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CHAPTER 1

Anemia in Pregnancy

INTRODUCTION

Anemia during pregnancy is a public health problem especially in developing countries. The World Health Organization (WHO) has defined anemia in pregnancy as the hemoglobin (Hb) concentration of <11 g/dL. According to WHO (2015 report), about 32.4 million pregnant women suffer from anemia worldwide, of which 0.8 million women are severely anemic. The global prevalence of anemia among pregnant women is 36.5% (WHO, 2019), the prevalence is higher (56%) among women living-in low and middle-income countries (LMIC). The prevalence rate is highest among pregnant women in Sub-Saharan Africa (57%), in South and Southeast Asian countries (52%) and lowest prevalence (24.1%) in South America. In Bangladesh 42.9% women suffer from anemia in pregnancy.

Iron deficiency anemia (IDA) during pregnancy is associated with adverse outcomes in pregnancy, increases the risk of low birth weight (LBW), preterm birth, maternal and perinatal mortality, and poor Apgar score. An estimate by WHO attributes about 591,000 perinatal deaths and 115,000 maternal deaths globally to IDA, directly or indirectly. According to Lone et al., anemic women as compared to nonanemic women are at fourfold higher risk of preterm birth, 1.9 fold increased risk of delivering LBW infants, and 1.8 fold increased risk of having neonates with Apgar score <5 at 1 minute.

ETIOLOGY OF ANEMIA IN PREGNANCY

The causes of anemia are multifactorial, include micronutrient deficiencies of iron, folate, vitamin A and B_{12}, anemia due to parasitic infections such as malaria and hookworm or chronic infections such as tuberculosis (TB) and human immunodeficiency virus (HIV), and anemia resulting from acute blood loss. Contributions of each of the factors vary due to geographical location, dietary practice, and season. According to WHO 50% cases of anemia in pregnancy are attributable to IDA with the rest due to conditions such as folate, vitamin B_{12} or vitamin A deficiency, chronic inflammation, parasitic infections, and inherited disorders (WHO 2015). Most IDA in pregnancy is related to the maternal and fetal demands of pregnancy, although some women start pregnancy with IDA, mainly due to menstrual losses, previous pregnancies, and/or inadequate dietary intake.

HEMATOLOGICAL CHANGES IN PREGNANCY

Pregnancy is associated with normal physiological changes that assist fetal survival and prepares the mother for labor, delivery, and breastfeeding. The changes start as early as 4 weeks of gestation and are largely as a result of progesterone and estrogen. The total blood volume increases steadily from as early as 4 weeks of pregnancy to reach a maximum of 35–45% above the nonpregnant level at 28–32 weeks. The plasma volume increases by 40–45% (1,000 mL). Red blood cell (RBC) mass increases by 30–33% (approximately 300 mg) as a result of the increase in the production of erythropoietin, which reaches approximately 150% of their prepregnancy levels at term **(Fig. 1)**. The greater increase in plasma

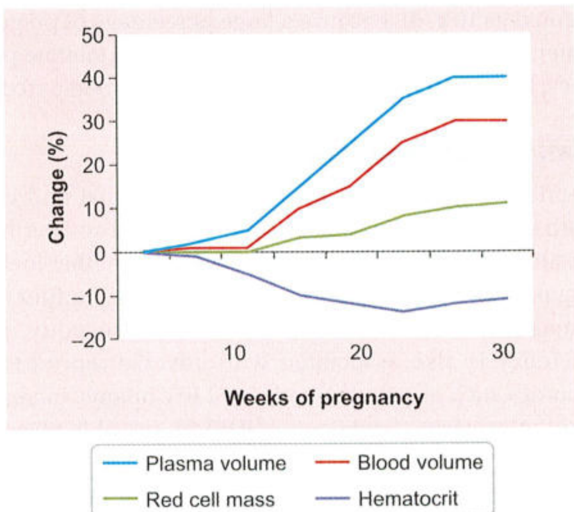

Fig. 1: Changes in plasma volume, blood volume, red cell mass, and hematocrit with pregnancy.
Source: Ezechi Oliver and Kalejaiye Olufunto. Management of Anaemia in Pregnancy. *www.intechopen.com.*

volume than the increase in RBC mass results in a modest reduction in hematocrit; peak hemodilution occurs at 24–26 weeks, resulting in physiological anemia of pregnancy. This dilutional picture is often normochromic and normocytic. Occasionally, physiologic anemia can also be associated with a physiologic macrocytosis, mean corpuscular volume (MCV) increases to 120 fL (average at term is 104 fL).

