 mg	100 mL	6 minutes
>10	to	20 mL	>500	to	1,000 mg	250 mL	15 minutes

Efficacy and safety of FCM originator vs. FCM similars (FCMS)

In a study, researchers compared the efficacy and safety of FCM vs. FCMS (5 weekly IV doses of 40 mg iron/kg body weight for both). The study revealed that:[48]

Efficacy

- Ferritin immunostaining in liver was significantly higher in FCM vs. FCMS group (Figure 3). This pattern of ferritin deposit (iron storage), which were far higher in the FCM group than with FCMS, indicated appropriate deposition in the RES (Kupffer) cells, where oxidative damage is less likely.
- Whereas for FCMS, despite the same dose of IV iron, less deposition of storage iron (ferritin) was observed, and ferritin was detected in non-RES hepatocytes within the liver.

Safety

- As compared to FCM, FCMS-treated group had significantly lower blood pressure, higher liver enzymes, increased proteinuria, and reduced creatinine clearance.
- After FCMS administration, markers for lipid peroxidation and antioxidant-enzyme activity were significantly increased vs.FCM.

Another study by Toblli showed that FCMS had a less favorable safety profile than iron sucrose originator (comparable to FCM originator), adversely affecting iron deposition, oxidative and nitrosative stress, inflammatory responses, with impaired liver and kidney function.

- Moreover, compared to the iron sucrose originator, the FCMS resulted in deranged iron distribution as indicated by increased serum iron, transferrin saturation and tissue iron (III) deposits as well as decreased ferritin deposits in the liver, heart, and kidneys.[49]
- FCMS-treatment led to unfavourable distribution of iron within the tissues. This suggests that iron from FCMS is able to bypass the regulated pathway through resident macrophages of the bone marrow, liver, and spleen.
- The higher TSAT values with FCMS may indicate the formation of larger amounts of non-transferrin-bound iron (NTBI), which may be taken up uncontrolled by the liver, heart, and kidneys tissues. This indicates iron-induced toxicity by FCMS, which is often linked to its suboptimal distribution and accumulation to non-hematopoietic tissues.[49]

- **FCM treatment is associated with higher ferritin levels in liver vs. with FCMS.**
- **FCMS caused an inappropriate deposition of iron and saturation of the physiological pathways for iron transport and storage, thereby increasing oxidative stress and inflammation. FCMS led to liver, heart, and renal toxicity, with adverse effects on blood pressure and liver and kidney function vs. FCM.**

SUMMARY OF RECOMMENDATIONS

- ID is defined as the decrease of the total content of iron in the body. ID may be the result of either excessive loss or, less frequently, decreased absorption.
- IDA occurs when ID is sufficiently severe due to excessive loss of iron or decreased iron absorption, which decreases plasma iron, ultimately limiting or reducing erythropoiesis.

- A high prevalence of anemia is reported among women in India; 53%, as per the latest published National Family Health Survey-4, 2015–2016.
- In India, the estimated maternal deaths due to IDA is approximately 3,26,000, with an associated disability-adjusted life years (DALYs) of 12,497,000.

- According to WHO report, about 32.4 million pregnant women suffer from anemia worldwide, of which 0.8 million women are severely anemic.
- Anemic women are at a higher risk of preterm birth; LBW; and low Apgar score as compared to non-anemic women.
- Causes of ID during pregnancy
- Physiological anemia owing to haemodilution
- Insufficient iron stores fail to meet the increasing demands of pregnancy
- Neglected nutritional deficiencies, infections, and hemoglobinopathies
- Consequences
- Increased maternal mortality and morbidity
- Perinatal morbidity and mortality - an increased risk of premature delivery fetal growth restriction and increased susceptibility to neonatal infections
- Infant & long term: Affects growth and development of the fetus in utero and of the newborn child in the long term during infancy

- A delicate balance of iron has to be maintained in the body. Only 1–2 mg of iron is absorbed from diet. Excess of iron is stored in the bone marrow and liver. Breakdown of RBCs by macrophages provides the iron required for erythropoiesis. A variable component of iron is also lost in blood through menstrual loss, blood donation, nose bleeds, and gastrointestinal bleeding.

