A Comprehensive Review of Anemia: Characterization, Challenges and Management

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ABSTRACT

Anemia, characterized by a low count of red blood cells (RBC) or lowered haemoglobin concentration in the RBCs, is one of the leading public health issues in developing countries. This review delves into different types of anemia such as Nutrition-based anemia, Hemolytic anemia, Sickle cell anemia, etc, their prevalence and associated factors with particular focus on India. Treatment for anemia includes restoration of haemoglobin concentrations to normal levels, and prevention and treatment of consequences are all cost-effective therapies for anemia. Despite significant efforts, anemia persists, warranting a deeper understanding of causes and challenges. To combat the condition, multidisciplinary programmes and policies focusing on population health and nutrition status, as well as increased education and socioeconomic level, are crucial. The article outlines various initiatives such as India's National Health Mission, emphasizing a holistic approach to combat anemia.

Keywords : *anemia, blood, diagnosis, treatment.*

1. Introduction

Anemia, characterized by a low count of red blood cells (RBC) or lowered haemoglobin concentration in the RBCs, is one of the leading public health issues in developing countries. Since haemoglobin is needed to carry oxygen, a lowered concentration or low count of RBC will decrease the capacity of blood to carry oxygen to the body's tissues. [1] The different types of anemia are Nutrition based anemia (Pernicious anemia, Iron deficiency anemia, Folate deficiency anemia, Vitamin- A deficiency anemia, etc.), Hemolytic anemia, Sickle cell anemia, Thalassemia, and Aplastic anemia. According to WHO, Iron deficiency anemia is the most common. Anemia can cause problems like weakness, dizziness, fatigue, and shortness of breath, [1] which are caused due to a range of nutritional deficiencies due to improper diet or improper absorption of nutrients, infections like parasitic infections, genetic disorders, and gynaecological and obstetric conditions.

According to WHO, 40% of children 6-59 months of age, 37% of pregnant women, and 30% of women 15-49 years of age worldwide are anemic. [1] As per recently released National Family Health Survey-V data, 52.2% of pregnant women aged 15-49 years are estimated to be anemic in India. WHO states that about 20% of the world's population of adolescents aged 10-19 belong to India. More than 100 million of these adolescents suffer from anemia. [2] Adolescence is when maximum physical, psychological, and behavioural developments occur. Suffering from anemia hinders their growth and affects their capacity to develop into healthy adults. In underprivileged sectors of society girls are more likely to suffer from this as they may be deprived of resources and their health may remain neglected. Iron deficiency in adolescent girls can result in growth retardation and physical and mental impairments. Countries around the world have taken several steps to tackle the problem of anemia. India has the most extensive universal adolescent anemia control program in the world. Even then, developing countries, including India, are faced with the challenge of populations affected with anemia. Diverse factors along with their complex interplay make it very challenging to manage anemia. [3] Some of the main factors contributing to the prevalence of anemia are malnutrition, poor sanitation, socio-economic practices, etc. It is crucial to study the causes and take proper steps at the right time to ensure good health of women. The present study draws a comparison among different types of anemia, their prevalence and age of occurrence along with the factors leading to their causes and challenges that the world faces in controlling and managing the occurrence of anemia in India in particular and the world at large.

2. Anemia : Variants

A decrease in the quantity of red blood cells (RBCs) as shown by the red cell count, hematocrit, or red cell

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Received: 31 March, 2024
Available online: 31 May, 2024

haemoglobin content is referred to as anaemia. In daily practice anemia is broadly classified based mainly on two factors- red blood cell morphology and its etiology.

2.1 Classification based on RBC Morphology

Human erythrocytes are biconcave, 7-8 µm in diameter, with a central pale area occupying one-third of their diameter. Any variations in size, shape, colour, or distribution suggest disease processes. Anemia is classified based on red cell diameters, which can be microcytic, normocytic, or macrocytic. Variation in red blood cell colour also helps differentiate haemoglobin content. In iron deficiency situations, microcytosis is often followed by hypochromia, while increased hemoglobinization is linked to defects in cell form, such as micro-spherocytes and sickled red blood cells. [4]

Microcytic Hypochromic Anemia : Red blood cells with this form of anemia have smaller sizes than normal and have lower haemoglobin (HB) concentrations. RBC colour consequently transforms into hypochromic colour.

Macrocytic Normochromic Anemia : Red blood cells in this kind of anemia are larger than they would normally be. However, the cell's haemoglobin concentration fell.

Normocytic Normochromic Anemia : The amount of haemoglobin in RBCs dropped in this type of anemia, while the size of RBCs in the blood remained normal.

Each type of anemia presents distinct characteristics in red blood cell morphology and haemoglobin concentration, aiding in diagnosis and understanding of the underlying causes.

Table 1 : *Anemia : Variants*

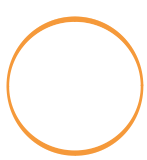
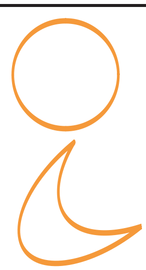
Type	Diagram	Condition
Microcytic Hypochro-mic Anemia		Small sized RBC with large central pallor with reduced haemoglobin. Hence, MCHC is reduced.
Macrocytic Normochro-mic Anemia		Large sized RBC with normal central pallor and haemoglobin concentration is normal. Hence, MCHC is normal.
Microcytic Hyperchro-mic Anemia		Small sized RBC with abnormal/ without central pallor along with increased haemoglobin concentration. Hence MCHC is increased.

Table 2 : *Cytometric Classification of Anemia [5]*

Type	Lab Values	Causes
Microcytic Hypochromic Anemia	Low MCHC Low MCV MCV < 80 fL MCHC < 30gm/dL	Iron Deficiency, Anemia of Chronic Inflammation, Sideroblastic Anemia, Globin deficiency – Thalassemia
Macrocytic Normochromic Anemia	Normal MCHC Increased MCV MCV > 100 fL MCHC=30-35 gm/dL	Vitamin B12 deficiency, Folate deficiency, Chronic Liver Disease, Alcoholism, Aplastic Anemia
Normocytic Normochromic Anemia	Normal MCHC Normal MCV MCV 76–96 fL MCHC 30–35 gm/dL	Hemolytic anemia, Bone marrow suppression

MCV : Mean corpuscular volume;
MCHC : Mean Cell Haemoglobin Concentration

Table 3 : *Recommended DietaryAllowances (RDAs) for Iron [7]*

Age	Male	Female	Pregnancy	Lactation
Upto 6 mths	0.27 mg*	0.27 mg*	□	□
7-12 mths	11 mg	11 mg	□	□
1-3 yrs	7 mg	7 mg	□	□
4-8 yrs	10 mg	10 mg	□	□
9-13 yrs	8 mg	8 mg	□	□
14-18 yrs	11 mg	15 mg	27 mg	10 mg
19-50 yrs	8 mg	18 mg	27 mg	9 mg
51+ yrs	8 mg	8 mg	□	□

* *Adequate Intake*

2.2 Classification based on Etiology

Iron-Deficiency Anemia : The most common ailment that primarily causes anemia is iron deficiency. According to WHO estimates, iron deficiency contributes to nearly 50% of Anemia. Its main causes include dietary variables (diet poor in iron), medications (like aspirin, ibuprofen, naproxen, and diclofenac), pregnancy or childhood growth spurts, heavy menstrual periods, inadequate iron absorption, bleeding from the gut (intestines).