The physiological demand for iron during pregnancy is three times higher than in nonpregnant women, and increases as pregnancy progresses. The net iron requirements for pregnancy have been calculated as 1,000 mg taking into account the requirements for fetus, placenta, expansion of maternal erythrocyte mass, and losses due to delivery. Though iron requirements decrease during the first trimester, there is an increase of 4–6 mg/day in the second and third trimesters which may reach up to 10 mg/day during the last 6–8 weeks of pregnancy. The iron absorption has been found to decrease during the first trimester of pregnancy, which rises during the second trimester, and this increase lasts the remainder of pregnancy. While the transferrin and total iron binding capacity rises, the serum iron falls. So, women who enter pregnancy in an iron deficient state are unable to meet the demands of pregnancy by diet alone and require supplementation. It takes approximately 2–3 weeks after delivery for these hematologic changes to revert to prepregnancy status.

DEFINITION OF ANEMIA

The World Health Organization defines anemia in pregnancy as a Hb concentration of <11 g/dL. The United States (US) Centers for Disease Control and Prevention (CDC) defines anemia in pregnancy as Hb concentration <11 g/dL in the first and third trimesters and <10.5 g/dL in the second trimester. In most developing countries the lower limit is often accepted as 10 g/dL because a large percentage of pregnant women in this setting with Hb level of 10 g/dL tolerate pregnancy, labor, and delivery very well and with good outcome.

IMPACT OF ANEMIA

Anemia is reported to have negative maternal and child health effect and increases the risk of maternal and perinatal mortality. The negative health effects for the mother include fatigue, poor work capacity, impaired immune function, increased risk of cardiac diseases, and mortality. Iron deficiency is also associated with adverse reproductive outcomes such as preterm delivery, LBW infants, increased risk of intrauterine fetal deaths (IUFDs), possibly placental abruption, and increased peripartum blood loss. Some studies have shown that anemia contributes to 23% of indirect causes of maternal deaths in developing countries. Tissue enzyme malfunction occurs in the early stages of iron deficient erythropoiesis, may contribute to maternal morbidity through effects on immune function with increased susceptibility to or severity of infections, poor work capacity and performance, and disturbances of postpartum cognition and emotions.

The fetus is relatively protected from the effects of iron deficiency by upregulation of placental iron transport. Evidence suggests that maternal iron depletion increases the risk of iron deficiency in the first 3 months of newborn's life and decreased iron stores for the baby, which may lead to impaired development. Impaired psychomotor and/or mental development are well described in infants with IDA, therefore, may negatively contribute to infant's social and emotional behavior and have an association with adult-onset diseases, although this is a controversial area.

CLASSIFICATION OF ANEMIA IN PREGNANCY

Classification Based on Etiology

- *Deficiency anemia:* Iron, vitamin B_{12}, and folic acid deficiency.
- *Blood loss:*
  - Acute [antepartum hemorrhage (APH), intrapartum hemorrhage]
  - Chronic (hookworm infestation, bleeding piles, and peptic ulcer disease)
- *Bone marrow failure:*
  - Aplastic anemia
  - Isolated secondary failure of erythropoiesis
  - Drugs (e.g., chloramphenicol, zidovudine)
- *Hemolytic anemia:*
  - *Inherited:*
    - *Hemoglobinopathy:* Thalassemia's, sickle cell hemoglobinopathies
    - *Red blood cell membrane defects:* Hereditary spherocytosis, elliptocytosis
    - *Enzyme defect:* Glucose-6-phosphate dehydrogenase (G6PD), pyruvate kinase deficiency
  - *Acquired:*
    - *Immune hemolytic:* Autoimmune, alloimmune, and drug induced
    - *Nonimmune hemolytic:*
      - Acquired membrane defect (paroxysmal nocturnal hemoglobinuria)
      - *Mechanical damage:* Microangiopathic hemolytic anemia
    - *Secondary to systemic disease:* Renal anemia, anemia due to liver disease
    - *Infection:* Malaria, sepsis, and HIV.

Classification According to Red Cell Morphology

Hypochromic microcytic:

- Iron deficiency
- Thalassemia
- Sideroblastic anemia
- Anemia of chronic disorders
- Lead poisoning

CHAPTER

2

Thalassemia in Pregnancy

INTRODUCTION

Thalassemias are a heterogeneous group of genetic disorder of hemoglobin (Hb) synthesis characterized by a reduction in the synthesis of one or more of the globin chains leading to imbalanced globin-chain synthesis, defective Hb production resulting in anemia. The precise structure of the globin chain is coded by genes on chromosomes 16 (the α-gene cluster, comprising the α- and ζ-globin chains) and chromosome 11 (the β-gene cluster, comprising the globin chains γ, ε, β, and δ). Hb must have the correct structure and be trimmed in such a way that the number of α-chains precisely matches that of the β-chains. Adult Hb consists of approximately 98% HbA ($\alpha_2\beta_2$), <3% HbA_2 ($\alpha_2\delta_2$), and traces of HbF ($\alpha_2\gamma_2$).