SUMMARY OF RECOMMENDATIONS

- The absorption of dietary heme iron is more efficient and is highly bioavailable than non-heme iron. Ferritin proteins are absorbed intact, contributing to the acquisition of non-heme iron.
- The absorbed iron is either stored intracellularly as ferritin or transported across the basolateral membrane of the enterocyte. Ferritin can sequester up to 4500 atoms of iron per molecule as ferrihydrite, thus restricting the availability of intracellular free iron.
- Iron binds to transferrin (Tf), the high binding affinity makes Tf 25%–30% saturated under physiological conditions in healthy humans, so there is negligible non-transferrin-bound iron in the plasma.
- Holo-Tf (transferrin with iron) binds to the transferrin receptors on the membrane of target cells, and acidification of which leads to dissociation of iron into the cytosol.
- Hepcidin is synthesized in the liver and secreted into the circulation. It is a key hormone regulator of iron homeostasis involved in causing anemia.
- Hepcidin controls iron release into the plasma during normal iron homeostasis.
- During inflammation, hepcidin is increased which degrades ferroportin and blocks the iron flow into the plasma, thereby limiting erythropoiesis, and ultimately causing iron deficiency.
- Iron supplements at doses of 60 mg Fe as $FeSO_4$ or higher increases hepcidin for up to 24 hours and are associated with lower iron absorption from the second dose on the following day.
- The soluble transferrin receptor/ferritin ratio and hepcidin are equivalent predictors of iron absorption from supplements.
- In pregnant women, the WHO and the Centers for Disease Control and Prevention (CDC) recommend 30 to 60 mg Fe per day.*
- The WHO recommends 30 to 60 mg of elemental iron and 400 µg of folic acid for pregnant women to prevent maternal anemia.#
- The CDC recommends that all pregnant women should take a 30 mg/day iron supplement, unless they have hemochromatosis.@
- Identification of ID is suggested before the occurrence of IDA, so that timely treatment can be offered and IDA can be prevented.

SUMMARY OF RECOMMENDATIONS

- We recommend that a full blood count (FBC) be obtained to screen for anemia at booking and at 28 weeks, as well as at any time during pregnancy if symptoms of anemia are present (1A).
- In a woman with microcytic or normocytic anemia, ID should be confirmed by a trial of oral iron (unless she is known to have a hemoglobinopathy) or a serum ferritin measurement (1B).
- In the absence of an hemoglobin (Hb) increment in response to a trial of oral iron conducted correctly, it is recommended to further evaluate iron status by checking serum ferritin and considering whether additional laboratory testing is needed (1C).
- In anemic women of Indian origin, it is recommended to confirm the presence or absence of a hemoglobinopathy either by selective (based on a family of origin questionnaire) or universal screening for hemoglobinopathies.
- Anemic women with a known hemoglobinopathy should have their serum ferritin checked and should only be offered oral iron therapy if their serum ferritin level is <30 $ngmL^{-1}$ (1B)
- Serum ferritin is the most sensitive and preferred initial diagnostic test. Iron stores in the body exist primarily in the form of ferritin.
- Mild ID can be diagnosed by fall in serum ferritin levels. High serum ferritin concentrations indicate iron overload in the absence of inflammation or liver disease.
- Ferritin measurements and corresponding cut-offs facilitate an indicator of the size of iron stores, reflects the iron status, and responds to iron interventions.
- Serum sTfR is a useful marker of ID; it is not an acute phase reactant like ferritin so it is not affected by inflammation and it increases with ID before the manifestation of IDA. sTfR-ferritin index are valuable in identifying ID before IDA, particularly where inflammation may coexist.
- The goal of PBM focuses in improving and conserving the patient's own blood, wherein transfusions can be avoided or reduced to prevent related-complications.
- Blood transfusions may not always be necessary and that tolerance to anemia has shown to be higher than often believed.

SUMMARY OF RECOMMENDATIONS

- Alternative management strategies such as use of IV iron along with ESAs have shown to be beneficial in managing patients in the operating rooms.

- Conservative management with IV iron without transfusion can be considered as an effective and a feasible option for women with profound anemia having hemoglobin levels as low as <5 g/dL.
- Before indicating blood transfusion, the clinician should:
  - » Carefully consider the decision on whether transfusion is required by taking into account the full range of available therapies.
  - » Be prescribed only when it is likely to offer a worthwhile benefit or that the risk of not transfusing is likely to be greater than the risk of transfusing.
  - » Allow the patient to make a choice between blood transfusion or non-transfusion interventions such as oral or IV iron.