Pernicious Anemia : It is an unusual inflammatory condition, hampers the absorption of vitamin B12, causing megaloblastic anemia. It usually affects people over fifty, has a genetic predisposition, and is more common in women and people with autoimmune diseases. Certain medications, like metformin and anticonvulsants, can also impact vitamin B12 absorption. [6]

Vitamin-B9 (Folate) Deficiency Anemia : Folate deficiency is a common side effect of protein-energy mal-nourishment. Anemia can be caused when there is folate deficiency or if the amount of folate absorbed by the body is not sufficient over time. Folate is necessary for the regular generation of red blood cells in the bone marrow, therefore a lack causes deformed red blood cells and decreased production, which leads to anemia. As a result of the elevated need for folate during pregnancy and lactation, the issue may arise. [8]

Vitamin-A Deficiency Anemia : It results from vitamin A deficiency alters iron metabolism, increasing the risk by affecting iron storage, release into the bloodstream, and regulation of red blood cell production. The pathophysiology and public health impact of "Vitamin A deficiency Anemia" need further investigation. It's challenging to predict the impact of eradicating vitamin A deficiency on anemia prevalence in underdeveloped nations. Community-based trials of multi-micronutrient supplementation should be considered to address anemia symptoms, similar to iron deficiency anemia, in children and women in developing nations. [9] Symptoms include lethargy, exhaustion, dizziness, breathlessness, headaches, and palpitations.

Haemolytic anemia : It is a type of low haemoglobin caused by red blood cell destruction, increased haemoglobin catabolism, decreasing haemoglobin levels, and increased bone marrow efforts to replace damaged products. It can have numerous causes like acute and chronic disease, immune vs. non-immune mediated, intravascular, or extravascular, inherited or acquired, and intracorpuscular or extracorpuscular. Hemoglobinopathy, membranopathy and enzymopathy contribute to intra-corpuscular causes. Extracorpuscular causes include mechanical, infectious, and immune-mediated factors. [10]

Sickle-cell anemia : Sickle cell anemia is a globin chain disease that is hereditary and results in chronic organ damage and hemolysis. It is an array of hemoglobino-pathies that result from changes in the gene that codes for the beta subunit of haemoglobin. At the sixth position of the beta-globin chain, the neutral valine replaces the negatively charged glutamine, resulting in the sickle cell mutation. The sickle shape of the RBCs sticks to the blood vessels, causing blockages and they cannot deliver oxygen. Sickle cell RBCs also die prematurely. It is inherited in an autosomal codominant manner and is passed on through the Mendelian inheritance pattern.

Thalassaemia : A heterogeneous hereditary disorder, arises from reduced production of alpha or beta chains of hemoglobin. This genetic condition affects the production of two crucial proteins, alpha and beta, constituting hemoglobin, leading to insufficient red blood cell formation and persistent anemia from infancy throughout life. Thalassemia is of type alpha and beta thalassemia. Alpha thalassemia is caused by alpha-globin gene deletion, causing reduced or absent production of alpha-globin chains. The disease severity ranges from mild to severe, with four allele deletions causing severe hydrops fetalis. Beta thalassemia is caused by point mutations in the beta-globin gene, categorized into three categories based on zygosity: beta-plus thalassemia minor, mild, asymptomatic, and beta-zero thalassemia major, resulting in total absence of beta chains. Another typical Hb variation seen in Southeast Asian people is haemoglobin (HbE). Considering that persons with thalassemia are frequently reported to have HbE in this region, it is associated with a beta-thalassemia phenotype.[11]

Aplastic anemia : Aplastic anemia is a disease of chronic primary hematopoietic failure brought on by trauma, resulting in decreased or missing hematopoietic precursors in the bone marrow and accompanying pancytopenia. It has two interconnected causes: intrinsic abnormalities of marrow progenitors and extrinsic immune-mediated inhibition of hematopoietic stem cells. [12] Damaged hematopoietic stem cells develop self-reactive T-helper cells, which release cytokines IFN and TNF, leading to a cytotoxic cascade. T1 cells target antigens like the glucose phosphate inositol protein, upregulating apoptosis, and death pathways. Immunosuppressive therapy affects two-thirds of idiopathic aplastic anemia and graft-versus-host disease patients. According to the second proposed theory, stem cells that have genetic defects lose their ability to differentiate and proliferate. [12]

Anemia of Inflammation and Infection : Numerous diseases are linked to anemia through a variety of processes, such as disease-specific effects on hemolysis, erythropoiesis, or blood loss, as well as through the effects of inflammation on iron metabolism. Hookworm, schistosomiasis, and malaria were the three main causes of anaemia in the global analysis of anemia burden between the years 1990 to 2010.

Anemia of Inflammation (AI): Inflammation associated anemia is often mild-to-moderate (Hb values 8–10 g/L) and characterized by normocytic RBCs with a low reticulocyte count. In AI, pro-inflammatory cytokines (majorly IL-6 and other cytokines) are released in the host defence response to infection altering iron metabolism, causing iron to be sequestered within cells of the reticuloendothelial system (liver and spleen) and intestinal enterocytes, and reducing RBC production and lifespan. Hepcidin, also called "master iron regulator" decreases ferroportin expression in intestinal enterocytes, macrophages, and hepatocytes. This prevents iron absorption and prevents the mobilisation of iron from stores into circulation. [13] Inflammatory cytokines also limit the life span of RBCs (perhaps by activating macrophages), interfere with erythropoietin generation, and function, and prevent the proliferation and differentiation of normal erythroid progenitor cells. After Iron deficiency anemia, AI has been cited as the second-most frequent cause of anemia. [13]

Hookworms : Necator americanus and *Ancylostoma duodenale* are primary species of hookworm that are associated with anemia. The loss of red blood cells occurs when the adult hookworm attaches to the intestinal mucosa and eats and digests the tissue inside its buccal capsule. In another situation, after attaching to the human gut, hookworms produce many proteases with the ability to break down haemoglobin in order to feed and survive. [8] An estimated 576–740 million infections are brought on by hookworms each year in sub-Saharan Africa and Southeast Asia, particularly in places where there is a lack of infrastructure, good water, sanitation, and hygiene. [13] Hookworm infection was classified as the third and fourth most common causes of anemia among males and females, respectively, in a systematic analysis that evaluated the sources of the world's anemia burden in 2010 by prevalence.