Thalassemias result from partly or completely suppressed synthesis of one of the two types of polypeptide chains (α or β) as a result of missense/nonsense mutations (single-base substitutions) or frameshift mutations of the genes controlling the structure of the Hb chain in one or both "allelic" globin genes. Depending on the genes affected, the resulting defect, and the corresponding effect on the globin chain, several types of thalassemia have been described, the most common types of clinical importance being α-, β/δ-, and β-thalassemia. A variety of thalassemia phenotypes can result from simultaneous inheritance of two different mutations from each parent or the coinheritance of thalassemia together with structural Hb variants (e.g., HbE-β thalassemia). **Figure 1** shows alpha and Beta globin genes on chromosomes 16 and 11.

The thalassemia syndromes are characterized by a basic defect in the synthesis of one type of globin chains. As a result, there is insufficient Hb content in the resultant red cells resulting in decreased Hb concentration, microcytosis, and anemia. The other type of globin chains whose synthesis is not affected accumulates in the red cells, resulting in defective red cells, which are released into the circulation. These damaged red cells undergo extravascular hemolysis.

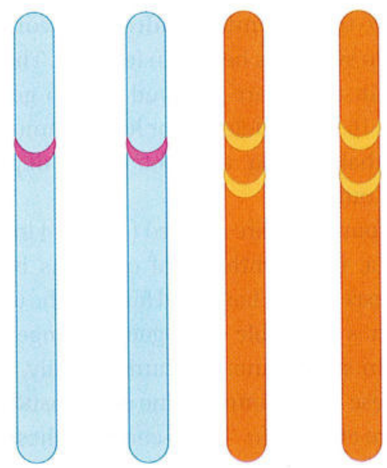

Fig. 1: Alpha- and Beta-globin genes on chromosomes 16 and 11.
Source: Thalassaemia.com

EPIDEMIOLOGY

The term thalassemia is derived from the Greek word "thalassa" for sea, and "hema" for blood. Thalassemias were initially distinctive in the tropics and subtropics but are now commonly found worldwide as a result of population migration. This defect is seen more often in the Indian subcontinent, the Mediterranean region, Southeast Asia, and West Africa. Approximately, 15 million people are globally affected by thalassemia. Alpha-thalassemia is more prevalent among individuals from African and Southeast Asian descent, whereas beta-thalassemia is most common in persons of Mediterranean, African, and Southeast Asian descent. Most children with thalassemia are born to women in the low-income countries. World Health Organization recommends screening and genetic counseling for Hb disorders as an intrinsic part of healthcare system for improvement of survival among children born with thalassemia.

INCIDENCE

Thalassemia is detected in approximately 4% women of reproductive age. More than 70,000 babies are born with thalassemia worldwide each year and there are 100 million individuals who are asymptomatic thalassemia carriers [Royal College of Obstetricians and Gynaecologists (RCOG), Green-top guideline].

GENETIC BASIS OF THALASSEMIAS

Alpha-thalassemia is the most common inherited disorder of Hb and is characterized by reduced or suppressed production of α-globin chains. Almost 5% of the world's population are carriers, and approximately 1,000,000 patients are affected by various α-thalassemia syndromes worldwide. The α-globin chain synthesis begins in fetal life. The responsible genes—four in total—are situated in two genetic loci in chromosome 16. Gene deletion or less commonly mutation results in α-thalassemia, and phenotype depends on the affected gene number.

When all four genes are affected (–/–|–/–) in homozygous α-thalassemia, fetal synthesis of α-chains is impossible, leading to an excess of γ-chains and forming the unstable Bart's Hb (γ_4), which is incapable of oxygen exchange. The affected fetuses sustain severe anemia, cardiomegaly, and hydrops fetalis, and these lead to intrauterine or neonatal death. When three genes are affected ($\alpha^{-/-/-}$), α-chain synthesis is restricted to a minimum. Therefore, β-chains that exist in excess form the unstable HbH (β_4). HbH disease has a phenotypic variability based on mutation type, ranging from mild anemia to a transfusion-dependent one. The existence of two α-genes (α-thalassemia trait) is expressed as a mild hypochromic microcytic anemia. Globin synthesis is still unbalanced, leading to hemolysis and iron overload.

