TAMIL NADU FEDERATION OF OBSTETRICIANS & GYNAECOLOGISTS

e - Newsletter

Issue 3

On

Anaemia in Pregnancy

9th July 2021

TAMIL NADU FEDERATION OF OBSTETRICIANS & GYNAECOLOGISTS

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TAMIL NADU FEDERATION OF
OBSTETRICIANS & GYNAECOLOGISTS

President's Message

Dear Comrades

We are meeting after our vibrant well appreciated TNFOG e-conference. My warm greetings to all of you. This month's Marathon CME is on "Anaemia in Pregnancy". All of us know how rampant anaemia is in our country. It is the most common nutritional disorder in the world. Anaemia begins in childhood, worsens during adolescence in girls and gets aggravated during pregnancy.

Anaemia is a major factor in maternal mortality. It is the direct cause of maternal mortality in 20% and in another 20% it is indirect cause

Maternal anaemia is –"**A preventable killer**"

Anaemia is multifactorial in etiology. It is the manifestation of undernutrition and poor dietary intake of iron affecting not only a section but entire population. By the time a person is diagnosed with anaemia, the body stores are nil and the RBC iron is to the minimal level.

Anaemia with other key micronutrients deficiencies can directly attribute to –depressed cognition, poor school performance, reduced future earnings and productivity, depressed immunity and repeated infections. Our Government is taking very many steps to prevent anaemia, inspite of that we still see pts with 3gms and 4 gms Hb.

This newsletter brings to you the pathophysiology of anaemia in pregnancy, how to diagnose, treat and prevent and also about molecules like FCM and factor VII, so it will be useful to read, practice and prevent anaemia in our population

Anaemia prevention is the lead to achieving the MDG goals

Jai Hind!!!

Dr Anjalakhi Chandrasekar

Founder President, TNFOG

Secretary's Message

Warm greetings to all.

This is our third e-newsletter and it is on the most common problem - Anaemia in pregnancy.

Why is this topic chosen?

Nutritional deficiency is the main reason for anaemia. Nutritional requirements of pregnant women should be given prime focus – at least during the gestational period!

How anaemia is to be prevented and how different types of anemia are treated are dealt in this newsletter. How is it managed in low resource setting is also dealt with.

Anaemia has to be corrected from adolescence itself to achieve clear results such as reducing MMR. Anaemia is the cause for more than 50% of the mortality in reproductive phase. We must ensure that any girl at the age of 12 should have 12gm Hb. It is with this in mind such a CME has been planned. Hope all will enjoy the CME & be benefited by the newsletter.

Dr Sampathkumari

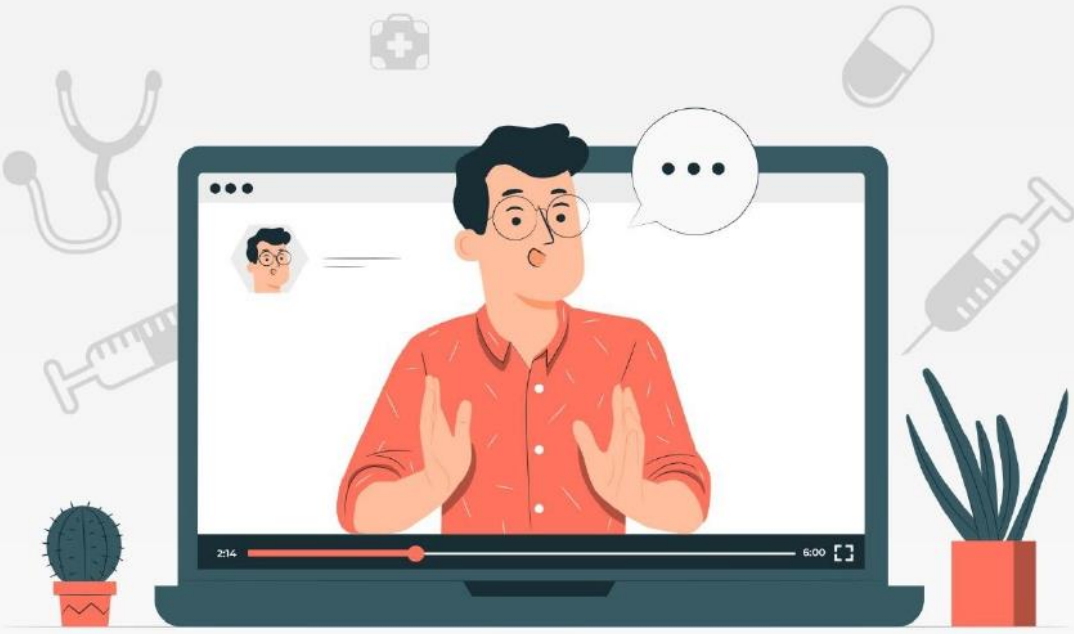
Founder Secretary, TNFOG

TAMIL NADU FEDERATION OF OBSTETRICIANS & GYNAECOLOGISTS

TNFOG Plans to conduct TWO CME Program Every Month

1. Marathon CME 2. Magalir Nalam

MARATHON CME??
THIS POINTS TO TWO THINGS



1. The YUVA OGCIAN Competition

Yes, every month 2nd Friday CME will have a session with 2 YUVA speakers, Consultants less than 35 years.

The session will be judged by the same judges and at the end of the year,
First, Second and Third prize will be awarded to the best speakers at the Annual conference.

All societies gear up and suggest one YUVA speaker of your society.

2. There is a question at the end of every session in the CME. The first Delegate who answers the question will be awarded a prize. This will continue in all the CMEs.

BE READY TO WIN THE PRIZE

TNFOG MARATHON CME ON "Anaemia in Pregnancy"

Date: 09.07.2021 (Friday) | Time: 4.30 – 7.15 PM

Scientific Programme

2 ICOG Credit Points Granted

DURATION	TOPIC	SPEAKERS
04.30 - 05.00 PM	INTRODUCTION	DR. S. SAMPATHKUMARI
	INAUGURATION	
	WELCOME ADDRESS	DR. ANJALAKSHI CHANDRASEKAR
	CHIEF GUEST ADDRESS	DR. SADHANA GUPTA
	Release of e - Newsletter (Issue. 3) on " Anaemia in Pregnancy "	
SESSION I - YUVA SESSION CHAIRPERSONS : DR. VIJAYALAKSHMI KANDASAMY & DR. NIDHI SHARMA		
05.00 - 05.30 PM	PATHOPHYSIOLOGY OF ANAEMIA IN PREGNANCY	DR. PRIYANKA VELCHAMY
	INVESTIGATION & DIAGNOSIS OF ANAEMIA IN PREGNANCY	DR. SUSHMA
	Q & A	
SESSION II CHAIRPERSON: DR. JAYSHREE K SRINIVASAN		
05.30 - 06.00 PM	ANEMIA IN PREGNANCY IN LRS	DR. SANJAY GUPTE
06.00 - 06.10 PM	ROLE OF FACTOR VII IN CLINICAL PRACTICE	DR. NIVEDITA BHARATHY. K
06.10 - 06.15 PM	Q & A	
SESSION III - PANEL DISCUSSION MODERATOR: DR. SHOBHA S		
06.15 - 07.15 PM	**"ANAEMIA IN PREGNANCY"**	**PANELISTS**
		DR. MANONMANI R
		DR. ANITA
		DR. SELVABHARATHY
		DR. KARPAGAMBAL SAIRAM
		DR. ALAMELU
		DR. NARMADHA D
		DR. DEEPA MUKUNDAN
		DR. BANU REKHA N
	EXPERT OPINION	DR. JAISHREE GAJARAJ
	Q & A	
07.15 PM	VOTE OF THANKS	DR. VIJAYALAKSHMI GNANASEKARAN
CONVENOR - DR. PRIYA KANNAPPAN		

After Each Session, Answer the 'Question' FIRST & GET EXCITING PRIZE!

TNFOG MARATHON CME ON "Anaemia in Pregnancy"

Date: 09.07.2021 (Friday) | Time: 4.30 – 7.15 PM

Dr. ANJALAKSHI CHANDRASEKAR
President , TNFOG

Dr. S. SAMPATH KUMARI
Hony, Secretary, TNFOG

Dr. VIJAYALAKSHMI GNANASEKARAN
Treasurer, TNFOG

Chief Guest

DR. SADHANA GUPTA

Speaker

DR. SANJAY GUPTE

Convenor

DR. PRIYA KANNAPPAN

Chairpersons

DR. VIJAYALAKSHMI KANDASAMY

DR. NIDHI SHARMA

DR. JAYSHREE K SRINIVASAN

Speaker

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DR. SUSHMA

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TNFOG MARATHON CME ON "Anaemia in Pregnancy"

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Moderator

DR. SHOBHA S

Expert opinion

DR. JAISHREE GAJARAJ

Panelists

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DR. KARPAGAMBAL SAIRAM

DR. ALAMELU

DR. NARMADHA D

DR. DEEPA MUKUNDAN

DR. BANU REKHA N

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TAMIL NADU FEDERATION OF OBSTETRICIANS & GYNAECOLOGISTS

Article - 1

PATHOPHYSIOLOGY OF ANEMIA IN PREGNANCY

Dr Priyanka Velchamy

Deepan Hospital, Trichy

Pregnancy is a state of physiological anaemia. Mean plasma volume increases by 40-50 % in pregnancy and red cell mass increase by 30% resulting in erythrocyte dilution by 5-15% and decrease in Haemoglobin by 2g/dL giving rise to physiologic anaemia or "Hydremia " of pregnancy. This is to facilitate placental circulation by reducing viscosity of blood and a mechanism to reduce wastage due to bleeding related to parturition.

According to CDC Hb values of 11gm/dl in the first and third trimester and less than 10.5gm/dl in the second trimester is defined as anaemia in pregnancy. WHO says less than 11gm/dl in pregnancy as anaemia.

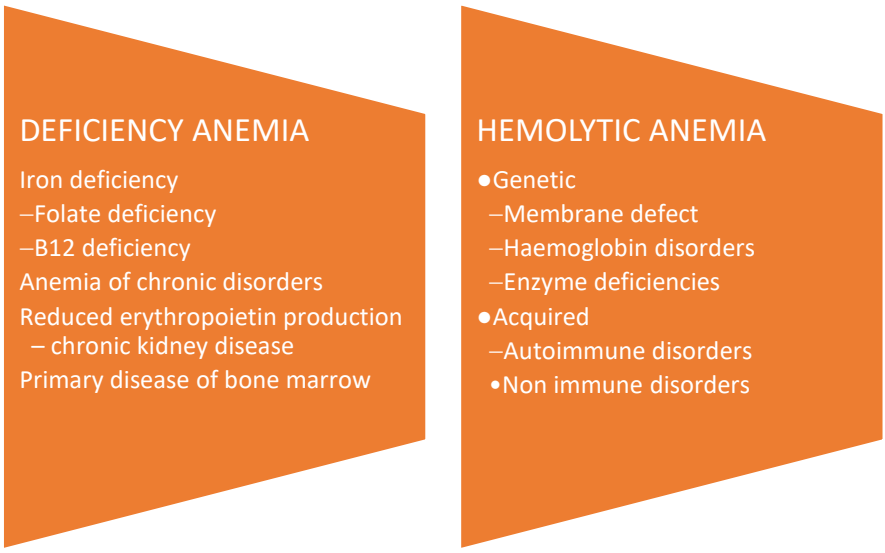
Haemoglobin level and its category	
Hb level (g/dl)	**Category**
<4	Very severe
4-6.9	Severe
7-9.9	Moderate
10-10.9	Mild

PREVALENCE OF ANEMIA IN PREGNANCY

Nutritional deficiency is the most common cause of anemia in pregnancy comprising about 95% of all anemia in pregnancy. Prevalence of anemia depends on multiple sociocultural and economic factors, and being a developing

country, India has a very high prevalence of anemia in pregnancy. Globally iron deficiency is the most common cause of pregnancy anemia. About 90% of all anemia has iron deficiency.