- In maternity patients who are not actively bleeding, non-transfusion therapies, including iron, should be considered as part of the treatment of anemia.
- In maternity patients, the risk of RBC alloimmunization and potential clinical impact should be considered when balancing the risks and benefits of RBC transfusion.
- Moreover, RBC transfusion is usually considered inappropriate in patients with Hb concentration of >9 g/dL.
- The requirement for packed red cell transfusion for severe anemia in pregnancy should be determined based on the hemodynamic status, gestational age, and ongoing hemorrhage.
- In pregnant women at less than 34 weeks of gestation, blood transfusion is recommended when Hb is less than 5 g/dL irrespective of signs of cardiac failure or hypoxia. In cases of impending heart failure at less than 34 weeks with Hb between 5-7 g/dL, transfusion should be considered.
- In women at more than 34 weeks of pregnancy, blood transfusion is recommended irrespective of the signs of cardiac failure or hypoxia when Hb less than 7 g/dL. (Grade B, level 3)

SUMMARY OF RECOMMENDATIONS

- In maternity patients with ID without anemia, a low dose of elemental iron (30–60 mg daily) may be considered, and may be better tolerated than higher doses.
- Parenteral iron is also recommended for pregnant women with severe anemia who are hemodynamically stable and require rapid restoration of iron stores in the second and early 3rd trimester of pregnancy.
- In maternity patients requiring iron, IV iron is preferred when oral iron is poorly tolerated (affecting compliance), or absorption is likely to be impaired.
- In maternity patients with IDA, if the response to oral iron is inadequate, IV iron should be used.
- In maternity patients, a therapeutic dose of 30–60 mg of ferrous iron daily should be prescribed.*
- Iron supplements of 60 mg ferrous iron daily appear sufficient to produce maximal hemoglobin response and appear to be adequate to prevent IDA in pregnant women.*
- The WHO guidelines have recommended that iron is provided to pregnant women during antenatal visits for daily supplementation of 60 mg elemental iron, for 6 months during pregnancy and 3 months postpartum.*
- When IV iron is prescribed, calculation of the dose should take into consideration the iron deficit.
- Parenteral iron should be administered in a healthcare set up with basic facilities for resuscitation including an emergency tray to manage anaphylactic reactions. (Grade A, Level 4)

- The Ministry of Health & Family Welfare, 2018, recommends IV FCM as a first line of management in pregnant women under different Hb levels ranging from mild to severe anemia.

- In areas with a high prevalence of anemia in pregnancy, it is recommended that daily oral iron (30–60mg) and folic acid (400 µgg) supplementation as part of routine antenatal care to reduce the risk of maternal anemia and ID and infant low birthweight (1B).
- It is recommended that for preventing maternal anemia in pregnant women, 30 to 60 mg of elemental iron and 400 µg of folic acid is recommended.#

SUMMARY OF RECOMMENDATIONS

- Once the Hb concentration is in the normal range, it is recommended that iron supplementation be continued for at least 3 months to replenish iron stores (1A)
- Iron amino acid chelates protects the iron from absorption inhibitors, are programmed for maximum absorption on demand and are less likely to cause gastrointestinal side effects.
- In non-maternity patients, iron amino acid chelates 30 mg can be recommended, since it is efficacious and safe oral iron therapy for the treatment of IDA.

- It is recommended that the administration of intravenous (IV) iron be considered in women with severe IDA (Hb<8 g/dL) or newly diagnosed IDA beyond 34 weeks of gestation (1B).
- It is recommended that the administration of IV iron be considered in women with confirmed IDA who fail to respond to the correct administration of oral iron (Hb concentration increase <10 or 20 g L^{-1} in 2 or 4 weeks, respectively) or are intolerant to oral iron treatment, if the gestational age is >14 weeks (1B).
- For anemia treatment, IV iron is recommended for moderate to severe pre-existing anemia, missing compliance with oral iron, to overcome the side effects associated with oral iron and in case of refusal for blood transfusion.