In α^0-thalassemia, the two deleted genes belong to the same allele (–/–|α/α), prevalent among Asian and Eastern Mediterranean populations, while α^+-thalassemia, prevalent among African people, the deleted genes belong to different homologous chromosomes. When only one α-gene is affected (α/–|α/α), the remaining three functional genes are capable of normal Hb production, the individual becomes a "silent" carrier **(Table 1)**.

Beta-thalassemia: The β-gene cluster region located on chromosome 11, regulates the synthesis of β-globin. It is extremely heterogeneous in terms of both genotype and phenotype, depending on the nature of β-gene mutation and the extent of impairment in β-globin chain production. β-thalassemia occurs due to one or more than 250 point mutations. Rarely, it may occur due to the deletion of two genes. β^0 refers to the complete absence of production of β-globin on the affected allele, β^+ refers to alleles with some residual production of β-globin, and β^{++} to a very mild reduction in β-globin production. Decreased production of β-globin chain leads to the excessive production of other chains, e.g., α-globulin chains, γ-globulin chains.

As a rule, heterozygous carriers of β-thalassemia (one-affected allele), are asymptomatic, and have only altered laboratory values. Thalassaemia minor causes mild-to-moderate microcytic anemia with no significant detrimental effect on overall health. In contrast, inheritance of two defective β-globin genes results in a wide phenotype spectrum, ranging from transfusion-dependent [thalassemia major (TM)] to mild or moderate anemia [thalassemia intermedia (TI)].

Thalassemia intermedia represents up to a quarter of β-thalassemia patients with a wide spectrum of genotypes and a clinical phenotype ranging between transfusion-dependent thalassemia and the asymptomatic carrier state. At the severe end of the clinical spectrum

TABLE 1: Thalassemia: Genetics and clinical features.

Alpha-thalassemia	***α-, γ-genes***	***Globin chains***	***Hemoglobin***	***Anemia***
Normal	αα/αα	$\alpha_2\beta_2$	A	None
Silent carrier	αα/α–	$\alpha_2\beta_2$	A	None
Trait	α–/α– ––/αα	$\alpha_2\beta_2$	A	Mild
HbH disease	––/–α	$\alpha_2\beta_2$, β_4	A, H	Intermediate
Hydrops fetalis	––/––	γ_4, $\zeta_2\gamma_4$	Bart's Portland	Lethal
Beta-thalassemia	***β-genes***	***Globin chains***	***Hemoglobin***	***Anemia***
Normal	β/β	$\alpha_2\beta_2$	A	None
Thalassemia minor	β^+/β β^0/β	$\alpha_2\beta_2$, $\alpha_2\delta_2$, $\alpha_2\gamma_2$	A, A_2, F	Mild
Thalassemia minor	β^+/β^+ β^0/β^0	$\alpha_2\beta_2$, $\alpha_2\delta_2$, $\alpha_2\gamma_2$, $\alpha_2\gamma_2$, $\alpha_2\delta_2$	A, A_2, F, F, A_2	Severe Severe
HPFH	γ/γ	$\alpha_2\gamma_2$	F	Mild

(HPFH: hereditary persistence of fetal hemoglobin)