The overall mean world figure of prevalence of gestational anemia is 25%. On an average it is 56% in developing countries and18% in developed countries. Anemia is implicated as the direct contributor of maternal death in 20% of cases.



The **main causes of anemia** can be usefully classified according to the associated **red cell changes**-

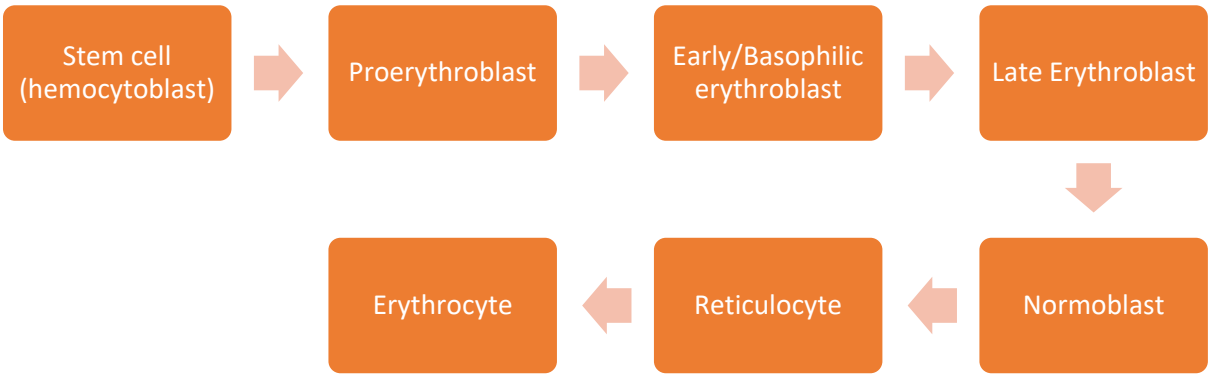
Hypochromic , microcytic – including iron deficiency (the most common cause of anemia) , thalassemia (common in some populations)
Normochromic , macrocytic – vitamin B12 or folate deficiency alcohol , myelodysplasia
Polychromatophilic , macrocytic – hemolysis
Normochromic , normocytic – chronic disorders , renal failure diseases of the bone marrow.
Leukoerythroblastic – myelofibrosis , leukemia , metastatic carcinoma.

ERYTHROPOIESIS

In adults, bone marrow is the site of erythropoiesis. From pluripotent stem cells or hemocytoblast to unipotent stem cell and then proerythroblast is formed. It takes 3-5 days to form a reticulocyte from a stem cell and 2 more days from reticulocyte to a mature erythrocyte. Iron is an essential and main element in the synthesis of haemoglobin. Traces of copper and cobalt are also required and protein is needed for synthesis of the globin part. Folic acid is needed for deoxyribonucleic acid (DNA) synthesis, and vitamin B12 is necessary for synthesis of ribonucleic acid (RNA) both of which are nucleoproteins. Vitamin C is necessary for conversion of folic acid to folinic acid.

Recently, it was found that vitamin D3 also has some role in erythropoiesis.

Erythropoietin is the hormone secreted by kidneys and is responsible for stimulation of bone marrow erythroblast for erythropoiesis. Normal red cell survival is 100-120 days in circulation. Daily Red blood cell (RBC) production requires 30-35 mg of iron per day, most of which come from recycling, and only about 1-2 mg of daily loss needs to be replenished.



IRON DEFICIENCY ANAEMIA

IRON METABOLISM IN PREGNANCY

During first half of pregnancy iron requirement is not very high and average a balanced diet is enough to provide a daily requirement of 1-2 mg in healthy mothers. In second half of pregnancy, demand is more due to increased red cell mass and rapid fetal growth . Demand is approximately 500 mg of iron for increased erythropoiesis and 300mg for the fetus and altogether , it is 800mg for a singleton pregnancy. Fetus derives its iron by active transport through the placenta. So the average daily requirement of iron is approximately 5-6 mg / day during pregnancy. Sources of iron are heme and nonheme. Heme iron is found in animal products and non heme is found in fresh leafy vegetables, lentils, legumes and beans , compounds like phytates , tannin , calcium and magnesium bicarbonates , carbonates oxalates and phosphates hamper iron absorption whereas vitamin C and citric acid enhances its absorption. Iron is **mainly absorbed in duodenum and proximal jejunum aided by gastric acid in ferrous form.** Absorption is more in deficient state and less in iron overload. Only **10-15% iron in diet is absorbed** and is bound to transferrin and then transported to bone marrow for utilization in haemoglobin synthesis.

Location	Form	Distribution (%)
Haemoglobin iron		70
Tissue iron • Storage iron • Essential iron	Hemosiderin Ferritin Myoglobin Enzymes • Cytochrome • Peroxidase • Catalases	29
Plasma transport iron	Transferring	0.19

HAEMATOLOGICAL AND NON HAEMATOLOGICAL EFFECTS OF ANEMIA IN PREGNANCY

In reality iron deficiency and iron deficiency anemia [IDA] have other major negative consequences on mother, newborn , neonate , child and on the adult in the long term.

Causes of iron deficiency anemia in pregnancy

- Poor intake – deficient diet
  - Vomiting
- Poor absorption
  - Diet rich in phosphate and phytates
  - Lack of vitamin C
  - Ferric forms of iron
  - Achlorhydria , taking of regular H2, receptor antagonists
  - Antacids
- Increased demand
  - Multiple pregnancy
  - Adolescent pregnancy
- Excessive iron loss
  - Repeated pregnancy
  - Hookworm infestation
  - Chronic malaria
- Miscellaneous
  - Chronic infection

- Intestinal malabsorption
- Asymptomatic bacteriuria

MATERNAL RISKS

Cardiac failure due to anemia is a direct contributor to maternal death. Association of anemia with other moribund conditions like preeclampsia and eclampsia also contributes to maternal death indirectly. As iron deficiency develops, initially there is low serum ferritin level and then serum iron level comes down. Anemia develops later when the storage iron is fully depleted. Iron-dependent enzymes of every cell are depleted , and there is a profound effect on body function. Tissue enzyme malfunctions occur and there is evidence showing relation of anemia with preterm labour and postpartum hemorrhage. Role of iron in immunity is also seen as anemic patients are prone to all infections leading to maternal morbidity and mortality due to sepsis.

FETAL RISKS

Fetus is a parasite in the mother which obtains necessary nutrients from the mother including iron regardless of maternal status of storage. In the last 4 weeks of pregnancy placenta actively transport Iron to the fetus from maternal transferrin and if needed from maternal RBC breakdown or maternal intestinal absorption. One third of iron is stored in the fetal liver and rest in fetal haemoglobin. If the mother is having IDA, fetal store will be less and consequences may be not only childhood anemia but some far-reaching effect like cognitive behavioural deficiency due to negative impact on brain development. These children will have delayed psychomotor development with

impaired performances in motor and language skills,
less coordination and a deficit of intelligence quotients by 5- 10 points.

STAGES OF IRON DEFICIENCY ANEMIA

If the serum ferritin level goes below 15µg/dL it is the deficiency state in reproductive age group women. When iron deficiency ensures, anemia is manifested in three phases.

Phase I – stage of negative iron balance when demand is more like blood loss, rapid growth spurt, pregnancy.

Phase II – stage iron deficient erythropoiesis when transferrin saturation decreases.

Phase III – microcytic hypochromic anemia.

MEGALOBLASTIC ANEMIA

Megaloblastic anemia is the second most common anemia in tropics contributing **3-4%** of all anemias in pregnancy. Multipara is 5 times more affected than nonpregnant and multiple gestations have an 8 times increased risk of developing megaloblastic anemias. Two common causes of megaloblastic anemia are folate and vitamin B12 deficiency. Folic acid is responsible for synthesis of thymidine which is the basis of nucleoprotein formation. Vitamin B12 is also necessary for DNA synthesis. In deficiency state RNA synthesis is normal and therefore there is increased cytoplasm compared to the nucleus. Growth of all types of hematopoietic cells line erythrocyte, granulocyte and megakaryocyte is affected. As vitamin B12 has longer storage life, deficiency anemias is extremely uncommon during pregnancy, whereas folate deficiency anemias are much more common. The average daily dietary intake of folic acid varies from 120µg/day to 300µg/day but this is usually inadequate for pregnant

women. Leafy vegetables contain folic acid but the majority is lost in cooking, the requirement of folate increases to **400 mcg/day during pregnancy**. Requirement is more in multiple pregnancy, infection, hyperemesis and blood loss. Inhibition of folate absorption occurs in presence of drugs like phenytoin, nitrofurantoin, alcohol and sulfasalazine. In case of dual deficiency of iron and folic acid, only iron replacement may aggravate megaloblastic anemia due to increased folate demand for hematopoiesis. Vitamin B12 is caused by deficient absorption. It can be due to autoimmune condition.

DIMORPHIC ANEMIA

In dimorphic anemia features of both macrocytic and microcytic anemia are present due to iron and folate deficiency. This type of anemia is common in our country due to nutritional deficiency in lower socioeconomic groups.

OTHER FACTORS OF ANEMIA

In tropical countries helminthic and protozoal infection are important causes of anemia in pregnancy. In a Delhi-based study ,41.8% had some form of infestation, out of which 36.9% was due to ancylostoma duodenale or hookworm infestation causing considerable fecal blood loss.

Vitamin C facilitates iron absorption. Vitamin A deficiency can also affect mobilization of iron stores. Other micronutrients like zinc are involved in nucleic acid and protein metabolism. Zinc dependent enzymes are involved in DNA RNA synthesis.

HEMOGLOBINOPATHIES

During pregnancy, hemoglobinopathies, particularly sickle cell disease, Hb S-C disease, and beta- and alpha-thalassemia, can worsen maternal and perinatal outcomes. Genetic screening genetic screening for some of these disorders is available.

Pre-existing **sickle cell disease,** particularly if severe, increases risk of the following:

- Maternal infection (most often, pneumonia, urinary tract infections [UTIs], and endometritis)
- Pregnancy-induced hypertension
- Heart failure
- Pulmonary infarction
- Fetal growth restriction
- Preterm delivery
- Low birth weight

Anemia almost always becomes more severe as pregnancy progresses. Sickle cell trait increases the risk of UTIs but is not associated with severe pregnancy-related complications.

Treatment of sickle cell disease during pregnancy is complex. Painful crises should be treated aggressively. Prophylactic exchange transfusions to keep Hb A at ≥ 60% reduce risk of hemolytic crises and pulmonary complications, but they are not routinely recommended because they increase risk of transfusion reactions, hepatitis, HIV transmission, and blood group isoimmunization. Prophylactic transfusion does not appear to decrease perinatal risk. Therapeutic transfusion is indicated for the following:

- Symptomatic anemia
- Heart failure
- Severe bacterial infection
- Severe complications of labor and delivery (eg, bleeding, sepsis)

Hb S-C disease may first cause symptoms during pregnancy. The disease increases risk of pulmonary infarction by occasionally causing bony spicule embolization. Effects on the fetus are uncommon but, if they occur, often include fetal growth restriction.

Sickle cell–beta-thalassemia is similar to Hb S-C disease but is less common and more benign.

Alpha-thalassemia does not cause maternal morbidity, but if the fetus is homozygous, hydrops and fetal death occur during the 2nd or early 3rd trimester.