Schistosomiasis : Freshwater snails infected with different Schistosoma parasite strains are the carriers of the parasitic disease schistosomiasis. The intestinal parasites *Schistosoma mansoni*, S*chistosoma japonicum* and *Schistosoma haematobium*, are the species that cause anemia. Majorly severe anemia is caused by Schistosoma haematobium. As per reports, anemia is caused by blood loss in the stool led on by developing eggs rupturing the intestinal lining, sequestration of red blood cells in an enlarged spleen, and autoimmune destruction of red blood cells. [8] Although, the precise mechanisms of schistosomiasis-induced anemia are not well understood, and it may depend on the species of Schistosoma parasite that causes infection. [13]

Malaria : It is caused by Plasmodium species by rupturing the red blood cells and suppressing their production. Additionally, it increases the splenic macrophages' activity, which causes them to eliminate both parasitized and non-parasitic red blood cells. Haemoglobin levels@decline with the red blood cells, to the point where the cell is no longer able to transport oxygen. If this condition is serious enough, there is a high danger of dying from profound hypoxia, which is caused by infected red blood cells blocking capillaries, congestive heart failure, or, less frequently, cerebral malaria. Anemia prevalence in the states that contribute the most to the malaria burden in India was estimated to be as high as 61.9% in Jharkhand, followed by Madhya Pradesh (52.8%), and the lowest was recorded in north-eastern region (35.7%), according to the National Family Health Survey - 4 (NFHS), conducted in the years 2015-2016. [14]

3. Signs and Symptoms

Anemia may cause a wide range of symptoms and impairments in almost every organ and tissue of the human body. The severity of these symptoms depends on various factors such as degree of anemia, age, rapidity of onset, compensatory mechanisms, comorbidities, and particularly the physiologic status of the patient. The symptoms experienced by patients due to anemia does not always correlate with the level of Hb and hence Hb level alone cannot be a significant contributor to predict the symptoms. [15] A detailed history and careful examination are the most common step to make the diagnosis and evaluate the etiology behind signs and symptoms experienced by a patient. Pattern of anemia needs to be recognized, whether it is acute developing or insidious in onset and needs to be managed accordingly. [16] Slowly developing anemia occurring in a young person may remain unnoticed and requires no management until a significant decrease in Hb or episodes of exertional stress occur. On the other hand, in elderly bedridden patients, small decrements in Hb levels can have significant effects such as drowsiness, falls, and increased episodes of angina attacks. [15] Patients having anemia show a wide range of symptoms. During physical examination by a physician, patients complain of several symptoms like dizziness especially when standing and headaches and sometimes experience tinnitus or vertigo. These patients may also have difficulty in sleeping or concentrating. The patient may experience syncope after the exercise. With more severe anemia, patients start to observe chest pain and reduced exercise tolerance. Usually, these patients are irritable and may have gastrointestinal symptoms. The patient may like to eat clay, ice, and starch.

Lethargy and malaise are most commonly observed in these patients. Women may experience irregular menstruation cycles, delayed menstruation or amenorrhea. On exertion, there is dyspnoea, palpitation and faster heart rate. The older patients may have cardiac failure, angina, or intermittent claudication or confusion. They may experience retinal hemorrhage, and this may complicate anemia of rapid onset. Koilonychias, also known as spoon nails, is also sometimes observed which can be a sign of hypochromic anemia, especially iron-deficiency anemia. It refers to abnormally thin nails (usually of the hand) which have lost their convexity, becoming flat or even concave in shape. In severe cases of anemia, patients are found to be clinically diagnosed with hypoxemia, this resultant hypoxemia can subsequently cause and leads to symptoms like compensatory decrease in intestinal blood flow, motility disorder, malabsorption, nausea, weight loss and abdominal pain. [17,18]. Different types of anemia have different patho-physiological states and thus symptoms vary in them which become significant to know because a particular range of symptoms could indicate what type of anemia a patient is suffering from, based on that further diagnosis criteria could be set up.

Table 4 : *Symptoms of variants of anemia*

Types of Anemia	Symptoms
Iron-Deficiency Anemia	Lethargy, exhaustion, feeling dizzy, being easily out of breath, headaches, palpitations, changes in taste, sore mouth, and ringing in the ears (tinnitus). Anemia during pregnancy may lead to low birth weight, premature delivery, and postpartum depression. Pica, particularly ice-eating (pagophagia), is a recognized symptom of iron deficiency.
Pernicious Anemia	Fatigue, rapid heart rate, pallor, or jaundice, tingling and numbness in the hands and feet, a loss of appetite, diarrhoea, dizziness, bleeding gums, confusion, and unsteadiness when walking.
Folate deficiency Anemia	Fatigue, muscle weakness, light-headedness, pallor, heart palpitations and dyspnea.
Haemolytic Anemia	Jaundice, leg ulcers, pain in upper abdomen and arrhythmias (irregular heartbeats), a heart murmur, an enlarged heart, or even heart failure.
Sickle-cell Anemia	Terrible, crippling pain that can occur everywhere on the body, but is most common in the long bones, back, pelvis, chest, and abdomen (Vaso-Occlusive Crisis), acute chest syndrome, stroke, fatigue, breathlessness, dizziness, headache, and chest pain
Aplastic Anemia	Pallor, dyspnea, neutropenia, thrombocytopenia, ecchymoses, mucosal bleeding, and petechiae.

4. Diagnosis

Anemia is predominantly present in low and middle-income countries and is a major health concern among females of reproductive age. The condition remains largely underdiagnosed in places that lack proper medical facilities. Anemia is a complex clinical condition to diagnose at home unless there is apparent bleeding. It can be easily identified by medical practitioners by performing a blood test for a complete blood count (CBC). The CBC may be performed as part of a routine general check-up or in case of the proximity of indications and side effects suggestive of paleness. [19] Physical examination and medical history are also important in determining the causes of weakness. Anemia in adults is defined as hemoglobin (Hb) levels below 13 g/dL in males and 12 g/dL in females. The complete blood cell report (CBC) includes hemoglobin and mean corpuscular volume (MCV), which help classify anemia as microcytic, normocytic, or macrocytic. [20]

Hb testing is important for detecting anaemia, but it does not reveal a definite diagnosis, particularly if iron shortage is the cause, because Hb concentration alone is insufficient. As a result, further iron status measurements are required, such as serum ferritin or serum soluble