Source: https://library-g.kau.edu.sa/Files/237/Researches/65509_36921.pdf

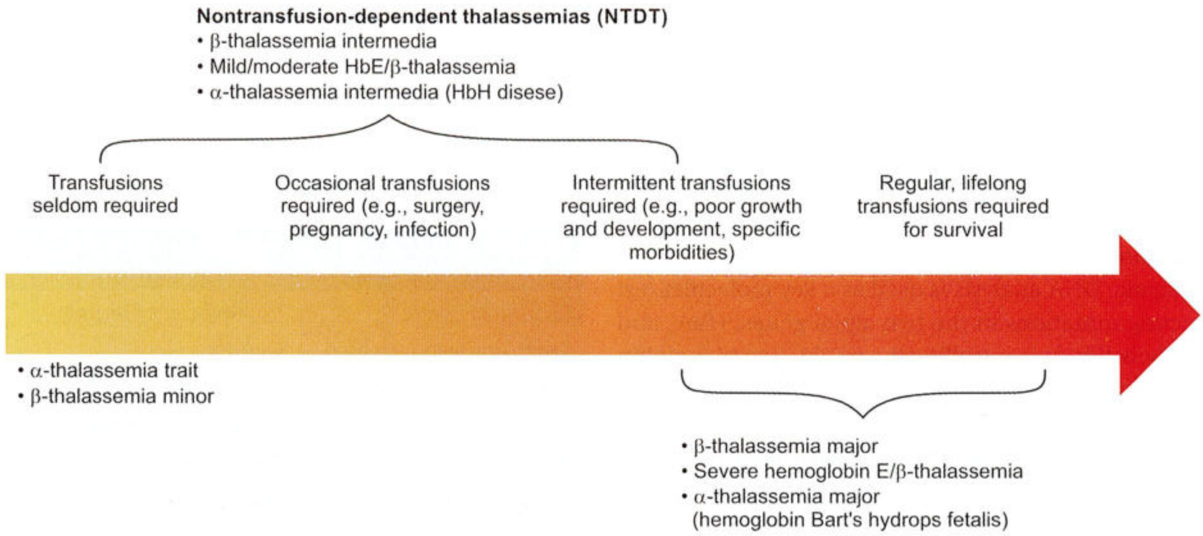

Fig. 2: Tranfusion need in different thalassaemia group.
(HbE: hemoglobin E; HbH: hemoglobin H)
(*Source*: Musallam KM, Rivella S, Vichinsky E, Rachmilewitz EA. Non-transfusion-dependent thalassemias. Haemotologica. 2013;98(6):833-44)

of TI, patients are usually diagnosed between the ages of 2 and 6 years and, although they survive without regular blood transfusions, growth and development are impaired. At the other end of the spectrum, there are patients who are completely asymptomatic until adulthood, when they present with mild anemia and splenomegaly often found by chance during hematological examinations or family studies.

Beta-TM or Cooley's anemia (β^0/β^0 or β^0/β^+) is characterized by severe hypochromic microcytic anemia, which becomes symptomatic at infancy or early childhood. TM (homozygous β-thalassemia) results from the inheritance of a defective β-globin gene from each parent. This results in a severe transfusion-dependent anemia, requiring regular red blood cell (RBC) transfusions for survival. The globin chain-synthesis reduction leads to an unbalanced β/α-globin chain production, where the chains in abundance precipitate, forming erythrocyte inclusions. These cells are destroyed in the bone marrow, giving rise to ineffective erythropoiesis, which is a prominent feature of the disease. This erythropoiesis causes skeletal deformities and bony fractures, megaloblastic anemia due to folate deficiency, and hyperuricemia with gout. Enlarged maxillary sinuses, a maxillary overbite, and "mongoloid" appearance of the face are commonly observed in thalassemic patients.

Peripheral blood smear will show the characteristic features of polychromatic RBCs, microcytosis, poikilocytosis and anisocytosis, basophilic stippling (punctate basophilia), nucleated RBCs (normal, mature RBCs are enucleated), and irregular distribution of Hb (resulting in "target cells" which appear like a bull's eye under the microscope).

Pathophysiology of TM is characterized by damaged RBCs, hemolysis, and erythroid-precursor release in the peripheral circulation, due to ineffective erythropoiesis. The phenotype includes anemia, bone marrow expansion, skeletal deformities, growth restriction, and late sexual maturity. The main clinical features in these patients are hypertrophy of erythroid marrow with medullary and extramedullary hematopoiesis and its complications (osteoporosis, masses of erythropoietic tissue that primarily affect the spleen, liver, lymph nodes, chest and spine, and bone deformities and typical facial changes), gallstones, painful leg ulcers, and an increased predisposition to thrombosis. Advances in care by optimal blood transfusion and iron-chelation therapy have improved patient survival into adulthood, as well as quality of life in recent years. Consequently, concern about favorable reproductive outcome has increased.

DIAGNOSIS OF THALASSEMIA

Hematological Indices

Screening for thalassemia is done by examining the hematological indices and measurement of HbA_2 levels. Thalassemia traits are associated with a reduced mean corpuscular volume (MCV), reduced mean corpuscular hemoglobin (MCH), and a normal to near-normal mean corpuscular hemoglobin concentration (MCHC); low, normal, or slightly subnormal hemoglobin levels. Of all these markers the most accurate is MCH. Additionally, β-thalassemia is associated with elevated HbA_2 levels (>3.5 g%). Deoxyribonucleic acid (DNA) analysis is required to confirm the diagnosis.

Iron Profile Analysis

Various parameters of the iron storage and usage by the body are measured which include serum iron, ferritin, unsaturated iron-binding capacity, total iron-binding capacity (TIBC), and percent saturation of transferrin. Indistinguishable β-thalassemia minor can be well-differentiated from iron deficiency or lead poisoning by using erythrocyte porphyrin tests.