TAMIL NADU FEDERATION OF OBSTETRICIANS & GYNAECOLOGISTS

Article - 2

INVESTIGATION AND DIAGNOSIS OF ANEMIA

Dr Niranjana Asokan
MS DNB MRCOG

INTRODUCTION:

According to WHO anemia is a common condition, and 50% of it is due to iron deficiency. Iron deficiency anemia is common in pregnancy and postpartum and can result in complications to mother and fetus. Pregnancy is a state of physiologic anemia due to disproportionate increase in plasma volume and red cell mass. This can lead to missed diagnosis of anemia unless properly investigated and end up in a complicated pregnancy if anemia is uncorrected.

TESTS AND SIGNIFICANCE:

HEMOGRAM:

Hemoglobin:

Hemoglobin is iron containing pigment required for oxygen transport. The definition of anemia is fall in hemoglobin below expected value for age, gender, pregnancy. It is an important and easy screening test to diagnose anemia.

The cut off to be diagnosed as anemia is <11g/dl in 1st and 3rd trimester, <10.5g/dl in 2nd trimester and <10g/dl in postpartum period. Hemoglobin needs to be estimated once in every trimester as the growing fetus might increase iron requirements and lead to iron deficiency anemia.

However individuals living in high altitudes, regular exercise, polycythemia vera can present with increased hemoglobin.

RBC count:

This refers to number of red blood cells present in 1ml of whole blood. In initial stages of iron deficiency, the count is maintained by the body producing hypochromic red cells, which gradually falls with severity of iron deficiency. But in thalassemia due to repeated transfusion and eryhtropoiesis, RBC count can be increased.

Packed cell volume:

Also called as hematocrit this value refers to percentage of red blood cells in blood volume. When hemoglobin is the only test available, hemoglobin*3 gives the value of hematocrit.

RED CELL INDICES:

Mean cell volume (MCV):

This refers to average size of red cells. Reduced MCV is called microcytic and increased MCV is macrocytic. This test can be used to differentiate between different types of anemia.

Mean cell hemoglobin (MCH):

This refers to amount of hemoglobin in a red cell and measured in picograms.

Mean cell hemoglobin concentration (MCHC):

Although megaloblastic anemia has macrocytic RBC, MCHC remains constant as it is proportion of hemoglobin in a red cell. The increase in cell size compensates

increased hemoglobin concentration, maintaining normal MCHC. The condition with raised MCHC is hereditary spherocytosis.

Reticulocyte count:

Reticulocytes are precursor of RBC. When RBC are formed in marrow, as they mature the reticulocytes lose nuclei and structures concerned with protein synthesis to form mature RBC. This value is an indicator of erythropoietic activity of marrow. Values are depressed in conditions of marrow failure, aplastic anemia. Reticulocyte count is also useful in assessing response to treatment with iron. When the deficiency is corrected, marrow has eryhtropoiesis causing increased reticulocyte count in peripheral blood. Levels more than 2.5x normal is suggestive of hemolytic anemia.

Red cell distribution width:

RDW refers to variation in red cell size. RDW values have 84.5% sensitivity, 70.6% specificity, 83.1% positive predictive value, 72.7% negative predictive value in determining type of anemia. Low values are seen in iron deficiency anemia and increased values with thalssemia. Anisopoikilocytosis associated with iron deficieny anemia greatly alters the size of RBC thus increasing the RDW, whereas thalassemia doesn't alter shape of red cells and has normal RDW.

Serum iron:

Iron deficiency anemia progresses in stages.

- Compensatory phase where serum iron levels are maintained, but serum ferritin levels are compromised as storage iron is utilized for body functioning
- Iron deficiency – where serum iron levels are low, but body compensates by other mechanisms and red cell indices are maintained.
- Iron depletion – where the serum iron levels are so low that no compensatory mechanism can counter the fall in red cell indices.

But when it comes to conditions like thalssemia, the frequent blood transfusions result in a state of iron overload characterized by increased serum iron in the presence of anemia.

Transferrin saturation:

Transferrin is required to transport absorbed iron to various sites in body such as marrow, liver. The amount of iron bound to transferrin expressed as percentage of TIBC is transferring saturation. This value is severely affected in iron deficiency when levels of iron in body are low.

Total iron binding capacity:

This refers to percentage of transferrin not bound to iron. The values are significantly increased in rion deficiency due to less iron available for transport.

Serum Ferritin:

Ferritin is storage form of iron and is a good marker to identify iron deficiency. This test is highly sensitive and specific. With severe iron deficiency, ferritin levels are very low, leading to compensatory rise in erythropoietin and fall in

hepcidin levels to improve iron transport. However following chronic diseases, the inflammatory markers cause rise in ferritin even with anemia. This is the drawback of this test, as ferritin is an acute phase reactant and can be elevated with inflammation.

Peripheral smear:

This test analyses the structure and numbers of various blood tests and is useful to classify type of anemia. Macrocytes are noted in liver disorder, B12 deficiency and folate deficiency. Hypersegmented neutrophils are a hallmark feature of megaloblastic anemia due to B12 deficiency. In conditions such as aplastic anemia there can be generalized pancytopenia.

Hemoglobin electrophoresis:

With this, the type of hemoglobin is assessed to find the type of anemia. The common form of adult hemoglobin is HbA2. When there is mutation in β globin gene, a variant of hemoglobin called HbS is formed which decreases the fragility of red cell membrane causing it to undergo sickling when exposed to hypoxia. Genetic alteration in α and β globin gene cause thalassemia which presents with variants of hemoglobin such as HbF.

Bone marrow examination:

This is an invasive procedure and is done to rule out or confirm other causes of anemia. Bone marrow iron levels denote severity of iron deficiency.

Serum vit B12 and folate:

The ened for this test is to differentiate between megaloblastic anemia. Although both present with similar investigation findings, folate deficiency can present with associated neural tube defect in fetus and B12 deficiency can have

neurologic manifestations. Supplementing iron without correcting the vitamin deficiency in megaloblastic anemia is of no use and proper supplements can be decided based on tests.

Bilirubin:

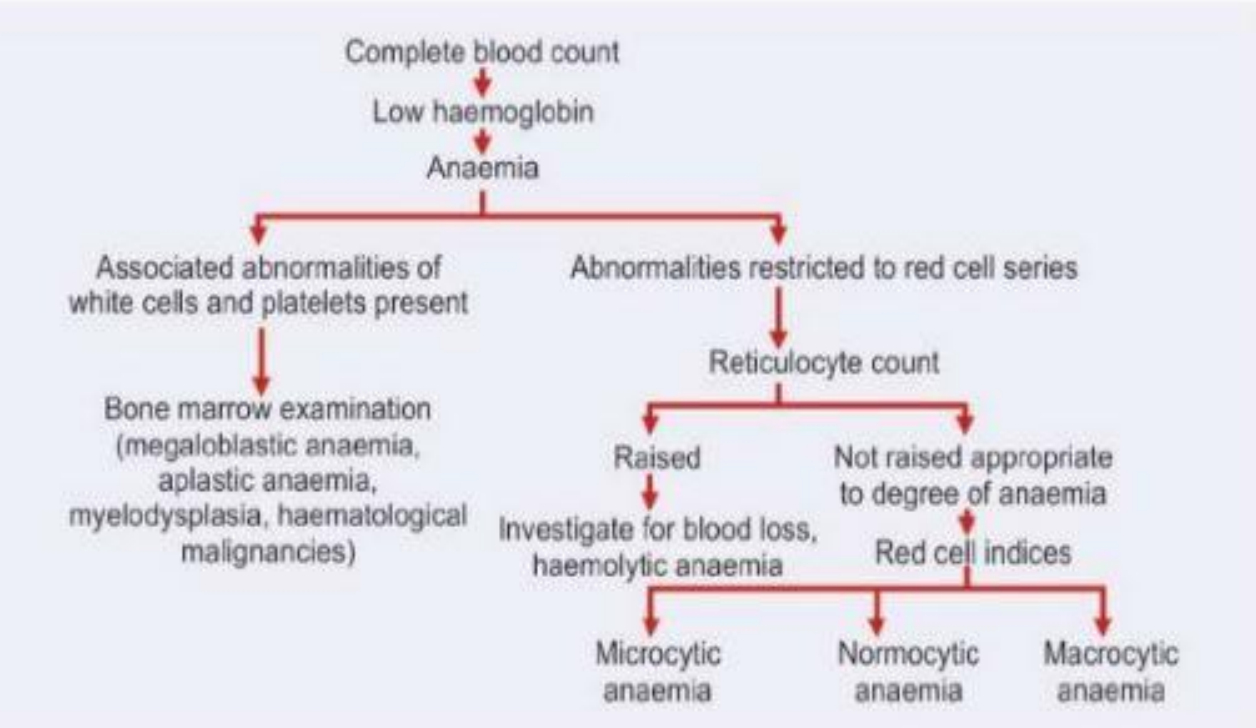
Hemoglobin when broken down forms bilirubin. This mechanism is the basis of using bilirubin as marker to identify hemolytic conditions causing anemia such as TTP, HUS, HELLP, pre eclampsia.

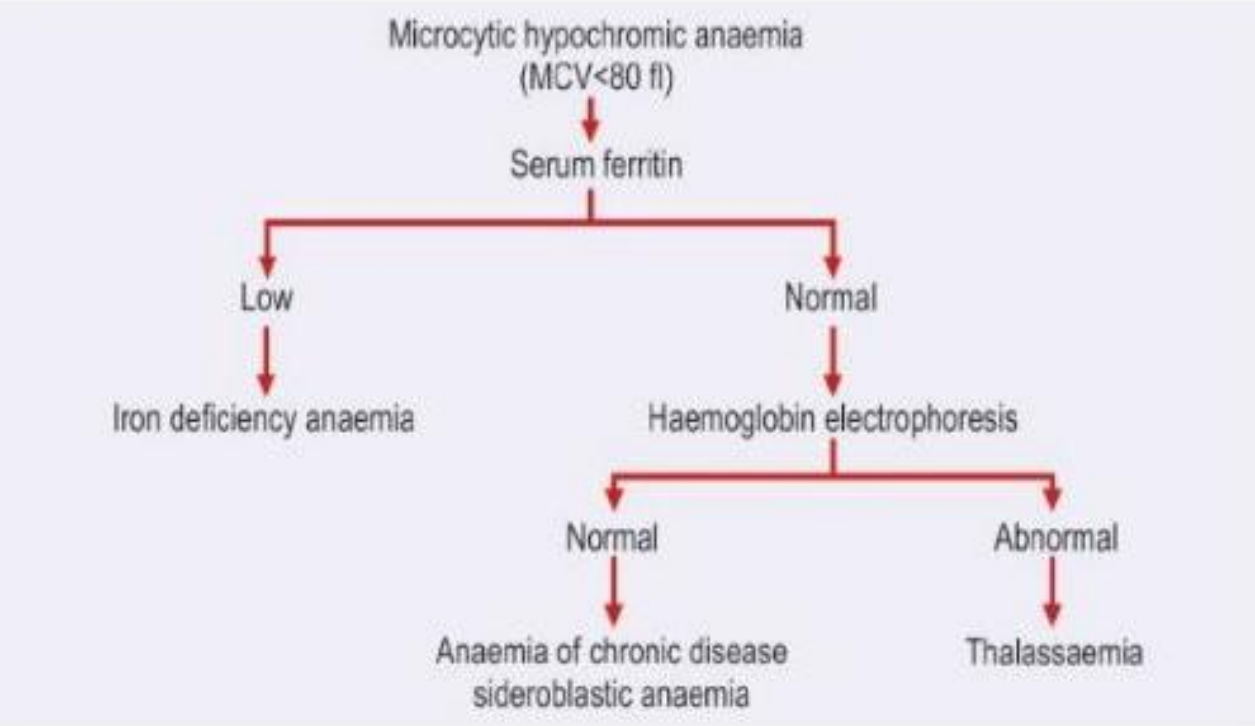
INTERPRETATION:

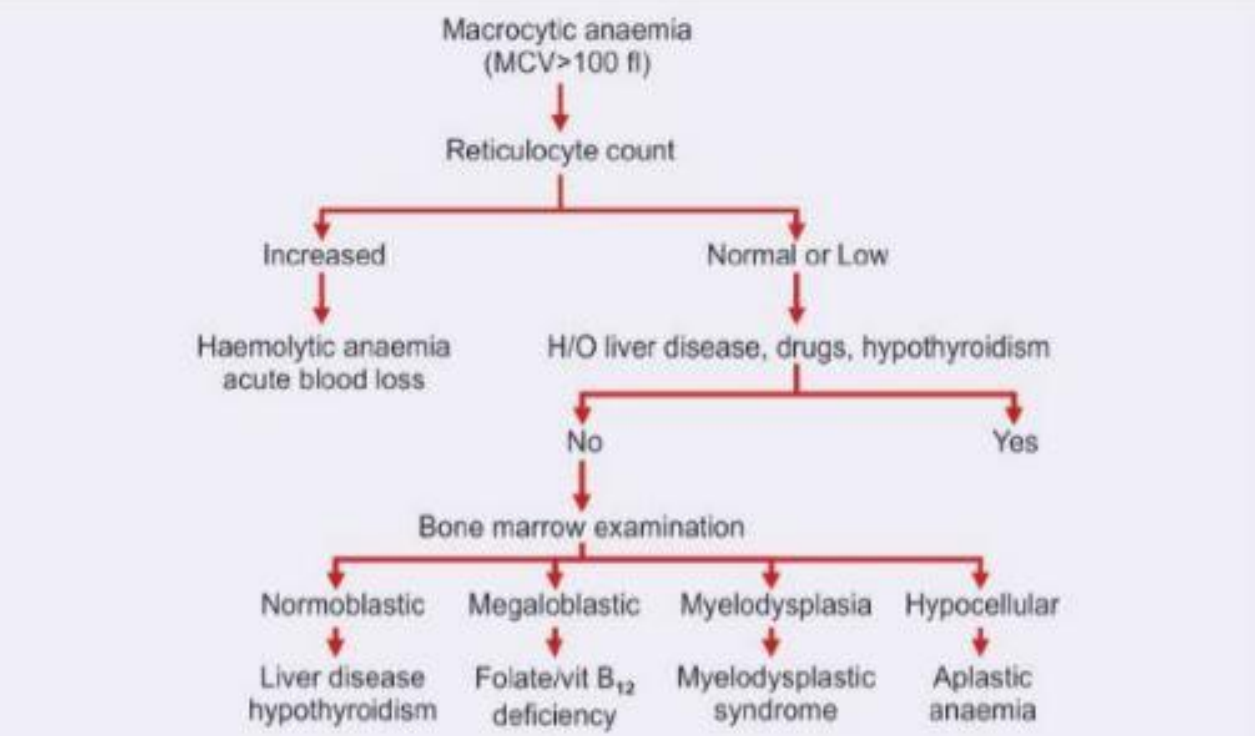
	Iron deficiency	B12 deficiency	Folate deficiency	Sickle cell anemia	Thalassemia	Aplastic anemia	Hemolytic anemia
Hemoglobin	↓	↓	↓	↓	↓	↓	↓
Hematocrit	↓	↓	↓	↓	↓	↓	↓
Ferritin	↓				↑/N		
Serum iron	↓				↑		
Transferrin saturation	↓				↑/N		
TIBC	↑				N		
Bone marrow iron	↓				↑↑		
RBC count	↓	↓	↓			↓	
Reticulocyte	↓/N			↑↑		↓	↑↑
MCV	↓↓	↑	↑			N	N
MCH	↓	↑	↑			N	N

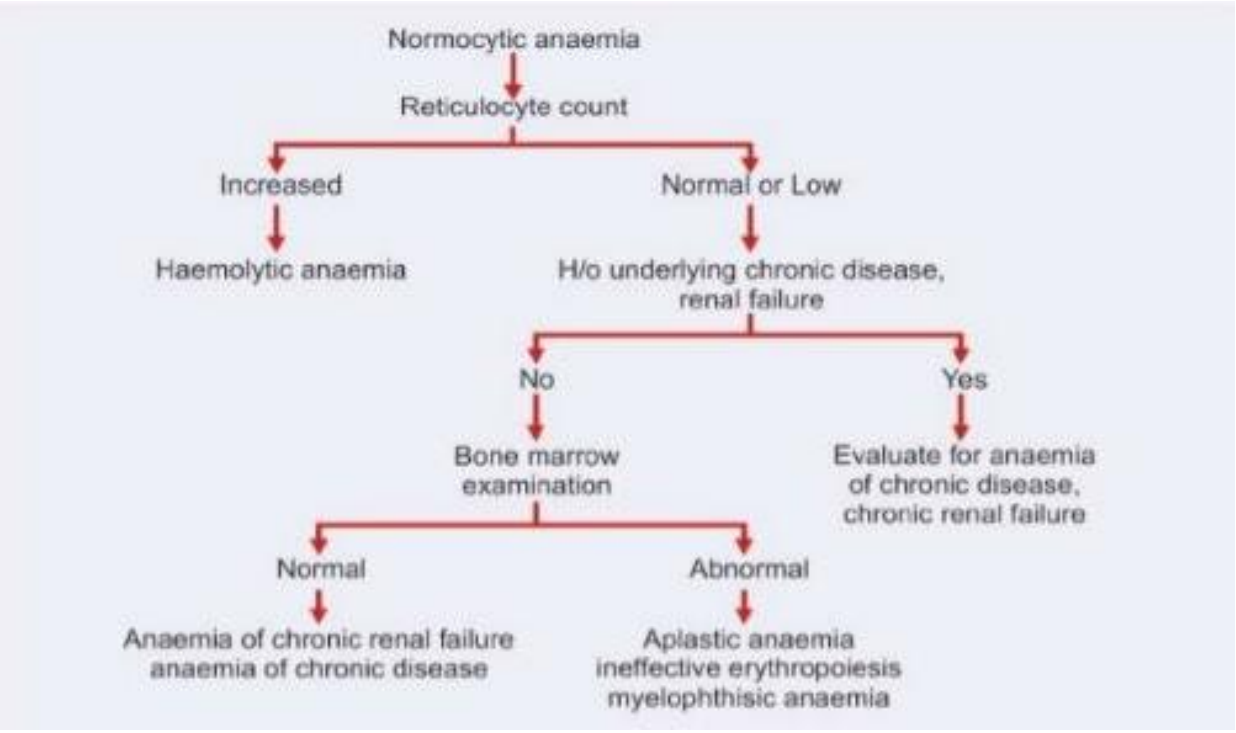
MCHC	↓	↓/N	↓/N			N	↑/N
RDW	↑	↑	↑		N		↑
P smear	Microcytic hypochromic	Macrocytic hyperchromic	Macrocytic hyperchromic	Sickle cells		Pancytopenia	Fragmented RBC
	Pencil cells	Hypersegmented neutrophils	Elliptocytes	Howell Jolly bodies	Target cells		Spherocytes, Schistocytes
Hb electrophoresis				HbS, HbF	HbF		
Osmotic fragility test							+
Vit B12		↓					
Folate			↓				
BIlirubin				↑/N			↑
Bone marrow	Low iron on Prussian blue staining	Erythroid hyperplasia					
Other tests		Schilling test, Pernicious anemia testing – anti IF antibodies					

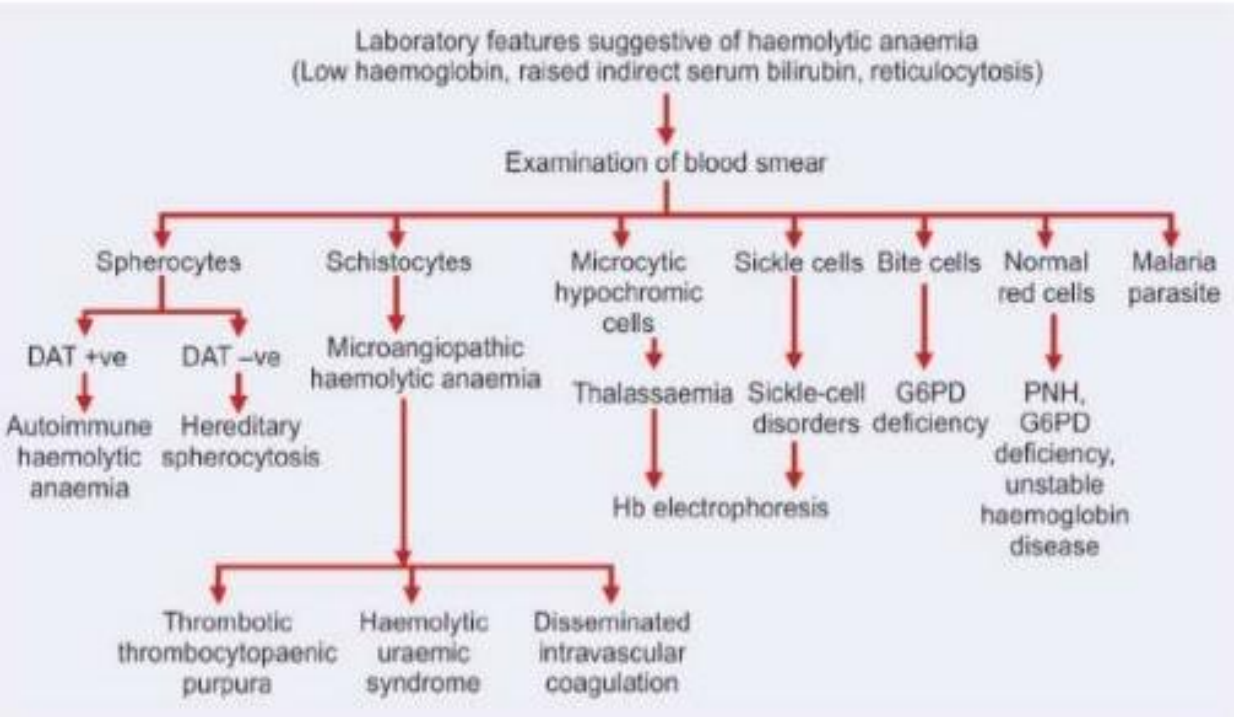
Test	Normal value
Hemoglobin	12-15g/L
RBC count	4-4.5*10^{12}/L
Reticulocyte count	0.5-2.5%
PCV	40-45%
MCV	84-96fL
MCH	26-36pg
MCHC	32-36%
RDW SD	40-45fL
RDW CV	12-14%
Ferritin	30µg/L
TIBC	300-360µg/dL




Microcytic hypochromic anaemia
(MCV<80 fl)
Serum ferritin
Low
Normal
Iron deficiency anaemia
Haemoglobin electrophoresis
Normal
Abnormal
Anaemia of chronic disease
sideroblastic anaemia
Thalassaemia


Macrocytic anaemia
(MCV>100 fl)
Reticulocyte count
Increased
Normal or Low
Haemolytic anaemia
acute blood loss
H/O liver disease, drugs, hypothyroidism
No
Yes
Bone marrow examination
Normoblastic
Megaloblastic
Myelodysplasia
Hypocellular
Liver disease
hypothyroidism
Folate/vit B12
deficiency
Myelodysplastic
syndrome
Aplastic
anaemia


Normocytic anaemia
Reticulocyte count
Increased
Normal or Low
Haemolytic anaemia
H/o underlying chronic disease, renal failure
No
Yes
Bone marrow examination
Evaluate for anaemia of chronic disease, chronic renal failure
Normal
Abnormal
Anaemia of chronic renal failure anaemia of chronic disease
Aplastic anaemia ineffective erythropoiesis myelophthisic anaemia


Laboratory features suggestive of haemolytic anaemia
(Low haemoglobin, raised indirect serum bilirubin, reticulocytosis)
Examination of blood smear
Spherocytes
Schistocytes
Microcytic hypochromic cells
Sickle cells
Bite cells
Normal red cells
Malaria parasite
DAT +ve
DAT –ve
Microangiopathic haemolytic anaemia
Thalassaemia
Sickle-cell disorders
G6PD deficiency
PNH, G6PD deficiency, unstable haemoglobin disease
Autoimmune haemolytic anaemia
Hereditary spherocytosis
Hb electrophoresis
Thrombotic thrombocytopaenic purpura
Haemolytic uraemic syndrome
Disseminated intravascular coagulation

CONCLUSION:

Anemia is a preventable cause of maternal mortality and morbidity.