Table 5 : *Effects of Anemia on various Organ Systems*

Organs	Signs and Symptoms	Physiological Changes Leading to Symptoms
Central Nervous System	Fatigue, dizziness, vertigo, depressed mood, impaired cognitive function, Irritability-malaise, papilledema, pseudotumor cerebri, 6th nerve palsy, restless leg syndrome, beath holding spell, attention deficit, learning difficult, behavioural disorder, decrease in perception functions, retardation in motor and mental developmental tests	Cerebral hypoxia in anemia may lead to symptoms such as headache, vertigo, tinnitus, and dizziness and furthermore serious signs and symptoms indicate severe anemia or manifestation of a disorder underlying the anemia.
Cardio-respiratory System	Tachycardia, palpitations, angina, exertional dyspnea, increased pulse pressure, systolic ejection murmur, Cardiac enlargement, eccentric hypertrophy, risk of life-threatening cardiac failure, cardiac decompensation, cardiomegaly	Increased velocity of blood flow, resulting in significant shortening of circulation time leading to increase in respiratory rate, pulse rate, blood flow, cardiac output, 2-3 DPG, oxygen-dissociation
Skin	Low skin temperature, pale skin, mucous membranes, conjunctiva, dermatitis herpetiformis, petechiae, generalized edema and swollen legs	The skin of patients suffering from moderate to severe anemia usually appears pale and cold as a result of blood shifting to vital organs and also because of cutaneous vasoconstriction, loss of normal skin elasticity and brittle or broken nails.
Kidney Function	Fluid retention, reduced perfusion, proteinuria	Increase in erythropoietin release, vasodilation, decrease in tissue pH and thus increase in O_2-extraction
Gastro-intestinal Tract	Anorexia, nausea, irregular bowel movements, loss of appetite, angular stomatitis, atrophic glossitis, dysphagia, pica, gluten sensitive enteropathy, plummer-vinson syndrome	Reduced perfusion of intestinal mucous membranes may in turn cause nausea, anorexia, and malabsorption. Other symptom is may be manifestations of the disorder underlying the anemia.
Genital Tract	Menstrual disturbance (dysmenorrhea, amenorrhea), loss of libido, impotence	Impaired secretion of sexual hormones is responsible for almost all the symptoms observed in genital tract.
Immune System	Immune deficiency (more susceptible to infections), impaired T-cell and macrophage function, T lymphocyte leading to more severe anemia and polymorphonuclear leukocyte dysfunction, lymphadenopathy	Symptoms may arise due to manifestations of the disorder underlying the anemia which leads to an activated immune system; activation of T-cells and macrophages result in increased expression of various inflammatory cytokines which leads to impaired iron utilization and decreased erythropoietin production. Moreover, the decreased perfusion of skin and mucous membranes in anemia may contribute to a higher rate of infections

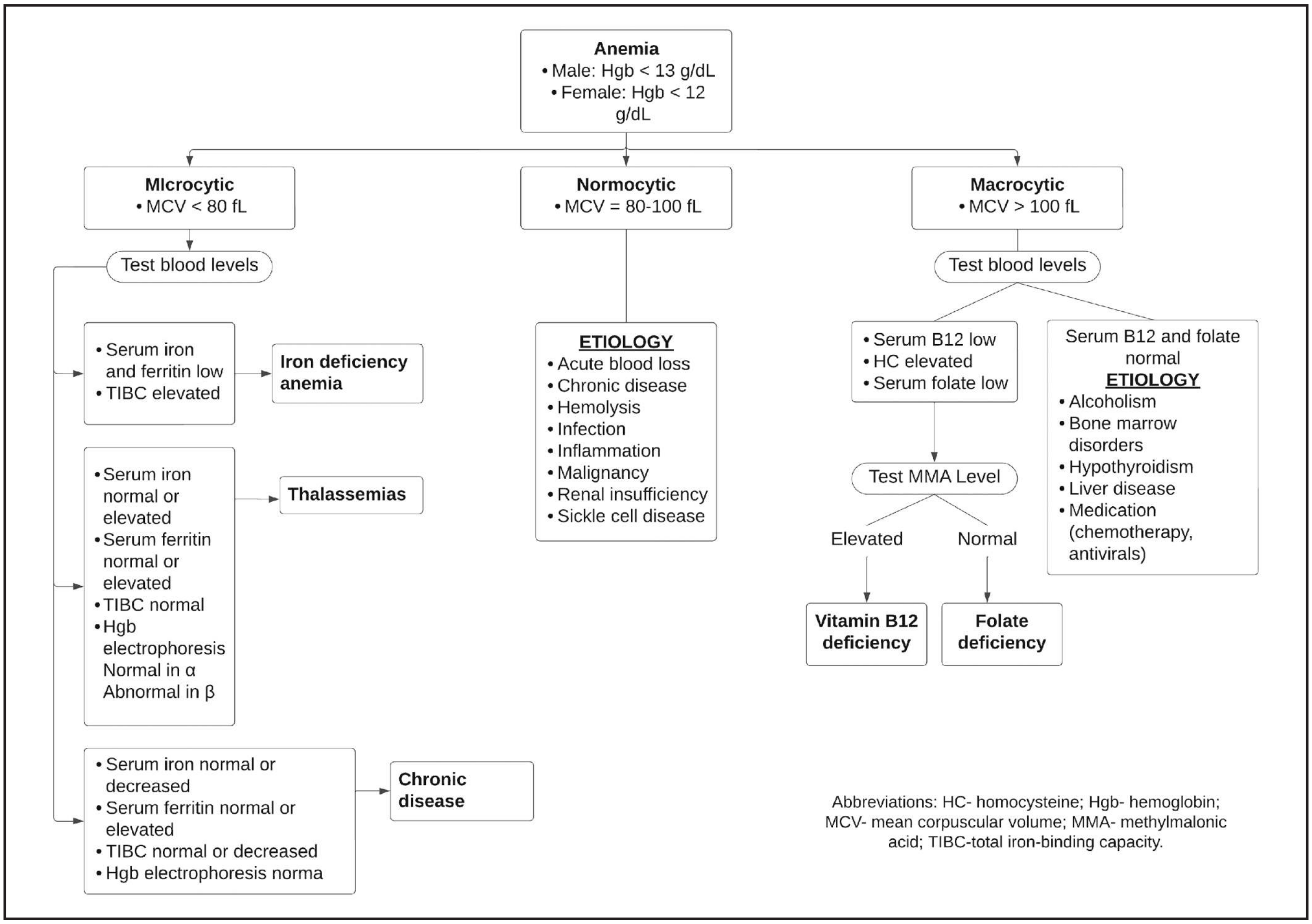


***Figure 1 :** Classification of Anemia [20]*

transferrin receptor (sTfR), which are the most widely utilised biomarkers. Total iron-binding capacity (TIBC), transferrin saturation, zinc protoporphyrin concentration, reticulocyte Hb, erythrocyte protoporphyrin concentration, and, in rare situations, bone marrow biopsy can all be used to determine iron status. [21]

Since ferritin content drops in absolute iron shortage but increases in response to infections and inflammation, its interpretive usefulness is restricted. Acute-phase proteins such as C-reactive protein (CRP) and alpha-1 acid glycoprotein (AGP) are used to detect infection or inflammation. In 2020, WHO announced new ferritin concentration cut-offs, with proposed adjustments for infection/inflammation. WHO suggests utilising serum ferritin in conjunction with Hb and inflammatory indicators to assess iron status at the population level. Serum transferrin receptor (sTfR) concentration is a semi-quantitative indicator of iron shortage, less influenced by inflammation than ferritin. It can be used along with ferritin concentration (sTfR:SF) to detect iron status in individuals with iron shortage, normal iron balance, or iron overload. Other tests that may be required include a bone marrow biopsy, Hb electrophoresis for Hb variations (i.e., HbS) or other beta globin gene disorders (such as thalassaemia), serum creatinine, erythropoietin, liver function, coagulation profile, or hemolysis profile. [21]

Hepcidin concentration measurement is an emerging tool for identifying absolute and functional iron deficiency. It is often utilized to predict iron responsiveness and personalize iron replenishment routes. Mass spectrometry