- The design of FCM allows controlled delivery of iron to the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins, ferritin and transferrin, with minimal risk of releasing large amounts of ionic iron into the serum.
- A high dose of FCM is safe and can be administered in a short time frame (15 min), rapidly replenishing iron stores.
- The recommended dose of IV FCM in pregnant and non-pregnant women is 1000 mg.

- FCM treatment is associated with higher ferritin levels in liver vs. with FCMS.
- FCM similars caused an inappropriate deposition of iron and saturation of the physiological pathways for iron transport and storage, thereby increasing oxidative stress and inflammation. FCMS led to liver, heart, and renal toxicity, with adverse effects on blood pressure and liver and kidney function vs. FCM.

Management of anemia with Ferric carboxymaltose (FCM) or Oral iron amino acid chelates		
	Iron formulation	**Dose**
In women with confirmed IDA who fail to respond or intolerant to oral iron, gestational age is >14weeks	IV iron recommended	
In women with severe IDA (Hb <8 g/dL) or newly diagnosed IDA beyond 34 weeks of gestation	IV iron recommended	
In pregnant women based on hemoglobin levels		
10–10.9 g/dl (mild anemia)	IV FCM as a first line of management	
7–9.9 g/dl (moderate anemia)		
5.0–6.9 g/dl (severe anemia)	First dose of treatment to be done with IV FCM	
In non-maternity patients	Oral iron amino acid chelates	30 mg
In areas with a high prevalence of anemia in pregnancy and to reduce the risk of maternal anemia and ID and infant low birthweight	Oral iron	Daily oral iron (30–60mg) and folic acid (400 µg) supplementation
In abnormal uterine bleeding, post-partum anemia, and explained fatigue in iron-deficient women	IV FCM	Single dose IV FCM (maximum 1000 mg)
In pregnant and non-pregnant women	IV FCM	1000 mg
WHO recommends	30 to 60 mg of elemental iron and 400 µg of folic acid for pregnant women to prevent maternal anemia	
CDC recommends	30 mg/day iron supplement in all pregnant women	

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CALCIUM IN WOMEN'S HEALTH

RECOMMENDATIONS FOR PRACTICE

FOGSI President	: Dr. Nandita Palshetkar
Moderators	: Dr. Hrishikesh Pai, Dr. Ameya Purandare
Panelists	: Dr. Dilip Walke, Dr. Basab Mukherjee, Dr. Priti Kumar, Dr. Shantha Kumari, Dr. Sheetal Sawankar, Dr. Rajendra Nagarkatti, Dr. Kawita Bapat, Dr. Aruna Suman, Dr. Archana Singh, Dr. Archana Verma

Calcium in women

Calcium is an important mineral component of diet and is the most abundant mineral in the human body. About 90% of the body calcium is distributed in the skeleton, while the rest 1% is found in the teeth and soft tissues (extra skeletal).[1] Calcium levels affecting extracellular and intracellular processes include neural transmission, membrane stability, bone structure, blood coagulation, muscle movement, and intracellular signalling.[2]

- Calcium salts provide rigidity to the skeleton and calcium ions play a role in several metabolic processes.[2]
- Other important functions of calcium include neuromuscular excitation, muscle contraction, membrane permeability, blood clotting and others.[3]
- Additional calcium is required during growth for skeletal development and during lactation for calcium in milk secreted.[4]

Calcium is absorbed in the proximal small intestine, both through an active intracellular vitamin D dependent pathway (especially when intake is low) and through a non-vitamin D dependent paracellular pathway (especially when calcium intake is high). About 35% of dietary intake is absorbed at an intake of about 400 mg per day. Absorption is dependent on vitamin D sufficiency, presence of calcium binders in diet (phosphate, oxalate, and phytate), and age group and physiological state.[1]

The clinical implication of dietary calcium deficiency are:[1]

- Calcium deficiency rickets in childhood and inadequate bone mass accrual
- Metabolic bone disease of prematurity
- Inadequate fetal bone mass accrual/other metabolic effects and programming
- Possible secondary vitamin D deficiency
- Post-menopausal osteoporosis

Adequate calcium and vitamin D levels are important in women's health to prevent osteoporosis and other conditions such as preeclampsia during pregnancy

Causes of calcium deficiency[5]

- Diet poor in calcium
- Vitamin D deficiency
- Few antibiotics (interact with calcium absorption)
- High intake of sodium, caffeine, and protein
- Stress and immobilization

Calcium deficiency in pregnant and lactating women can affect:[6]

- Pregnancy outcomes (high rates of eclampsia)
- Lactational performance
- Child growth (rickets, growth retardation, reduced bone mineral content)
- Maternal health (osteoporosis, fracture)

The main resource of calcium is diet. An inadequate intake of dietary calcium has both short-term and long-term effects. Hence, supplementation of calcium is emphasized.