A simple screening test can pick up anemia and greatly improve maternal outcome in pregnancy. This emphasizes the need for investigation and diagnosis of anemia in pregnancy. There are various types of anemia which need to be evaluated with a series of investigations to ensure appropriate treatment.

TAMIL NADU FEDERATION OF OBSTETRICIANS & GYNAECOLOGISTS

Article - 3

IRON DEFICIENCY ANEMIA

Dr M.Meena

MD, DGO, DNB (OB&G)

Anemia

It is defined as low hemoglobin concentration resulting in decrease in oxygen carrying capacity of blood. Anemia in pregnancy is associated with high maternal morbidity and mortality.

WHO Definition

Haemoglobin concentration less than 11g/dl and haematocrit less than 33% is defined as anemia in pregnancy.

CDC Definition

Hemoglobin concentration of less than 11g/dl in first trimester and third trimester; and less than 10.5g/dl in second trimester during pregnancy.

Severity of anemia

- Mild anemia – 9-10.9g/dl
- Moderate anemia – 7-8.9g/dl
- Severe anemia - <7g/dl

Diagnosis

Symptoms

- Mild anemia – usually asymptomatic
- Moderate anemia – Generalized fatigue, exhaustion, loss of appetite, giddiness, breathlessness
- Severe anemia – Palpitation, breathlessness

Signs

- Mild anemia – No signs
- Moderate & Severe anemia - Pallor, nail changes (platynychia, koilonychia), cheilosis, glossitis, stomatitis, signs of congestive cardiac failure

Investigations

- Hemoglobin estimation – Minimum of 4 Hb estimation is compulsory, with an interval of 4 weeks between 2 tests. Usually done at 14-16 weeks, 20-24 weeks, 26-30 weeks and 30-34 weeks in all pregnant women.
- Peripheral blood smear
- Normal – Normocytic normochromic RBCs
- Iron deficiency anemia – Microcytic hypochromic RBCs, Anisopoikilocytosis
- Reticulocyte count – slightly raised in IDA but rises more after anemia correction with IDA
- Haematocrit – reduced in IDA
- Blood indices – MCV, MCH, MCHC – all reduced in IDA; MCHC being independent of RBC count is the most sensitive index of IDA

- MCV/RBC ratio
- Serum iron binding capacity
- Stool ova and cyst
- Urine routine to look for albumin, sugar & deposits, should be done to rule out refractory anemia & Urine Culture

Treatment

Gestational age	Hb levels	Treatment	Follow up
At 14-16 weeks	Hb > 11g/dl	Prophylactic dose of IFA tablets	
	Hb 7.1-10.9 g/dl	Therapeutic dose of IFA tablets	
	Hb < 7g/dl	Blood transfusion	
At 20-24 weeks	Hb > 11g/dl	Prophylactic dose of IFA tablets	
	Hb 9-10.9 g/dl	Therapeutic dose of IFA tablets	
	Hb 7.1-8.9 g/dl	IV Iron sucrose	Repeat Hb after 4 weeks
	Hb < 7g/dl	Blood transfusion	Repeat Hb after 24 hours
At 26-30 weeks	Hb > 11g/dl	Prophylactic dose of IFA tablets	
	Hb 9-10.9 g/dl	Therapeutic dose of IFA tablets	
	Hb 7.1-8.9 g/dl	IV Iron sucrose	Repeat Hb after 4 weeks
	Hb < 7g/dl	Blood transfusion	Repeat Hb after 24 hours
At 30-34 weeks	Hb > 11g/dl	Prophylactic dose of IFA tablets	
	Hb 9-10.9 g/dl	Therapeutic dose of IFA tablets	
	Hb < 9 g/dl	Blood transfusion	Repeat Hb after 24 hours

Deworming: One tablet of Albendazole 400mg at 14-16 weeks

IRON SUPPLEMENTATION IN INDIA

Ministry of Health, Government of India Recommendation – Indian National Iron Programme, April 2018 guidelines recommend intake of 100mg elemental iron with 500mcg of folic acid from 14th week for a period of 180 days and to be continued for 180 days post-partum.

Oral Iron:

- Iron in the form of ferrous sulphate is the best choice.
- After deworming, Prophylactic or therapeutic dose of oral iron therapy is to be started, along with vitamins supplementation (1 tablet of vitamin B12 15mcg & Vitamin C 100mg once daily)
- **Prophylactic dose:** Tab. IFA (100mg of elemental iron with 0.5mg of folic acid) once daily for 100 days.
- **Therapeutic dose:** Tab. IFA (100mg of elemental iron with 0.5mg of folic acid) twice daily for 100 days.

Oral iron preparations:

- Sodium feredetate
- Ferrous sulphate
- Ferrous ascorbate
- Ferrous fumarate

Sodium feredetate

- Sodium feredetate is effective in improving haemoglobin profile in pregnant anaemic women and it is tolerated well.

- Moderate iron supplementation with sodium feredetate is beneficial in improving iron deficiency and oxidative stress, and it is better than ferrous sulphate.
- Sodium feredetate is effective in reducing the prevalence of iron deficiency in women of childbearing age.

Adverse effects of oral iron

- Constipation
- Bloating, diarrhoea, abdominal cramps
- Heartburn, nausea
- Dark stools
- Oxidative radical injury

Drug interactions of oral iron

- Oral iron decreases the absorption and efficacy of antibiotics (by forming insoluble complexes in gastrointestinal tract), levothyroxine and methyldopa.
- Iron absorption is decreased by antacids, H2 receptor blockers, proton pump inhibitors, antibiotics and calcium supplements.

Parenteral Iron:

- Discontinue oral iron therapy while patient on IV Iron sucrose till repeat Hb estimation after 4 weeks of IV Iron sucrose.
- Oral iron must not be administered concomitantly with IV Iron. After a period of 5 days from the final dose of IV iron, oral iron can be restarted.

Formulate to calculate IV iron sucrose

- Body weight [kg] x (Target Hb – Actual Hb) [g/l] x 2.4 + Iron stores [mg]

Parenteral Iron

Indications	Contraindications
• Intolerance to oral iron • Malabsorption • Poor compliance • Routine supplementation to TPN • Patients on erythropoietin • No response to oral iron in 2 weeks (Hb rise/ reticulocyte count) • IDA in third-trimester	• Anemia not attributable to iron deficiency • Iron overload • Hypersensitivity to IV iron • Liver cirrhosis • Acute or chronic infection • First-trimester of pregnancy • Acute renal failure • H/o severe asthma, eczema or other atopic allergies
NHS 2018; IDA: iron deficiency anemia; TPN:total parenteral nutrition; Hb: haemoglobin.	

Parameters	Injection ferric carboxy maltose (FCM)	Injection Iron sucrose
Dose	1000 mg IV in 200 ml normal saline over 15-20 mins in one sitting. Minimum time 15 min.	100 mg IV in 100 ml normal saline (NS) in 15 to 20 mins thrice weekly OR 200 mg in 100 ml NS in 15 to 20 mins thrice weekly. Total dose not to exceed 600 mg per week to avoid toxicity.
Maximum dosage	1000 mg in a week	600 mg in a week
Number of visits	Less	More

Adverse events	• Injection site reaction • Transient hypophosphatemia	• Injection site reaction • Transient hypophosphatemia
Advantage	• Gradually releases iron, no acute toxicity • Deposits in reticuloendothelial system (RES), no oxidative stress • Can be given as rapid infusion	• Large dose should be avoided as it can cause iron toxicity • Causes oxidative stress • Slow infusion
Contraindications	• Hypersensitivity reactions • Hepatic impairment • Chronic infections like HIV, hepatitis • Iron overload disorders	• Hypersensitivity reactions • Hepatic impairment • Chronic infections like HIV, hepatitis • Iron overload disorders
HIV: human immunodeficiency virus.		

Summary of iron therapy in pregnancy and post-natal period

- Oral iron is ideal for prophylaxis and mild to moderate iron deficiency in pregnancy mostly up to 30 weeks.
- If oral iron is not very effective/ poor compliance/ not tolerable, it is better to reassess the response to treatment by 3 to 4 weeks and opt for parenteral iron early rather than later.

- Parenteral iron: Dextran molecule is no longer preferred for either IV or IM as safer and better option of iron sucrose IV is available.
- Ferric carboxy maltose is not administered in antenatal period as studies are still awaited, but it is a wonderful option to treat post-natal anemia with single dose option.

Blood transfusion

Indications:

Antepartum period
1. In any trimester a. Severe anemia Hb < 7 g/dl with or without signs of cardiac failure or hypoxia **2. In third trimester** a. Hb < 9 g/dl even without signs of cardiac failure or hypoxia **3. Acute haemorrhage** a. Hb < 7 g/dl b. Anemia with signs of shock/ hemodynamic instability due to ongoing hemorrhage
Intrapartum period a. Hb < 7 g/dl (in labour) b. Decision of blood transfusion depends on medical history or symptoms
Postpartum period a. Anemia with signs of shock/ acute haemorrhage with signs of hemodynamic instability b. Hb < 7 g/dl (postpartum): Decision of blood transfusion depends on medical history or symptoms

Article - 4

ANEMIA IN PREGNANCY IN RESOURCE POOR SETTING

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The most prevalent yet preventable disease prevailing in lower socio-economic group of people in our motherland is ANEMIA. Of course, it is also predominant in the upper socioeconomic group as well. Having said so, it is contributing to major and minor morbidity as well as mortality either directly or indirectly. Its significance has been underscored over the years and now it is the major player in almost all comorbid situations.

Anemia in pregnancy is a global health problem and always detrimental to the final maternal and neonatal outcome unless it is identified and treated early. Challenges are encountered in the diagnosis, investigation, interpretation of the various investigations performed and in the treatment. In the resource poor setting it is further compounded by the severity of anemia. While some degree of dilutional anemia is part of normal pregnancy physiology, iron deficiency anemia can have serious adverse health consequences for the mother and child. Thus, it is critical to distinguish iron deficiency anemia from physiologic anemia, as well as to identify other less common causes of anemia that may require treatment. IDA remains the most common cause, primarily due to recurrent menstrual loss and secondary due to poor supply of iron in the diet.

Definitions and prevalence of anemia are different in pregnant women compared with non-pregnant, and the lower limit of normal for the hemoglobin concentration may vary in different populations. WHO data shows 40.1% of

pregnant women worldwide were anemic in 2016. India contributes to about 80% of the maternal death due to anemia in South Asia.

There is marginally decrease in prevalence of anemia in pregnant women in India from 58% in NFHS-3 in 2005-06 to 50% in NFHS-4 survey in 2015-16. ICMR considers haemoglobin level below 10.9 g/dl as cutoff point for anaemia during pregnancy.