***Table 6 :** Types of Diagnostic Test for Anemia*

Test	Normal Range
Ferritin test	19-300 ng/mL (men) 10-150 ng/L (women)
TIBC Test	250-450 mcg/dL
Vitamin B12 test	160-950 pg/Ml
Folate test	5-25 ng/ml
Reticulocyte count test	0.5% - 1.5%
Erythropoietin level test	4-26 mU/mL
Soluble transferrin receptor test	2-5 mg/L

***Note :** Values may differ based on lab equipment utilized for testing, patient age, and ethnicity* and immunochemistry methods are used, but hepcidin levels can vary significantly depending upon the method used. Standardization and comparability are crucial for routine clinical testing. [21]

Malaria is a major cause of anemia globally, with 241 million cases in 2020. Iron deficiency is common in malaria-endemic areas, and the relationship between iron deficiency and malaria is complex. WHO recommends providing iron supplements alongside public health measures to prevent, diagnose, and treat malaria. Diagnosis involves techniques like blood smear examination, rapid diagnostic tests, and molecular methods. Rapid diagnostic tests are feasible but may remain positive for weeks due to antigen persistence.

Inherited genetic Hb diseases, including the thalassaemia trait and the sickle cell trait, are among the top three causes of anemia worldwide. A major Hb variation is predicted to be carried by 5% of the global population, with the percentage being highest in Africa (18%) and Asia (7%). The geographical distribution of this category of disorders is shifting, and screening for hemoglobinopathies with high frequency and health impact is important in areas where incidence is rising. Every year, around 330,000 children are born with a serious genetic Hb problem, with the majority (83%) having sickle cell anemia and the remainder (17%) having a form of thalassemia.[21] Diagnosing thalassemia involves CBC, reticulocyte count, Hb electrophoresis for beta thalassemia, or genetic testing for alpha thalassemia. Sickle cell anemia or trait identification requires HbS presence and mutations in genes. POC analyzers are also utilized for diagnosing anemia and sickle cell disease/trait simultaneously.

Existing methods for measuring haemoglobin and diagnosing common causes of anemia are expensive or complex, making them unsuitable for primary healthcare settings in countries with limited resources. Factors such as equipment maintenance, reagent availability, and logistics make assessing anemia difficult. To address this, more accurate and easily accessible field-based diagnostic and point-of-care screening techniques are needed, especially in areas lacking well-equipped laboratories. There is an urgent need for simple yet reliable equipment for simultaneous, low-cost assessment of various biomarkers, including Hb, malaria, parasitic infections, ferritin, CRP/AGP, and hepcidin. [21]

5. Treatment

Treatment depends on the severity or the underlying cause. So, for proper treatment the type of anemia first needs to be identified. Primary focus of treatment is to cure the factor that is causing deficiency or decrease of red blood cell number and haemoglobin in the blood. Most common approach to treatment is dietary supplements.

For uncomplicated Iron deficiency (ID) without comorbidity, oral iron (i.e. iron supplements) are readily available and is generally given as first choice treatment to the majority of population because of its efficacy, safety and convenience. Ferrous sulfate, gluconate, and fumarate are the most widely available and inexpensive oral iron formulations and patients are able to improve as compared to the symptoms observed in them during diagnosis. However, it has also been seen that most of the patients for whom oral iron is prescribed report significant gastrointestinal side effects, symptoms seen are constipation and sometimes diarrhea, a metallic taste, gastric cramping and thick, green, tenacious stool. [26-27] For those patients, the Intravenous (IV) route is preferred. The particles consist of a core of iron-hydroxide gel surrounded by a shell of carbohydrate stabilizing the core and allowing slow release of the iron while the remaining particles stay in a colloidal suspension. [28-29] Except for patients with ID associated with chemotherapy administration or dialysis, a single infusion of a replacement dose offers convenience and cost benefit. [28]

Vitamin B12 deficiency patients are treated with parenteral administration of vitamin B12, and it is seen that hematological levels generally return to normal within one month. For patients with a permanent decrease in the ability to absorb dietary vitamin B12, such as those associated with pernicious anemia or total gastrectomy, lifelong treatment is necessary. During hematopoietic recovery, an iron deficiency may develop. Although it is not an established treatment, recently it has been reported that oral treatment is more effective, because 1%-5% of vitamin B12 absorption in the terminal ileum is by passive diffusion, which does not involve intrinsic factor. [31] In case of Folate deficiency anemia, patients are usually treated with oral folic acid if the cause of folate deficiency is nutritional deficiency or recommend increased nutritional requirements.

For severe cases of aplastic or hemolytic anemia, supplement do not suffice, and thus other intensive treatment methods are also to be followed along with supplements (if recommended). Generally, blood transfusion and stem cell therapy are recommended, and for patients who have a matched sibling donor, Hematopoietic stem cell transplantation (HSCT) represents the first-choice treatment as it successfully cures about 90 % of patients. This treatment can be applied to patients aged below 50 years although the age limit can be increased to below age 60 if the patient is medically fit. [32]

For those people aged below 50–60 years, who lack an identical donor in the family, combined immunosuppression still represents a reasonable front-line option. Antithymocyte globulin (ATG) and Ciclosporin

(CSA) represent the most used agents in first line immunosuppressive therapy. Their combined use has been demonstrated to be much more effective than ATG alone [33]. Even in younger patients i.e., children and adolescents, Immunosuppressive Therapy (IST) can still be a first line option because the high survival rate, which peaks to about 90 %, enables in case of failure good rescue treatment with second line HSCT. However, in this age group, front-line HSCT, if a matched unrelated donor is rapidly made available, can be a very effective alternative.

In India, the general population mainly suffers from nutritional anemia, either with iron deficiency, folate deficiency, vitamin B12 deficiency, or mixed deficiency. Interventions to prevent and correct nutritional anemia, therefore, must include measures to increase essential micronutrients uptake such as iron and folic acid through food-based approaches, namely dietary diversification, and food fortification with iron and nutrient supplementation. Dietary diversification basically means encouraging the consumption of micronutrient rich foods such as dark green leafy vegetables, lentils and vitamin C rich fruits which may be available but are underutilised by the deficient population. Food fortification refers to the addition of micronutrients to processed foods. In many situations, this strategy can lead to relatively rapid improvements in the micronutrient status of a population, and at a very reasonable cost. An approach in fortification is the use of 'sprinkles', a small sachet containing iron and other nutrients which can be sprinkled onto the complementing food prior to consumption has proven to be effective to prevent and correct (mild to moderate anemia) iron deficiency anemia and other nutritional anemia [34].

But in the general scenario, it is difficult to influence dietary behaviour, thus, the key step towards addressing iron deficiency and other nutritional deficiency becomes the implementation and scaling up of the supplementation programme. Supplementation, especially iron and folic acid (IFA) supplementation to manage nutritional anemia (specifically IDA) is the most common and followed short term strategy of various national schemes for reduction of anemia in India. IFA supplementation can be itself a complete treatment for an individual having mild or moderate anemia.