Calcium supplementation is indicated for individuals with osteopenia or osteoporosis, pregnant women, perimenopausal and postmenopausal women, mothers who breastfeed multiple infants, vegans, amenorrheic women, residents of long-term care facilities, lactose intolerant patients and for patients on chronic corticosteroid therapy.

Calcium supplementation is indicated for individuals with osteopenia or osteoporosis, pregnant women, mothers who breastfeed, perimenopausal and postmenopausal women, vegans, and adolescents.

Calcium should be given in divided doses. In clinical practice, to obtain optimal clinical outcomes related to calcium supplementation, the dose of calcium should not exceed 500 mg at one time.[7]

Calcium should be given in divided doses. In clinical practice, to obtain optimal clinical outcomes related to calcium supplementation, the dose of calcium should not exceed 500 mg at one time.[7]

Calcium measurement

Laboratories report total serum calcium concentrations and the normal range is 8.5–10.5 mg/dL (2.12 to 2.62 mmol/L). The ionized calcium (Ca) must be determined before concluding a 'true' case of hypocalcemia.

For pregnant mothers, changes in the serum chemistries and calciotropic hormones can easily be mistaken as a disorder of calcium. During pregnancy, hemodilution causes the serum albumin and hemoglobin to decrease while the albumin remains low until birth. This fall in albumin causes the total serum calcium to fall to levels normally associated with symptomatic hypocalcemia. During pregnancy, serum phosphate and magnesium levels remain normal while the ionized calcium remains constant during gestation and this shows that the fall in total calcium is due to pregnancy.[2]

Calcium deficiency in adolescents and women of reproductive age

Calcium needs are elevated as a result of the intensive bone and muscular development and thus adequate calcium intake during growth is extremely important to reach the optimum peak bone mass and to protect against osteoporosis in the adult age. Most children and adolescents worldwide fail to achieve the recommended calcium intake. The hormonal changes associated with the pubertal period promote greater mineral utilization, which needs to be satisfied with suitable calcium consumption. Diet, therefore, must contribute nutrients in sufficient quality and quantity to allow maximum bone mass development.[9]

Calcium need is increased in adolescents due to intensive bone, muscular development, growth and hormonal changes. Most children and adolescents worldwide fail to achieve the recommended calcium intake.

It has been reported that 76% children and 80% adolescents did not meet the RDA for calcium.[10] The mean calcium intake was 57% of the RDA in children and 53% in adolescents. Dietary calcium intake has reduced over the past several decades in the adolescents and an inadequate serum vitamin D levels have also been reported in up 54% of this population. Calcium and vitamin D are crucial for bone mineral accrual and cellular calcium concentration.[11]

Calcium deficiency in pregnancy and lactation

During pregnancy, 25–30 grams of calcium are transferred to the fetus via active transport. Most of this transfer occurs in the 2nd and 3rd trimester when mineralization of the fetal skeleton occurs. Increased absorption in the gut allows this transfer while relatively preserving the maternal skeleton. This increased absorption is balanced not only by the fetal transfer but also by increased urinary excretion.[9]

Dietary calcium intake has reduced over the past several decades in the adolescents and an inadequate serum vitamin D levels have also been reported in up 54% of this population.

Vitamin D and its metabolites play an important role in calcium homeostasis and bone metabolism. Vitamin D is the only vitamin that can be derived in humans as well as ingested. In healthy adults, vitamin D levels are maintained by appropriate dietary intake.

During pregnancy, 25–30 grams of calcium are transferred to the fetus via active transport. Most of this transfer occurs in the 2nd and 3rd trimester when mineralization of the fetal skeleton occurs.