Govt. policies are perfect in the setting of an office, but in reality they seldom or occasionally reach the beneficiaries. The Ministry of H&FW, GOI has given emphasis to prevent anemia under RMNCH+A services. National Health Policy 2017 also addressed malnutrition and micronutrient deficiencies interventions. National Iron Plus initiative launched in 2013 is also a comprehensive strategy to combat the public health challenge of IDA. National Nutrition Mission aims to reduce anemia among young children, adolescent girls and women of reproductive age (15-45 yrs) by one third of NFHS-4 levels by 2022. Yet, anemia continues to lead the list of nutritional deficiency diseases.

ISSUES IN RESOURCE POOR SETTINGS:

- Lack of awareness in the society
- Lack of knowledge for planning a pregnancy [contraception]
- Prevailing myths in the society
- Preexisting moderate to severe anemia prior to pregnancy
- Delay in diagnosis of pregnancy
- Lack of facilities for proper care [poor access]
- Lack of qualified manpower
- Nonavailability of diagnostic facilities
- Poor interpretation of the results
- Refusal to treatment

- Nonavailability of parenteral iron therapy
- Foeto-maternal complications
- Enhanced maternal and perinatal morbidity and mortality
- Lack of faith in the system and the vicious cycle continues

MY EXPERIENCE OF 34 YEARS IN LOW RESOURCE SETTING:

Poor awareness with limited access to health care facilities drive the initial scenario, which results in pregnant women attending much late when damages have already been established. Clinical skill of the provider is pivotal to diagnose iron deficiency in such settings. Estimation of haemoglobin is available under all National Health Mission facilities and that is the rate limiting step in your investigation. Peripheral blood smear study apparently sounds pretty simple investigation and should have been available in all low resource settings. Sadly, we miss them in our day- to-day practice. NHM guideline supports parenteral iron therapy based only on Hb estimation. Oral irons are never patient friendly and ideal iron salt is far from being easily available. Under the scenario we have no alternative but to load the system with either iron sucrose or ferric carboxy maltose as per availability. Few trivial reactions here and there also is a negative factor for the wide acceptance of this modality which to me is most suitable for the low resource settings. In many anemia in pregnancy iron deficiency is compounded by dimorphic anaemia, thalassemia or refractory anemia and this requires further investigations. So, in spite of correcting iron deficiency the anemia persists and exerts its ill effect on foeto-maternal health. But we must continue to correct iron deficiency with either oral or parenteral iron as majority of the pregnant women are benefitted with this protocol. Deworming and concomitant treatment of malaria [if diagnosed] also is important and should never be left out of your mind. Trimester specific clinical examination combined

with other antenatal investigations with a priority on ultrasonography is the rule, but not routinely available in all resource poor health care facilities. Some brainstorming is required how we can implement this for all across the country. I am ashamed that I belong to the state which has highest maternal mortality in the country. Yet, policy makers should enroll ground realities into their guidelines so that it reaches to the furthest in this diverse country. Only care providers can not change the scenario, though we remain a very important component in the system.

Coming to the intrapartum management the picture is far from satisfactory and risk stratification is once again pivotal. Due to multi-facted reasons pregnant women want to remain in close proximity to their homes by all counts. In all low resource facilities this is another challenging task. Non availability of anaesthetist, paediatrician and pathologist are also a concern. Availability of blood and blood components is another major concern.

Overall, we all are dependent on the almighty during the journey of labour and delivery for every parturient and more so when there is associated major comorbidity like anemia.

REMEDIAL STEPS:

- Early detection and correction of anemia
- Parenteral iron is the game changer
- Trimester specific antenatal checkup
- Timely referral to higher centre
- Postpartum contraception

[Disclaimer: opinion documented is personal and has no outside influence]

Article - 5

MEGALOBLASTIC ANAEMIA IN PREGNANCY

Dr Abha Rani Sinha

DGO,MS ,FICOG

Anemia is one of the most important public health problems leading to significant maternal and perinatal morbidity and mortality The term megaloblatic anaemia is used to describe a macrocytic anaemia that is associated with megaloblastic change in the erythroid precursors in the bone marrow.

Both Folic acid deficiency and Vitamin B12 deficiency can cause megaloblastic anaemia but majority of the cases are due to deficiency of Folic acid .Association of Folic acid deficiency with abruption and Preeclampsia has been suggested but it has not been established .Folic acid deficiency is also associated with FGR and Neural tube defects in fetus.

Pathophysiology

In Megaloblastic anemia there is ineffective erythropoiesis secondary to intramedullary apoptosis of hematopoietic cell precursors, which results in DNA synthesis abnormalities. Both vitamin B12 and folate deficiencies may cause defective DNA synthesis. Subsequently, the nucleus and cytoplasm do not mature simultaneously. The cytoplasm (in which hemoglobin synthesis is unaltered) mature at the normal rate, and the nucleus (with DNA impairment) is not fully mature. The asynchronous maturation between the nucleus and cytoplasm of erythroblasts, explains the large size of the megaloblasts.

Folic acid Deficiency

The most common cause of folic acid deficiency is dietary insufficiency from intake of diet low in animal proteins, fresh leafy vegetables, and legumes Other causes could be Multiparity ,Multifetal Pregnancy.Use of medication eg, phenytoin, sulfasalazine, trimethoprim, methotrexate, malabsorption, inflammatory bowel disease and major intestinal resection or bypass, celiac disease, significant liver disease, renal failure requiring dialysis, and ethanol abuse and Methylenetetrahydrofolate reductase (MTHFR) polymorphisms

Prophylaxis

Recommended daily folate intake is 400 to 800 mcg beginning at least one month prior to attempting conception and continuing throughout pregnancy for all women of child bearing age.

In individuals with documented folate deficiency, supplemental folic acid (1 mg/day) is advised prior to conception. This dose is more than sufficient for prevention of folate deficiency and fetal neural tube defects associated with folate deficiency in the vast majority of individuals. In women with a previous pregnancy affected by fetal neural tube defects the recommended dose of preconception folic acid is 4 mg/day.

ACOG recommends at least 0.4 mg per day folic acid for women with diabetes contemplating pregnancy, and opines that higher doses (0.8 to 1 mg) may be beneficial in high risk women, such as those with other risk factors for NTDs The American Diabetes Association also suggests a minimum dose of at least 0.4 mg per day The SOGC recommends 1 mg per day The Endocrine Society

suggests 5 mg/day beginning three months before discontinuing contraception or otherwise trying to conceive, and reducing the dose to 0.4 to 1.0 mg/day at 12 weeks of gestation through the completion of breastfeeding.

Diagnosis

Complete Blood count

MCV> 100fl
White cells and platelets may be moderately reduced

Peripheral blood smear

- Hypersegmented neutrophils, Macrocytes
- Low serum folic acid and red cell folate levels
- Elevated serum LDH levels
- Elevated serum homocystein levels

Treatment

- Oral Folic acid tablets 1mg
- Dietary advice
- Correct concurrent Iron deficiency

Folate therapy should not be instituted in a patient with megaloblastic anemia if cobalamin deficiency has not been definitively ruled out. The danger is that folic acid will improve the anemia but not the neurological complications of cobalamin deficiency, and the neurological

disorder will worsen. Both cobalamin and folate should be given if cobalamin deficiency has not been ruled out

Vitamin B12 Deficiency

Anaemia due to isolated Vitamin B12 deficiency is rare

Causes

Inadequate dietary intake (Vegans and Vegeterians),Pernicious anaemia caused by lack of intrinsic factor, Gastrectomy and gastritis, Malabsorption syndrome,Zollinger-Ellison syndrome,HIV infection,Hereditory disorders

Clinical symptoms -Takes a long time to manifest.If there is Iron deficiency anaemia Vit B12 deficiency may get masked

Signs and symptoms of severe Vitamin B12 deficiency

Smooth beefy tongue with loss of papillae

GI symptoms-Anorexia,nausea and vomiting,Heartburn,Flatulence

Neurological Symptoms

- Paresthesia,
- Numbness,
- Weakness,
- Impaired memory
- Skeletal changes-Osteoporosis

Diagnosis

Complete Blood Count

- Low Hb and Haematocrit
- Low RBC count
- High MCV> 100fl
- Low MCHC
- Normal or low Reticulocyte count

- Normal or Low white blood cell count
- Low Platelet count

Peripheral blood smear

Macrocytic RBC's

Hypersegmented Neutrophils Howell-Jolly bodies, anisocytosis, and poikilocytosis.

Serum levels

Low Vitamin B12 Levels- Levels of less than 200 pg/ml of vitamin B12 indicate a deficiency

Lab tests to confirm and distinguish B-12 and folate deficiencies

Serum homocysteine and methylmalonic acid (MMA) levels are helpful confirmatory tests for cobalamin and folate deficiencies. Both are increased in cobalamine deficiency. Homocysteine but not MMA is increased in folate deficiency. Homocysteine and MMA levels should be used if the clinical presentation and serum vitamin B-12 and
folate levels are ambiguous.

Treatment

Intramuscular Cobalamin is administered

Dose- Usually, patients receive 1000 ug of vitamin B12 daily in their first week. In the following month, they receive weekly and then monthly injections. Usually, reticulocytosis occurs within 3 to 5 days. By the tenth day, hemoglobin starts to increase, and a total resolution of anemia normally occurs after 2 months of treatment. The reversal of neurological changes typically takes a longer time, and some manifestations will not disappear even if treatment starts promptly. The

treatment should be continued indefinitely at a dose of 1000 ug/month. In some cases, particularly in patients with prior total gastrectomy or extensive ileal resection, preventive treatment with vitamin B12 is for life.

Monitoring Response to Therapy

Although patients may feel better as soon as therapy is started, improvements must be monitored with laboratory tests which should include the following:

- Complete blood cell count
- Reticulocyte count
- Lactate dehydrogenase (LDH) level
- Indirect bilirubin
- Hemoglobin level
- Serum potassium level
- Serum ferritin

Elevated levels of LDH and indirect bilirubin should fall rapidly. A prolonged elevation of the LDH level indicates a failure of therapy, development of iron deficiency, or an error in diagnosis.

Reticulocytosis should be evident within 3-5 days and peaks in 4-10 days. Leukocyte and platelets counts are usually restored to normal within days after therapy has been started, but hypersegmented neutrophils may persist for 10-14 days. The hemoglobin should rise approximately 1 g/dL each week. This rise is valuable for monitoring a complete response. If the hemoglobin does not rise appropriately and is not normal within 2 months, other causes of anemia, such as iron deficiency, should be considered.

Serum potassium levels can fall during therapy for severe cobalamin or folate deficiency and can lead to sudden death. Therefore, potassium should be monitored and supplements may be indicated.

Iron deficiency can occur in the course of treatment due to the consumption of iron stores for RBC production.

The development of iron deficiency can impede the response to cobalamin or folate therapy. Iron therapy may be indicated.

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Article - 6

THALASSEMIA AND SICKLE CELL ANAEMIA IN PREGNANCY

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Bangalore

Thalassaemias and Sickle cell Anaemias are inherited disorders of Haemoglobin synthesis and come under the category of Haemoglobinopathies, one of the commonest monogenic inherited diseases.

Some important features of all Haemoglobinopathies are:

- Seen frequently in Africa, Mediterranean region and Far-East Asia
- Prognosis varies with the access to medical care. However, in modern times, almost 90% survive into adulthood.
- Almost 7% of the world is in a carrier state.