6. Anemia in Context to India – Risk Factor and Causes

In India, it has been seen that multiple factors are associated and can cause anemia. Nutritional anemia is a major public health problem in India which is mostly caused by not having enough iron and significant micronutrients in diet. In India, according to NFHS-5, the prevalence of anemia is 67.1% in children <5 years, 57% in women 15-49 years, 25% in men 15-49 years. (MoHFW. National Family health Survey – 5. 2019-22).

***Table 7 :** Management of anemia on the basis of haemoglobin levels*

Categories	Level of Hb (gm/dl)	Treatment
Children (6 month to 5 years)	If Hb range lies in 7-10.9 gm/dl (i.e., mild to moderate anemia)	3 mg of iron/ kg/ day for 2 months or 1-2 ml of IFA syrup (as per age) once in a day
Children (5-10 years)	If Hb range lies in 8-11.4 gm/dl (i.e., mild to moderate anemia)	3 mg of iron/kg/day for 2 months
Adolescents (10–19 years)	If Hb range lies in 8-11.9 gm/dl (i.e., mild to moderate anemia)	60 mg of elemental iron daily for 3 months
Pregnant and Lactating Women	If Hb range lies in 8-11 gm/dl	2 IFA tab lets (1 in the morning and 1 in the evening) per day for at least 100 days (at least 200 tablets of IFA).
	If Hb range lies in 7-8 gm/dl	Injectable IM iron therapy in divided doses along with oral folic acid daily if women do not have any obstetric or systemic complication.
	If Hb range lies in 5-7 gm/dl	Continue parenteral iron therapy as per prescribed by the physician.

***Sources :** https://www.nhm.gov.in/images/pdf/programmes/child-health/guidelines/Control-of-Iron-Deficiency-Anaemia)*

Anemia is quite common in infants, children, and even some teenagers in India. Most of the time, it happens because they don't have enough iron in their bodies, which leads to IDA specifically seen among children aged 1-4 years. There are other reasons too, like not getting enough folate or Vitamin B12, which can cause megaloblastic anemia and pernicious anemia, suggesting anthropometric failure to be a significant predictor of anemia in developing countries like India. Iron deficiency anemia and normocytic anemia are also found to be largely due to menorrhagia (in women) occurring as a result of various hormonal instabilities and malabsorption observed in hypothyroid patients. [35, 36].

In children aged 6 to 59 months, the overall prevalence of anemia is 53.4% according to the WHO's 2019 Anemia Report. In 2017, the prevalence of anemia in Indian children was 59.7%, with a notable decrease seen in high socio-demographic index (SDI) states from 2000 to 2010

Table 8 : *Prevalence of the Dietary Iron Deficient as the leading cause of Years Lived with Disability (YLDs) and Disability-Adjusted Life Years among men and women of different age groups in India*

Year	2019			
Measure	YLD		DALY	
Gender	Male	Female	Male	Female
Age 5-14	12.31%	22.23%	7.11%	13.95%
Age 15-49	2.28%	9.9%	0.95%	6%

References : *Global Burden of Disease 2019 Report (Available from URL: https://vizhub.healthdata.org/gbd-compare/india*

Table 9 : *Prevalence of Dietary Iron Deficient as the leading cause of Years Lived with Disability (YLDs) and Disability-Adjusted Life Years among men and women of different age groups in India*

Year	2021			
Measure	YLD		DALY	
Gender	Male	Female	Male	Female
Age 5-14	11.33%	20.9%	7.1%	13.97%
Age 15-49	1.98%	9.17%	0.75%	5.26%

References : *Global Burden of Disease 2021 Report (Available from URL: https://vizhub.healthdata.org/gbd-compare/india*

and further decline is seen across all SDI groups from 2010 to 2017. These findings reflect the changing landscape of child anemia in India over the years. [37]

Severe anemia is most prevalent among young children living in low-income families who face economic challenges. These children often suffer from undernutrition, which is consistently linked to anemia in various studies in India. This connection makes sense because kids who don't get enough calories are also likely to lack essential micronutrients, especially iron. [38]. Additionally, vitamin B12 deficiency in infants and premature babies is often tied to maternal deficiency during pregnancy, leading to insufficient stores of B12 at birth. These disadvantaged infants, who are further exclusively breastfed for extended periods (sometimes 3-5 years), can develop B12 deficiency because their mothers have lower-than-normal B12 levels in their breast milk, often due to poverty-related vegetarian diets (poverty-vegetarianism exclusive prolonged breast-feeding axis). [39-40]. A large percentage of these children also come from economically weaker backgrounds with poor sanitation and environment and are more prone to infections and thus doubling the risk of anemia through infections like malarial parasitic infections, hookworm infections, gastrointestinal infections associated with diarrhoea due to poor hygiene.

In infants and children, the demand for iron is exceptionally high due to rapid growth (i.e., substantially more iron must be absorbed than is lost from the body). In the first two months of life, there is minimal dietary iron absorption and thus their body relies on stored iron to meet its needs. By the time they reach four to six months of age, the iron stores have usually been depleted and diet becomes the vital source for iron. The transition from feast to famine with respect to iron is primarily because of infants requiring a significant amount of iron to maintain a consistent hemoglobin level of around 12.5 g/dl as their blood volume rapidly increases between four and twelve months of age and thus iron requirement in them are almost 10 times higher per kilogram of body weight than that of an adult male and it gets more severe when there is inadequate supply of iron in the diet. Improving maternal nutrition and addressing maternal anemia can play a vital role in mitigating the severity of anemia observed in infants during this critical growth phase.@ [41]

A recent report from 'UNICEF INDIA' says India has the largest adolescent population in the world, 253 million, and every fifth person is between 10 to 19 years of age. Prevalence of anemia is higher in India, where six out of ten adolescent girls are anemic [42]. According to National Family Health Survey 2019–21, India accounts for 31.1 and 59.1% of anemic boys and girls in the 15–19@years of age group, respectively. Comparing this with National Family Health Survey 2015-16 reports, 54.1% adolescent girls were anemic and 29.2% adolescent boys were anemic indicating a significant rise in anemia cases among adolescent girls. The main cause is that@the female child is more likely to be neglected, particularly in families with limited resources with the added burden of menstrual blood loss (whether normal or abnormal) precipitates the crises too [43]. Other associated risk factors for anemia are low intake of meat [fortified food with iron], frequent dieting, vegetarian eating styles, skipping meals, significant weight loss, heavy menstrual period, rapid growth, participation in endurance sports and intensive physical training [44].@

Anemia continues to be a major cause of maternal mortality and low birth weight (LBW) in India. In many instances, the girl child is not only breastfed for a less duration but food supplementation to her is also lowered and thus anemia begins in childhood, worsening in adolescence, and gets complicated during pregnancy. [45]. Inadequate nutrition during adolescence can have serious consequences throughout the reproductive years of life and beyond. Very often, in India, girls get married and pregnant even before the growth period is over, thus increasing the risk for anemia [42] as getting pregnant during adolescence deprives the girl to achieve her adequate growth and healthy life. Other possible factors associated with the problem may be low literacy and poor nutritional status of the mother,@increased number of pregnancies, shorter interval between births and poor dietary intake of iron, vitamin B complex and vitamin A rich foods during pregnancy. [43]

Anemia is one of the major health problems of women in India. Women and adolescent girls are particularly more prone to anemia (especially nutritional anemia) because of increased demand of iron and other microenvironment for hemoglobin, myoglobin and to make up for the loss of iron due to menstruation and poor dietary habits as compared to men. It has been seen that the severity of anemia was inversely related to educational background and economic status in women.