To accommodate the increased calcium demands of pregnancy, fractional calcium absorption in adult women increases significantly during the 3rd trimester of pregnancy compared with pre-pregnancy or postpartum values. The additional calcium demands of pregnancy may affect bone mass over the course of pregnancy. Longitudinal bone density studies in adult women typically report bone mineral density (BMD) losses of 3.2%–4.6% at trabecular sites over the 9 months course of pregnancy compared with pre-pregnancy values.[12]

- **In general, RCOG and NICE guidelines recommends vitamin D 400 units/day for all pregnant women**
- **Women at high risk of pre-eclampsia are advised to take at least 800 units a day of Vitamin D combined with calcium as per RCOG.**

Calcium deficiency in peri/post -menopausal women

Calcium requirements for skeletal maintenance fluctuate throughout a woman's life. Calcium requirements remain stable until menopause, when the bone resorption rate increases in association with the decrease in ovarian estrogen production.

- **Calcium requirements for skeletal maintenance fluctuate throughout a woman's life.**
- **During the teen years, calcium requirements are high because of the demands of a rapidly growing skeleton.**
- **After the teens, less calcium is required for bone health as bone turnover stabilizes and peak adult bone mass is achieved.**
- **Calcium requirements remain stable until menopause, when the bone resorption rate increases in association with the decrease in ovarian estrogen production.**

Calcium needs rise at that time because of decreased efficiency in the utilization of dietary calcium, which is due, in large part, to estrogen related shifts in intestinal calcium absorption and renal conservation.

The daily intake of calcium recommended by ICMR, Table 1:[4]

Table 1. Daily intake of calcium as recommended by ICMR

Group		Calcium (mg/d)
Adult women		600
Pregnancy		1200
Lactation		1200
Post-menopausal women		800
Infants		500
Children	1–3 years	600
	4- 6 years	600
	7- 9 years	600
	10-12 years (Girls)	800
	13-15 years (Girls)	800
	16–18 years (Girls)	800

Table 2. Recommended daily elemental calcium intake for peri- and postmenopausal women

Institute of Medicine	
Aged 31-50	1,000 mg
Aged 51 and older	1,200 mg
National Institutes of Health	
Premenopausal women aged 25–50	1,000 mg
Postmenopausal women younger than age 65 and using estrogen therapy	1,000 mg
Postmenopausal women not using estrogen therapy	1,500 mg
All women aged 65 and older	1,500 mg
Osteoporosis Society of Canada	
Menopausal women	1,500 mg

In general, postmenopausal women have low calcium intake (median intake approximately 600 mg/day). The probability of calcium adequacy in the diet is approximately 46% for women. In specific populations of postmenopausal women at extra risk of inadequate calcium intake include women who are lactose intolerant, follow a pure vegetarian diet (vegan), or have poor eating habits. Hence, the 2005 Dietary Guidelines Advisory Committee classified calcium as a shortfall nutrient.[13]

Calcium and vitamin D supplementation in adolescents and women of reproductive age

During the teen years, calcium requirements are high because of the demands of a rapidly growing skeleton. For a woman's in her 20s, less calcium is required for bone health as bone turnover stabilizes (ie, bone formation and resorption rates become balanced) and peak adult bone mass is achieved.

Many calcium supplements are available in the market with varying calcium salt and amount of elemental calcium available, dosage strength as well as the absorption and bioavailability of the calcium in these supplements (Table 3).

Dietary sources rich in calcium are milk, cheese, curd, green leafy vegetables, spinach, fenugreek, sesame seeds, ragi, fish and nuts. Several preparations of calcium supplements are available commercially, and because of their various rates of disintegration in-vitro and dissolution characteristics, it has been suggested that calcium absorption from different preparations can vary widely.

Calcium from natural coral sources has possible better absorption, due to bioactive microporous structure. The bioavailability of coral calcium tablets has been shown to be superior as compared to non-coral calcium carbonate and calcium citrate malate.

Better absorption and assimilation of coral calcium carbonate is because of its physicochemical structure, porosity, ionizing ability and particle size.