Haemoglobinopathies are broadly classified into

1. **Thalassemia Syndromes**: there is a **quantitative** defect in the production of one of the Globin sub-units, either total absence or marked reduction
2. **Sickle cell disorders**: there is a **structural** defect in one of the Globin sub-units
3. **HbC**
4. **C-B Thalassemia**
5. **HbE**

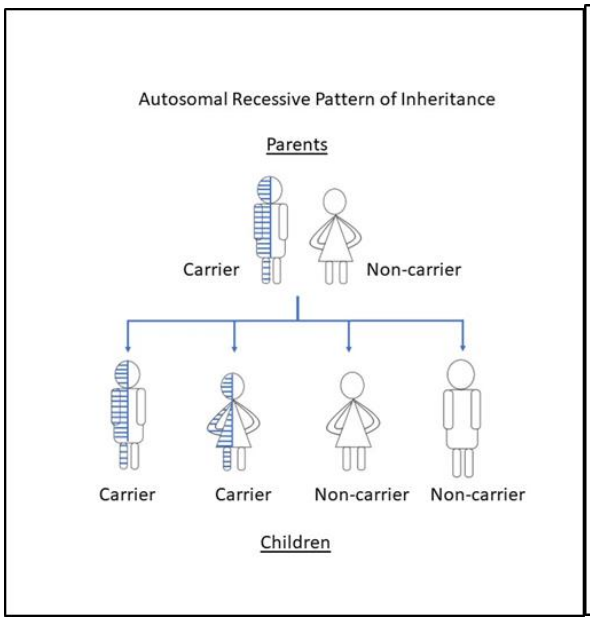
Thalassemia syndromes are broadly classified into

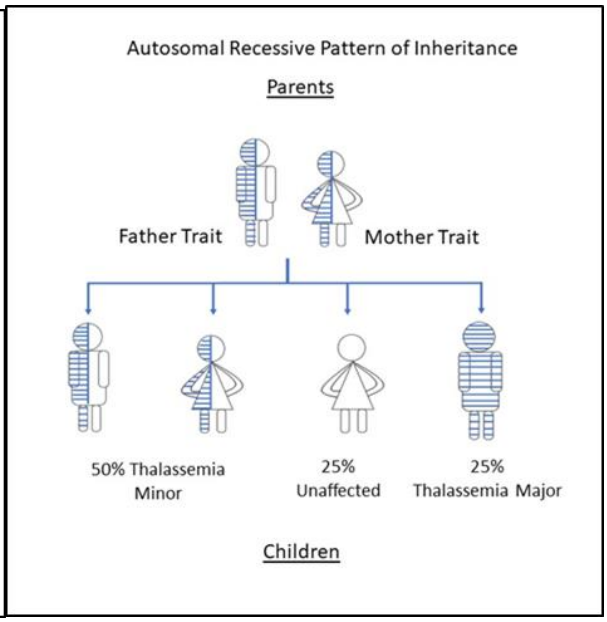
1. **Alpha thalassemia**: deletion of alpha-globin gene
2. **Beta thalassemia**: defect in the beta-globin gene

Thalassemia: most common recessive, genetic disorder affecting the production of Hb, resulting in ineffective erythropoiesis, haemolysis and varying degrees of anaemia.

Incidence: It is estimated that there are about 200,000 thalassemics in the world, among whom 5000 to 8000 are in India. It is seen to occur in 1 in 300 to 500 of all pregnancies. It is common in areas of the world where Malaria was/is endemic. This is because the thalassemia gene affords protection against Malaria and consequently the thalassemia gene thrives in those regions. In India too, it is seen in areas where Malaria is/was endemic, like Kutch.

Inheritance: Both types of thalassemia are inherited in the same manner. The disease is passed to children by parents who carry the mutated thalassemia gene. A child who inherits one mutated gene is a carrier- thalassemia trait or thalassemia minor. Most carriers lead completely normal lives. A child who inherits two thalassemia genes- one from each parent, will have the disease- thalassemia major. Transfusion requiring and non-transfusion requiring thalassemia, are 2 new terms used frequently today.





α-Thalassemia: The inheritance of α-thalassemia is complicated because of the presence of 4 α-globin chains. Four types can therefore result:

1. **Homozygous α-thalassemia or Hb Bart disease**, (γ4): deletion of all four globin chain genes (--/--), characterized by non-immune hydrops fetalis and stillbirths. Ultrasound at 12 to 13 weeks is 100% sensitive in identifying affected fetuses by measuring the cardiothoracic ratio whereas Doppler flow measurement of the middle cerebral artery velocity can detect fetal anemia. Occasionally, these fetuses can be saved by Intra-uterine transfusions, but the child has to have transfusions throughout life as in β-Thalassemia major.
2. **Hb H disea**se (β4): deletion of three of four genes (--/-α), is compatible with extra-uterine life. It is characterized by hemolytic anemia which

develops postnatally due to replacement of Hb Bart by HbH. The anemia worsens in pregnancy.

3. **α-thalassemia minor:** deletion of two genes. Can be (-α/-α) or (--/αα), the two being differentiated only by DS-DNA analysis. Except for mild anemia with hypochromic and microcytic RBCs, pregnancy is usually uneventful. Haemolysis is not seen here, unlike the previous two types.

4. **The Silent carrier state**: single gene deletion (-α/αα), with no clinical abnormalities.

Frequency: The frequency of α-Thalassemia minor, Hb Bart disease and Hb H disease vary among different races. All three are seen in Asians.

Diagnosis: α-thalassemia minor and major can be diagnosed in utero by

a. Prenatal diagnosis with chorionic villi sampling at 8 to 10 weeks or by

b. Amniocentesis at 14 to 20 weeks' gestation in high-risk families

β-thalassemia: This is the more familiar type of thalassemia. It involves decreased production of normal adult Hb (Hb A), the predominant Hb which is seen soon after birth and continues until death. The hallmark of β-thalassemia is the presence of elevated HbA2.

Types: There are two forms of β-thalassemia---thalassemia major or Cooley's anemia and thalassemia minor or trait.

Thalassemia minor: Persons with thalassemia minor have only one copy of the thalassemia gene along with another normal β-chain and are said to be heterozygous for β- thalassemia.

Diagnosis: As thalassemia minor is a carrier state,
it is typically asymptomatic.

a. **Low Hb% and low MCV: Mild anemia** is seen similar to mild iron deficiency anemia.
b. **Iron indices**: Serum iron level is normal to raised, Serum Ferritin- 300 – 3000 ng/dl, TIBC- 70%
c. **Mentzer index** (MCV divided by RBC count) < 13 - probably thalassemia, >13 – iron deficiency anaemia
d. **Low RDW** unlike in Iron deficiency and Sideroblastic anemia where it is high
e. **Peripheral smear:** Hypochromic and microcytic RBCs, with Poikilocytes, Anisocytes, Heinz Bodies, Target cells, tear drop cells, granular cytoplasmic inclusion bodies, polychromasia and marked reticulocytosis >10 %
f. **Hemoglobin electrophoresis:** Normal- 95% to 98% of Hb A, Hb A2- < 2-3% and Hb F- <2%

   β- thalassemia major- higher Hb A2 and Hb F, less Hb A

   β-thalassemia minor- Hb A2 > 3.5%, Hb F > 2%. A co-existing iron deficiency will mask β-thalassemia minor giving a normal report. Iron deficiency makes the HbA2 % normal- the key finding in β-thalassemia minor. The Iron deficiency anaemia should be treated before HPLC.

Alkali denaturation tests, DNA analysis, Erythrocyte porphyrin levels, ZPP test and Dichlorophenolindophenol (DCIP) are some other tests to diagnose beta- thalassemia.

Treatment: Mild thalassemia (Hb: 6 to 10g/dl): normal blood volume expansion and subnormal red cell expansion are seen in pregnancy. Signs and

symptoms are generally mild. Rarely, patients may need a transfusion following surgery, etc. There is no specific treatment for β- thalassemia minor during pregnancy. Prophylactic iron and folic acid are given. Fetal growth restriction and oligoamnios are increased two fold in affected women.

B-Thalassemia major (Cooley's anemia): At birth the baby with thalassemia major seems entirely normal as the predominant Hb at birth is still Hb F so the baby is protected at birth from the effects of thalassemia major. Within the first month of birth, anaemia develops and becomes progressively more severe. The infant fails to thrive and has feeding problems (due to early fatigue from lack of oxygen), bouts of fever (due to infections) and diarrhoea as a direct consequence of anaemia.

Complications:

- Increased extramedullary haematopoiesis may result in brittle and thin bones with deformed facial bones - chipmunk face
- Bronze coloured skin due to iron deposition
- Arrhythmia, cardiomyopathy and heart failure may ensue due to iron deposition in myocytes following multiple transfusions leading to high mortality
- Cholelithiasis, hepato-splenomegaly, jaundice, cirrhosis and chronic liver failure may result either because of the disease itself or the treatment.
- Neurological complications such as peripheral neuropathies
- Slow growth rate and delayed puberty
- Increased risk of parvovirus B19 infection
- Increased risk of Diabetes and Hypothyroidism

Without treatment, the spleen, liver and heart enlarge and death follows infection and heart failure. With treatment and adequate transfusions, the child

develops normally until the end of the first decade.
Then effects of iron loading become apparent. Prognosis improves with iron chelation therapy.

Treatment: In moderate to severe thalassemia (Hb less than 5 to 6g/dl), the following are necessary:

Blood transfusions: frequently needed every couple of months, to keep the Hb% around 9-10gms%

Chelation therapy: Due to multiple transfusions, iron gets deposited in various organs and Deferoxamine (parenteral) or Deferiprone (oral, off-label) are given at the same time to remove this extra iron.

Stem cell transplant, Gene therapy, Splenectomy (to reduce extra-medullary hematopoiesis) and **Cholecystectomy** have been tried.

Thalassemia and pregnancy: Pregnancy with β-Thalassemia is now possible because of transfusions and chelation therapy. Pregnancy is advised only when cardiac function is normal.

- A multidisciplinary team with a hematologist, perinatologist and a genetic counselor instituted
  There is an increased need for transfusions to maintain the Hb at 10 gms%
- Iron should not be given to prevent overloading
- Folic acid to be given till 12weeks to assist in cell division
- Vitamin C 100 to 150 mgs daily to remove excess iron from the gut
- Frequent screening for Diabetes

Prenatal Diagnosis:

- Genetic counseling is necessary to assess fetal risk
- Prenatal diagnosis of β-thalassemia major is difficult because of many mutations
- Targeted mutation analysis to be done after identifying the mutation in that family
- Can be done by PCR of fetal DNA by CVS, pre-implantation blastomere biopsy or NIPT
- If both parents are carriers, then fetal DNA based tests have to be done.

Sickle cell Disorders

Classification:

A. Sickle cell disorders

a. SA, sickle cell trait

b. SS, sickle cell anemia/disease

c. SC, HbSC disease

d. S/β thal, sickle β-thalassemia disease

e. S with other Hb variants: D, O-Arab, other

f. SF, Hb S/HPFH

B. Hemoglobins with decreased stability (unstable hemoglobin variants)

C. Hemoglobins with altered oxygen affinity

D. Methemoglobinemia

E. Posttranslational modifications

Sickle Cell disease (SCD) or Sickle Cell Anemia (SCA) is an autosomal recessive genetic disorder with over-dominance. RBCs assume an abnormal, rigid, sickle shape due to a mutation in the Hb gene which reduces the cell's

flexibility resulting in various complications. Hemoglobin usually exists in a soluble form, but here, it is precipitated as insoluble crystals, leading to RBCs of abnormal shape and size, which get phagocytosed. Earlier, SCD was considered as a disease of children. But today, due to advances in immunization, screening and management, the average survival age is about 50 years in SCD while HbSC or HbS/ß+-thalassemia genotypes have an almost normal lifespan.

Frequency: Seen commonly in people from tropical or subtropical regions where Malaria is or was more common. It is part of the newborn screening protocol in USA since 2006. One third of all indigenous inhabitants of Sub-Saharan Africa carry the gene. Sickle cell disease is prevalent in many parts of India in the range of 9.4 to 22.2 %.