Women in the reproductive age group are more vulnerable to iron deficiency resulting in anemia, especially during pregnancy and lactation as they are physiologically and nutritionally at a higher risk. A pregnant woman has higher nutritional needs to meet the physiological demands of the body during pregnancy for fetal growth, alterations in maternal tissues, metabolism and lactation. They also require nutritious food to store calories to produce an adequate quantity of milk without compromising their physical well-being. [44]

According to World Health Statistics 2022, India has the world's third highest prevalence of iron deficiency anemia among women of reproductive age with 53% (15–49 years). WHO has recognised anemia as a global problem with serious consequences for mothers and their babies [45]. Anemia has also been found associated with increased prevalence of ante-partum and postpartum haemorrhage and thus, severe anemia is strongly correlated with maternal morbidity secondary to known clinical and biological factors [46, 47].

Severe anemia in pregnancy impairs oxygen delivery to the fetus and interferes with normal intrauterine growth, resulting in intrauterine growth retardation, stillbirth, LBW and neonatal deaths. Therefore, anemia is a major contributor to poor pregnancy and birth outcomes in developing countries as it predisposes to premature delivery, increased perinatal mortality and increased risk of death during delivery and postpartum. [48]

Anemia prevalence is higher in India not only among women, but men too, one in every four men in India suffer from anemia (NFHS-5. 2019-22). Anemia among men has not been given due importance as a public health issue because only a handful of studies have captured the prevalence of anemia among men. Thus, men should also be screened on a regular basis to reduce the national burden of anemia. [53] Among adolescent boys, as increment of body mass, muscle and expansion of blood volume increase their iron requirement in adolescence, lack of which can affect their growth and develop-ment [54]

Hereditary hemolytic disorders like beta-thalassemia syndrome, sickle cell disease, and G6PD enzyme deficiency, are the significant contributors to anemia, especially hemolytic anemia in tropical and subtropical countries including India [55]. According to National Health mission guidelines on Hemoglobinopathies in India, 2016, about 10,000 -15,000 babies with thalassemia major are born every year. The carrier frequency of the Sickle cell gene varies from 1 to 35 % and hence there are a huge number of people with Sickle cell disease. Hemolytic anemia is very much profound in patients suffering from those diseases. For Example, in case of thalassemia the deficiency in one globin chain leads to an overall decrease in hemoglobin and the intracellular precipitation of the excess chain, which damages the membrane and leads to clinically evident hemolysis.

Looking at the global trends indicating widespread iron deficiency, the situation in India is more pronounced, reflecting the need for targeted interventions and robust

Table 10 : *Data of women with anemia (aged 15-49) in India*

Categories of Women Aged 15 to 49	Prevalence (%)	Numbers (in thousands)	Mean haemoglobin level (g/dl)
Reproductive age	53.0	1,87,325	117
Non-pregnant	53.1	1,80,000	117
Pregnant	50.1	7,582	109

Source : *Data collected from WHO Anemia 2019 Report*

Table 11 : *Prevalence of Hemoglobinopathies and Hemolytic Anemia as the leading cause of Years Lived with Disability (YLDs) and Disability-Adjusted Life Years among men and women of different age groups in India.*

Year	2019			
Measure	YLD		DALY	
Gender	Male	Female	Male	Female
Age 5-14	3.77%	3.26%	2.3%	2.13%
Age 15-49	0.63%	1.66%	0.3%	1.04%

References : *Global Burden of Disease 2019 Report (Available from URL: https://vizhub.healthdata.org/gbd-compare/india*

Table 12 : *Prevalence of Hemoglobinopathies and Hemolytic Anemia as the leading cause of Years Lived with Disability (YLDs) and Disability-Adjusted Life Years among men and women of different age groups in India*

Year	2021			
Measure	YLD		DALY	
Gender	Male	Female	Male	Female
Age 5-14	3.41%	3.11%	2.26%	2.16%
Age 15-49	0.55%	1.54%	0.25%	0.92%

References : *Global Burden of Disease 2021 Report (Available from URL: https://vizhub.healthdata.org/gbd-compare/india*

Table13 : *Prevalence of Dietary Iron Deficient as the leading cause of Years Lived with Disability (YLDs) and Disability-Adjusted Life Years among men and women of different age groups across the globe*

Measure	YLD		DALY	
Gender	Male	Female	Male	Female
Age 5-14	8.47%	12.44%	4.38%	7.41%
Age 15-49	1.1%	4.86%	0.41%	2.83%

References : *Global Burden of Disease (Updated version of May16, 2024) Report available from URL: https://www.healthdata.org/gbd*

nutritional policies to mitigate the health and economic impacts of this deficiency. The disparity highlights the critical necessity for focused efforts to improve iron intake through fortified foods, supplements, and educational campaigns tailored to the unique needs of the Indian population.

7. National Schemes for reduction of Anemia in India

National Health Mission (NHM), a flagship scheme of the Government, provides financial and technical support to States and Union Territories for implementation of 'Anaemia Mukt Bharat Strategy'. Various programs under the scheme include:

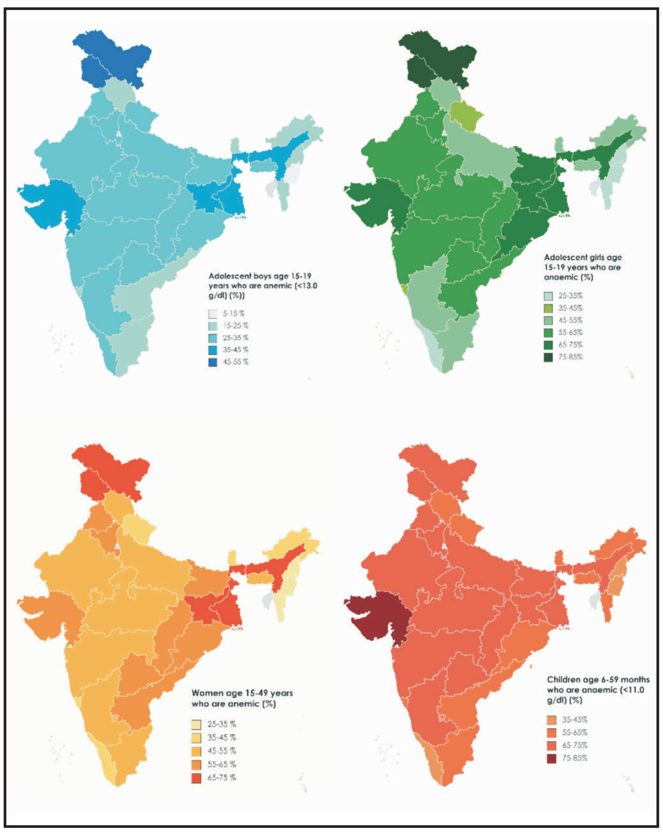


Figure 2 : *Anemic representation of Adolescents boys and girls, women and children*