Single calcium tablet should be taken with meals (lunch and dinner). Tablets should not be taken on empty stomach as it causes gastritis. Calcium and iron-folic acid tablets should not be taken together since calcium inhibits iron absorption. Iron- folic acid tablets

Table 3. Oral calcium salts comparison[7]		
Formulation	**% Elemental calcium (W/W)**	**Comments**
Calcium carbonate	40	• Provides the highest amount of elemental calcium • Most widely use • Well absorbed and well-tolerated specially when taken with a meal • Limited solubility and absorption in patients with high gastric pH • Formulation of choice in patients with hyperphosphatemia in chronic renal failure due to good phosphate binding ability
Calcium citrate malate	21	• Better absorption than calcium carbonate in patients with higher gastric pH. • Recommend for those on H2 blocker or PPI, those suspected with achlorhydria, inflammatory bowel disease, or absorption disorders. • Can be taken on empty stomach. • More doses necessary to get the equivalent elemental calcium compared to calcium carbonate. • Formulation of choice in patients with achlorhydria. • Calcium Citrate Malate is also recognized as a calcium source that does not increase the risk of kidney stones, and in fact it protects against stone-forming potential.
Calcium phosphates	31-38	• Low solubility compared to calcium carbonate.
Calcium acetate	25	• Formulation of choice in patients with hyperphosphatemia in chronic renal failure due to good phosphate binding ability. • Eighty percent of the elemental calcium is bound to phosphorus in the body and excreted.
Calcium gluconate	9	• Multiple doses need to be taken to get sufficient amount of elemental calcium. • More soluble than calcium citrate
Calcium lactate	13	• Multiple doses need to be taken to get sufficient amount of elemental calcium. • Similar solubility as calcium gluconate

should be taken preferably two hours later. Usually there are no side effects with 1 gm of calcium dosage. Some patients may experience mild gastritis hence calcium tablet should be taken with meals. Excessive calcium intake i.e. >3 gms daily may increase risk of urinary stone and UTI and reduce the absorption of essential micronutrients. Medications like antibiotics (doxycycline, gentamicin, and quinolones), β blockers, steroids, and antiepileptics reduces the absorption of calcium.

- **The bioavailability of Coral calcium tablets was shown to be superior as compared to non-coral calcium carbonate and calcium citrate malate**
- **Better absorption and assimilation of coral calcium carbonate is because of its physicochemical structure, porosity, ionizing ability and particle size**

Recommended daily intake of calcium in adolescents and women of reproductive age

The daily intake of calcium recommended by ICMR, Table 4:[4]

Table 4. Daily intake of calcium as recommended by ICMR	
Group	**Calcium (mg/d)**
Pregnancy	1200
Lactation	1200

Impact of tablet size of calcium on patient compliance/adherence

Tablet size has been shown to affect the swallowability and esophageal transit in adults. Smaller tablets

are considered easier to swallow and show faster esophageal transit as compared to larger tablets.[18]

Calcium and vitamin D supplementation during pregnancy and lactation

Pregnancy and lactation are stress situations for calcium and bone homeostasis in women. In fact, during the last weeks of human pregnancy, about 30 g or more of calcium is transferred to the fetus, and during a 6 month to 9 month lactation period an additional 30 g of calcium is provided via the milk to the neonate. This corresponds to a mean calcium transfer rate to the fetus of 30 to 50 mg/day during pregnancy (60 mg/per day at mid-term and 300 mg/day during last weeks) and of 200 mg/day through the milk to the neonate.[19]

Calcium is helpful in developing fetus's bones and teeth. Prudent practice is daily administration of calcium administered in divided doses of 500 mg elemental calcium per dose.[20]

Oral swallowable calcium tablets to be taken twice a day (total 1g calcium/day) starting from 14 weeks of pregnancy up to six months post-partum.

Right form of vitamin D in pregnancy and lactation

The rationale for inclusion of Vitamin D is to enhance the absorption of calcium.[21] The vitamin is available as ergocalciferol (vitamin D2); and cholecalciferol (vitamin D3 activated form). Cholecalciferol (vitamin D3) is preferred over ergocalciferol for replenishment. Supplementation with cholecalciferol appears to be more efficacious at increasing serum vitamin D concentrations than that with ergocalciferol.[22] Lactating women receiving vitamin D3 daily showed increased levels of 25(OH)D which also transferred into their milk to satisfy an infant's requirement.