Inheritance: If one parent has Sickle cell anemia (SS) and the other has Sickle cell trait (AS), there is a 50% chance of a child having Sickle cell disease (SS) and a 50% chance of a child having Sickle cell trait (AS). When both parents have Sickle cell trait (AS) then a child has only 25% chances of getting Sickle cell disease (SS).

Sickle cell diseases occur in 3 different forms

1. **Homozygous state**: Sickle cell anemia- Hb SS

2. **Heterozygous state**: Sickle cell Trait- Hb SA- point mutation of only one of the β-globin chains, carrier state. Such patients do not suffer from the disease.

3. **Double heterozygous states**: one copy of Hb S and one copy of other abnormal forms:

-Sickle Cell C disease – Hb SC

-Sickle Cell D disease – Hb SD

-Sickle Cell E disease – Hb SE

-Sickle Cell O Arab disease – Hb SO Arab

-Sickle Cell thalassemia disease – Hb S/ B° or Hb S/B+

-Unstable Haemoglobinopathies

Maternal and perinatal morbidity and mortality are high in all.

Pathophysiology:

- The loss of RBC elasticity is central to the pathophysiology of Sickle cell disease.
- Normal RBC are quite elastic and distort while passing through capillaries.
- In Sickle cell disease however, low oxygen tension promotes sickling and repeated episodes of sickling and de-sickling damage cell membranes and further decrease the cell's elasticity
- These cells fail to return to their normal shape on restoration of normal oxygen tension.
- As a result, the rigid RBCs are unable to distort while passing through capillaries leading to vessel occlusion and ischaemia.
- Any slowing of RBC passage through the microcirculation can contribute to vasoocclusion
- This can lead to ischaemia in various organs causing very severe pain called a sickle cell crisis.
- The anemia is caused by hemolysis due to phagocytosis by macrophages, of the misshapen RBCs in the spleen.
- The bone marrow tries to compensate by producing new RBCs, but it cannot match the rate of destruction.
- Normal RBCs have a life span of about 90-120 days, while sickle or Holly leaf shaped cells survive only for 10-12 days.

Clinical features:

Symptoms appear after the 6th month of life when most of the HbF has been replaced. Sickle cell crisis is an important manifestation and complication of the disease.

Sickle cell crisis: This term is used to describe several independent acute conditions occurring in patients with Sickle cell disease. Most episodes of sickle cell crises last for five to seven days. Sickle cell crisis can be of many types:

- **Vaso-occlusive crisis**
- **Aplastic crisis**
- **Sequestration crisis**
- **Hemolytic crisis**
- **Dactylitis:** one of the earliest manifestations, can present itself as early as six months postnatally and can be seen in children with sickle trait too. It may last up to a month.

- **Acute chest syndrome:** the mortality of Acute chest syndrome has come down to 1%, with a perinatal mortality of 9% with improved ventilator care.

Complications: some of the complications seen are

- **Overwhelming post (auto) splenectomy infection (OPSI):** less seen nowadays with improved Immunization status.
- **Stroke**
- **Silent stroke:** 5 times more frequent than symptomatic stroke. About 10 to 15% of children with sickle cell disease suffer from silent strokes.
- **Cholelithiasis and cholecystitis** due to prolonged hemolysis.

- **Avascular necrosis**: (aseptic osteo-necrosis) ischaemia of the hip usually causing a limp
- **Osteomyelitis:** probably as a result of patchy ischemia following intravascular sickling of the bowel and Salmonella infection
- **Acute papillary necrosis in the kidneys** and **chronic renal failure**: nephropathy with hypertension, proteinuria, hematuria and worsening anemia with a poor prognosis.
- **Pulmonary hypertension**
- **Progressive retinopathy**, **vitreous hemorrhages** and **retinal detachment** can lead to blindness.

Diagnosis: HbSS

- **Hb:** usually in the range of 6 to 8 gms%. In other forms of sickle cell disease, Hb level tends to be higher.
- **Peripheral blood smear**: may show a Normocytic normochromic picture, Fragmented RBCs, Anisopoikilocytosis, Reticulocytosis, Target cells and Howell-Jolly bodies (features of hypersplenism)
- **MCV/MCH**: normal, **MCHC**: increased
- **ESR**: decreased due to reduced RBC count
- **Bone-marrow**: erythroid hyperplasia
- **Osmotic fragility**: decreased
- **Sickling test**: positive-rapid and reliable test
- **Sickling solubility test**
- **Urine analysis** for occult infection
- **Chest X-ray** to look for occult pneumonia should be routinely done.
- **Gel electrophoresis**: abnormal Hb forms move at different speeds and can be identified, especially HbS and HbSC.

- **High Performance Liquid Chromatography (HPLC):** diagnosis further confirmed
- **Genetic testing**: rarely needed as other tests are highly specific for HbS and HbC

Prenatal Diagnosis: amniocentesis, CVS or **pre-implantation genetic screening** can be offered.

Pregnancy and Sickle cell syndrome: Pregnancy is risky in women with any of the major sickle Haemoglobinopathies, especially Hb SS disease as it can be a serious burden on the already compromised hematological system. Maternal mortality (1%) is usually due to acute chest syndrome, pneumonia, pulmonary infarction and pulmonary embolism.

Maternal complications:

- Pre-existing medical disorders like Pulmonary hypertension, Cardiomyopathy, Asymptomatic bacteriuria and Renal failure can further complicate the pregnancy

- Pregnancy complications: the following may be seen more often-

- Cerebral vein thrombosis
- Acute chest syndrome
- Pyelonephritis
- DVT- pulmonary embolism
- Sepsis syndrome
- Pre-eclampsia

Complications during labour: Placental abruption and stillbirths seen more often.

Fetal risks

- Miscarriage (20%)
- IUGR (37.5%)
- Prematurity
- Increased Perinatal morbidity and mortality (11-22%)

Management during pregnancy

- Prenatal Folic acid 4mgs daily recommended to support the rapid turnover of RBC. (ACOG 2007)
- Before prescribing haematinics, the serum Ferritin should be checked. If high, iron should not be given.
- About Hydroxyurea continuation, the woman should consult a Materno-fetal Medicine specialist about the pros and the cons. She can stop it during the first trimester and restart later.
- Sickle cell crisis may mimic other acute conditions associated with pain, for example, ectopic pregnancy, appendicitis, abruption, pyelonephritis, etc and it should be diagnosed only after excluding other conditions associated with pain, fever and anemia.
- Sickling in the bone can be managed with Intravenous fluids, narcotics, and oxygen inhalation to reduce capillary sickling
- Prophylactic RBC transfusions can prevent further sickling crises.
- Therapeutic transfusions are not advocated. Partial volumetric transfusions are given to maintain the Hct>35%, HbA1 at 40%
- Monthly urine cultures to be done and any infection promptly treated as pyelonephritis can cause increased destruction of RBC along with suppression of erythropoiesis by endotoxins.

- Pneumonia caused by Streptococci pneumoniae is seen often and needs to be tackled energetically.
- The following vaccines are recommended: Polyvalent pneumococcal, H influenzae Type B and Meningococcal vaccines.
- Prophylactic Low Dose Aspirin advocated as Preeclampsia is more common.

Fetal surveillance: Since FGR and PNM are increased, serial growth scans to monitor growth and volume of amniotic fluid are recommended from 26-28 weeks' gestation. Non stress tests should be done in the presence of FGR from 32 weeks onwards. The Non stress tests are usually nonreactive during a crisis and become reactive once the crisis is over.

Management of Labour and Delivery: similar to that of a patient with cardiac disease.

- A comfortable position during labour with Epidural analgesia for pain relief and packed cell transfusion if the hematocrit goes below 20.
- Circulatory overload and pulmonary edema should be prevented.
- LMWH for 6 weeks post-delivery to prevent VTE

Contraception: Issues like chronic debility, pregnancy related complications and a shortened life span make contraception, temporary or permanent very relevant.

- COCs are not recommended due to their adverse vascular and thrombotic effects
- Progesterone containing pills or implants are better as they reduce painful sickling crises
- DMPA is not advised as it can cause VTE

- IUCDs are not advised because of their potential to cause infection
- Condoms though safe are not promoted because of high failure rate
- Sterilization is a safe option

Sickle cell trait: Can occasionally cause Hematuria, Asymptomatic Bacilluria, Urinary infection and Renal papillary necrosis, however, it has no adverse effects on pregnancy. There is no increased incidence of miscarriages, FGR, Pre-eclampsia or perinatal deaths. Pregnancy is therefore not risky in women with Sickle cell trait and should not be discouraged. COCs have been known to cause increased VTE in Africans, though more evidence is needed.

Haemoglobinopathy in the Newborn: The MCH Bureau (2005) recommendation that all newborns be tested for sickle-cell disease by cord blood electrophoresis, has decreased mortality rates in identified infants.

TNFOG CME ON "CONTRACEPTION"

Date: 11.07.2021 (Sunday) | Time: 4.00 – 6.30 PM

Scientific Programme

DURATION	TOPIC	SPEAKERS
4.00 - 4.15 PM	**INAUGURATION**	
	Introduction	Dr. S. Sampathkumari
	Inauguration	Tamil Thai Vazhthu & Lamp Lighting
	Welcome Address	Dr. Anjalakshi Chandrasekar
SESSION I CHAIRPERSONS : Dr. Revathy Janakiram, Dr. Amala Devi & Dr. Shanthirani		
4.15 - 4.30 PM	LARC	Dr. Arulmozhi Ramarajan
4.30 - 4.45 PM	Non-Contraceptive Benefits of LNGUS	Dr. Ramanidevi.T
4.45 - 5.00 PM	Fourth Generation OCP-Scores Over Others	Dr. Anitha Singh
5.00 - 5.15 PM	Govt Initiative in Family Welfare	Dr. Sumathi Baskaran
5.15 - 5.25 PM	Q & A	
SESSION II - Panel Discussion on Contraception MODERATORS - Dr. Niranjana Asokan & & Dr. Boomika Gunasingh		
5.25 - 6.25 PM	**" Right Choice for Right Women "**	**PANELISTS**
		Dr. Kaarthiga R.G
		Dr. Nanthini Saravanan
		Dr. Ramya .G
		Dr.C.Suhashini Karnal
		Dr. Mahalakshmi .V
	Expert Opinion	Dr.Kavitha Senthil
6.25 PM	Vote of Thanks	Dr. Vijayalakshmi Gnanasekaran

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Dr. ANJALAKSHI CHANDRASEKAR
President , TNFOG

Dr. S. SAMPATH KUMARI
Hony, Secretary, TNFOG

Dr. VIJAYALAKSHMI GNANASEKARAN
Treasurer, TNFOG

Chairpersons

DR. REVATHY JANAKIRAM

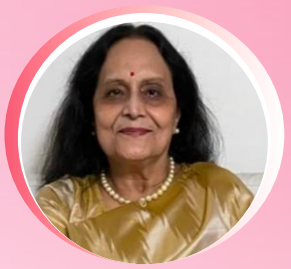
DR. AMALA DEVI

DR. SHANTHIRANI

Speakers

DR. ARULMOZHI RAMARAJAN

DR. RAMANIDEVI.T



DR. ANITHA SINGH

DR. SUMATHI BASKARAN

TNFOG CME ON "CONTRACEPTION"

Date: 11.07.2021 (Sunday) | Time: 4.00 – 6.30 PM

Moderators

DR. NIRANJANA ASOKAN

DR. BOOMIKA GUNASINGH

Expert opinion

DR. KAVITHA SENTHIL

Panelists

DR. KAARTHIGA R.G.

DR. NANTHINI SARAVANAN

DR. RAMYA G

DR. SUHASHINI KAMAL C

DR. MAHALAKSHMI V

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