Table 14 : *Prevalence of Hemoglobinopathies and Hemolytic Anemia as the leading cause of Years Lived with Disability (YLDs) and Disability-Adjusted Life Years among men and women of different age groups across the globe*

Measure	YLD		DALY	
Gender	Male	Female	Male	Female
Age 5-14	2.33%	2.52%	1.68%	2.2%
Age 15-49	0.34%	1.03%	0.27%	0.85%

References : *Global Burden of Disease 2021 (Updated version of May16, 2024) Report available from URL: https://www.healthdata.org/gbd*

Surakshith Matritva Aashwasan (SUMAN): This initiative focuses on assured delivery of maternal and newborn healthcare services encompassing wider access to free, and quality services, zero tolerance for denial of services, assured management of complications along with respect for women's autonomy, dignity, feelings, choices, and preferences, etc. [56-57]

Janani Suraksha Yojana (JSY): It is a safe motherhood intervention under the National Rural Health Mission (NRHM) being implemented with the objective of reducing maternal and neonatal mortality by promoting institutional delivery among the poor pregnant women. [57,58]

Janani Shishu Suraksha Karyakram (JSSK): every pregnant woman is entitled to free delivery, including caesarean section, in public health institutions along with the provision of free transport, diagnostics, medicines, other consumables & diet. [57]

Pradhan Mantri Surakshith Matritva Abhiyan (PMSMA): The program aims to provide assured, comprehensive and quality antenatal care, free of cost, universally to all pregnant women on the 9th of every month. [57, 59]

LaQshya: Improves the quality of care in labour room and maternity operation theatres to ensure that pregnant women receive respectful and quality care during delivery and immediate postpartum. [57, 60]

National Iron Plus Initiative (NIPI): The National Nutritional Anaemia Prophylaxis Programme initiated in 1970, was revised and expanded to include beneficiaries from all age groups namely children aged 6-59 months, 5-10 yrs., adolescents aged 10-19 yrs., pregnant and lactating women and women in reproductive age group under the National Iron Plus Initiative (NIPI) programme in 2011. [57, 60]

Monthly Village Health, Sanitation and Nutrition Day (VHSND): is an outreach activity at Anganwadi centers for provision of maternal and child care including nutrition in convergence with the Integrated Child Development Services (ICDS). It was conceptualized under the National Health Mission (NHM). [61]

The Government of India has taken several step to bring about substantive change in anemic conditions including Prophylactic Iron and Folic Acid Supplementation in all six target age groups; Intensified year-round Behaviour Change Communication (BCC) Campaign for:(a) improving compliance to Iron Folic Acid supplementation and deworming, (b) enhancing appropriate infant and young child feeding practices, (c) encouraging increase in intake of iron-rich food through diet; Management of severe anaemia in pregnant women undertaken by administration of IV Iron Sucrose/Blood transfusion; Field level awareness by ASHAs through community mobilization activities and IEC and BCC activities. [42]. Beside these, the MCP Card and Safe Motherhood Booklet are also distributed among the pregnant women for educating them on diet, rest, pregnancy related danger signs, beneficial schemes and post-natal care and health services.

International Efforts : India has the largest universal adolescent anemia control programme in the world, targeting 116 million adolescent girls and boys. The programme plays a pivotal role in protecting adolescents from the debilitating effects of anemia, breaking the country's intergenerational cycle of malnutrition and safeguarding the health and potential of future generations. There is evidence on the positive impact of weekly iron and folic acid supplementation on reducing anemia among adolescents. The Government of India, with technical support from UNICEF, agreed to explore the effectiveness of an adolescent girls' anemia control programme delivered through existing government service delivery systems. [2]

8. Conclusion

Anemia is not a stand-alone disease, instead a clinical condition in general practice and is one of the major public health issues worldwide; especially in low- and middle-income countries like India. It is mainly caused by nutritional deficiencies and parasitic infections. Nutritional deficiency including iron deficiency anemia, vitamin B12 deficiency anemia and folate deficiency anemia are the major causes of anemia. Blood loss due to hookworm, schistosomes, Trichuris trichiura and iron absorption blockage due to Ascaris lumbricoides are also a significant cause of anemia. An extensive medical history and examination are the most usual steps in making a diagnosis. Before moving on to high-end examinations, one should try to interpret simple investigations (such as full blood count with general blood picture and other indices). The cause of anemia should be dealt with first, followed by the replacement of iron or vitamin deficiencies. The pattern of anemia must be recognised, whether it is acute or gradual in onset, and it must be addressed accordingly. In children, anemia impairs mental and psychomotor development, reduces work performance, and causes growth retardation. A large proportion of these children also come from low-income families with inadequate sanitation and environment, making them prone to infections and thus doubling the risk of anemia from infections. Women and adolescent girls are more susceptible to nutritional anemia due to increased iron demand, menstruation, and poor dietary habits. Factors include low literacy, advanced pregnancy age, pregnancies, short birth intervals, and poor vitamin A intake. Other risk factors include low meat intake, frequent dieting, vegetarian eating, weight loss, and intense physical training. In India, women often struggle to consume necessary food and supplements due to socio-economic, political, and societal stereotypes. The National Health Mission (NHM) is a government scheme that provides financial and technical support to States and Union Territories for implementing the 'Anemia Mukt Bharat Strategy'. It includes programs like Surakshith Matritva Aashwasan (SUMAN), Janani Suraksha Yojana (JSY), Janani Shishu Suraksha Karyakram (JSSK), Pradhan Mantri Surakshith Matritva Abhiyan (PMSMA), LaQshya, National Iron Plus Initiative (NIPI), and monthly village health, Sanitation and Nutrition Day (VHSND). The government has implemented several initiatives to improve anemic conditions, including prophylactic iron and folic acid supplementation, behaviour change communication campaigns, and management of severe anaemia in pregnant women. India's universal adolescent anemia control programme is the world's largest programme aiming to tackle the problem of anemia at the grass root level.

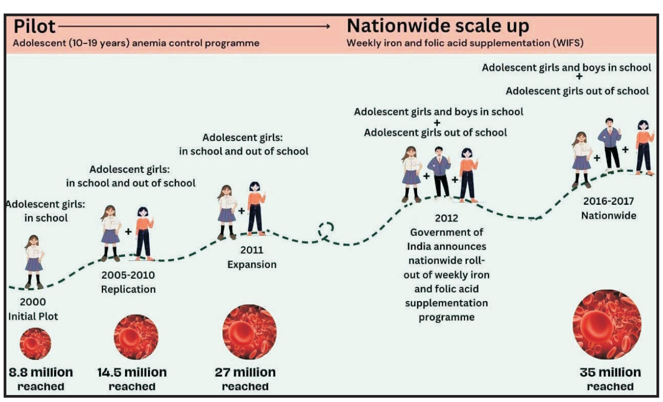


Figure 3 : *Anemia Control Programme*

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