Supplementing pregnant women with vitamin D in a single or continued dose increases serum 25-hydroxy vitamin D at term and may reduce the risk of pre-eclampsia, low birthweight and preterm birth. RCOG guidelines recommend vitamin D 400 units a day for all pregnant women, which is in accord with the national guidance.[23]

Recommended daily intake of calcium and vitamin D in high risk groups like pre-eclampsia/PIH

Low dietary calcium might account for the high prevalence of pre-eclampsia and eclampsia in low-income countries. Calcium supplementation in the second half of pregnancy is known to reduce the serious consequences of pre-eclampsia.[24] Clinical evidence indicate the effectiveness of calcium supplementation to treat pre-eclampsia and eclampsia. The WHO guideline on calcium supplementation in pregnant women points out a possible protective effect of calcium on the prevention of preterm birth among those women who consumed between 1.5 g and 2.0 g of calcium per day.[25]

A meta-analysis of 13 randomized controlled trials in a Cochrane systematic review found that calcium supplementation of at least 1 g daily from mid-pregnancy (20 weeks) was associated with a 55% reduction in pre-eclampsia. It also reduces preterm birth and the occurrence of the composite outcome 'maternal death or serious morbidity'.[26]

Various international evidences are available on the benefit of daily maternal calcium supplementation during pregnancy. These include the Lancet 2013 series in maternal and child nutrition, several meta-analysis, WHO 2011 and WHO 2013 guidelines and the 2014 Cochrane systematic review. A summary of these evidences is that the daily intake of at least 1 gm/day of calcium in pregnancy after the 1st trimester reduces the risk of pre-eclampsia by at least 50%, with an additional 24% reduction in the risk of pre-term birth.

For prevention of pre-eclampsia, WHO 2013 guidelines recommend inclusion of routine prenatal calcium supplementation in high doses (>1 gm/day), especially in areas where dietary calcium intake is low.[27]

Calcium supplementation of at least 1 g daily from mid-pregnancy (20 weeks) was associated with a 55% reduction in pre-eclampsia. It also reduces preterm birth and the occurrence of the composite outcome 'maternal death or serious morbidity'.

Calcium supplementation and vitamin D in peri/post-menopausal women

Osteoporosis affects nearly 200 million people and may lead to fractures that are most common in women after 55 years of age which in turn might result in substantial bone-morbidity, rising mortality and healthcare expences.[28] Numerous risk factors for osteoporosis have been reported in women such as low calcium intake, vitamin D deficiency, genetic predisposition and poor knowledge on bone health. Apart from these, age-dependent factors like early menopause and low estrogen production post menopause increases the risk in older women.[29]

Calcium supplementation along with vitamin D is being extensively endorsed to prevent osteoporosis and subsequent fractures

The National Osteoporosis Foundation through an expert panel proved that calcium plus vitamin D supplementation showed a statistically significant reduction in total and hip fractures by 15% and 30%, respectively.[30] According to ESCPG, postmenopausal women with low BMD and high-risk of fractures with osteoporosis, should be recommended calcium and vitamin D supplementation as an adjunct to osteoporosis therapies.[31] Postmenopausal women with high-risk of fracture with osteoporosis who cannot tolerate bisphosphonates, estrogen, selective estrogen response modulators, denosumab, tibolone, teriparatide and abaloparatide, should be recommended with daily calcium and vitamin D supplementation to prevent hip fractures.[31]

SUMMARY OF RECOMMENDATIONS

- Calcium supplementation is indicated for individuals with osteopenia or osteoporosis, pregnant women, mothers who breastfeed, perimenopausal and postmenopausal women, vegans, and adolescents.
- Calcium should be given in divided doses. In clinical practice, to obtain optimal clinical outcomes related to calcium supplementation, the dose of calcium should not exceed 500 mg at one time
- RDA of 1gm of elemental calcium and vitamin D 400 units per day is recommended for all pregnant and lactating women from 14 weeks of gestation upto 6 months post-delivery/ lactation.
- Adequate calcium and vitamin D levels are important in women's health to prevent osteoporosis and other conditions like preeclampsia during pregnancy. Women at high risk of pre-eclampsia are advised to take at least 800 units a day of Vitamin D combined with calcium as per RCOG.
- The recommended daily calcium intake in post-menopausal women is 1000 mg/day along with daily dose of vitamin D 400 IU/day. The requirements may be higher in older women increasing up to 1000–1200 mg of calcium per day to improve bone health and prevent fractures.

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