Anemia in pregnancy

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Epidemiology

- Anemia of pregnancy is a well-recognized global health problem, affecting **almost half of pregnant women**

World Health Organization. Iron Deficiency Anaemia: Assessment, Prevention and Control: A Guide for Programmed Managers. Geneva,Switzerland: World Health Organization; 2001

- WHO has classified the world into different zones according to prevalence of anemia:

  High Prevalence - >40%

  Medium - 15-39%

  Low - 5-14.9%

  Not a problem - <5%

- Sub Saharan Africa and South East Asia come in high prevalence area
- Globally, incidence is about 30 %

- Physiological anemia
- Pathological anemia

CLASSIFICATION

Definition

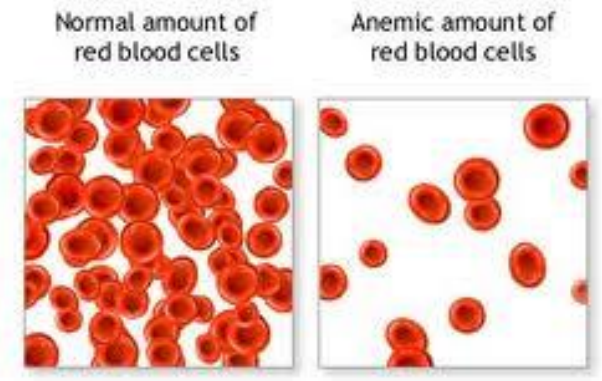
- **The World Health Organization (WHO)** defines anemia of pregnancy as hemoglobin (Hb) ,11 g/dL, or hematocrit ,33%, at any time during the pregnancy.

- **The Centers for Disease Control and Prevention (CDC)** define anemia of pregnancy as Hb ,11 g/dL, or hematocrit ,33% during the first and third trimesters, and ,10.5 g/dL or a hematocrit ,32% in the second trimester.

- The WHO defines severe anemia in all persons as a Hb of ,7 g/dL and very severe anemia as a Hb of ,4 g/dL

Definition - Anemia

- A condition where circulating levels of Hb are quantitatively or qualitatively lower than normal
- Non pregnant women — Hb < 12gm%
- Pregnant women (WHO) — Hb < 11 gm%
  Haematocrit — < 33%
- Pregnant women (CDC) — Hb <11 gm%
  1^{st}&3^{rd} Trimester
  2^{nd} trimester — Hb < 10.5 gm%



PATHOLOGICAL ANEMIA

- Deficiency anemia :
  - Iron deficiency (60%)
  - Macrocytic anemia(10%)- Folic A., Vitamin B12 deficiency
  - Dimorphic anemia (30%) – both
  - Protein deficiency – in extreme malnutrition
- Haemorrhagic anemia :
  - Acute – blood loss
  - Chronic - hookworms ,bleeding piles
- Hemoglobinopathies : Thalassemia, Sickle cell anemia
- Aplastic anemia
- Anemia of infection

Classification of anemia according to

MCV

MICROCYTIC(<80)	MACROCYTIC(>100)
Sideroblastic anemia	Megaloblastic anemia
Iron deficiency anemia	Liver disease
Anemia of Chronic Ds	Hypothyroidism
Thalessemia	Cytotoxic drugs

NORMOCYTIC (80-100)

HIGH RETICULOCYTE COUNT	LOW RETICULOCYTE COUNT
Sickle cell anemia	Aplastic anemia
Hereditory spherocytosis	Renal failure
Autoimmune hemolytic anemia	Myelofibrosis
PNH	
Acute blood loss	

Mentzer index is an index used to differentiate IDA from thalessemias.

Formula is MCV/RBC count

Value for IDA>13

Value for thalessemia<13

Outcomes/consequences of anemia during pregnancy

- Anemia is an important risk factor for both maternal and fetal morbidity.
- **Iron-deficiency anemia** is associated with higher rates of preterm birth, low birth weight (LBW), and small-for gestational age (SGA) newborns.
- **Maternal iron deficiency affects iron concentrations in umbilical cord blood.**
- Fetal neonatal iron deficiency causes diminished **auditory recognition memory in** infants, a reflection of its impact on the developing hippocampus.

- **Children born to iron-deficient mothers demonstrate learning and memory impairments that may persist into adulthood.**

- **Folic acid deficiency**, especially at the time of conception, is strongly correlated with increased neural tube defects (NTDs).

- **Low maternal RBC folate** is also associated with LBW, and an increased risk for SGA.

- **Maternal vitamin B12 (cobalamin)** status affects **fetal growth and development**.

- **Low cobalamin** is associated with an increased fetal risk of low lean mass and excess adiposity, **increased insulin resistance**, and **impaired neurodevelopment**.

- **Maternal risks include fatigue, pallor, tachycardia, poor exercise tolerance, and suboptimal work performance.**

- Depleted blood reserves during delivery may increase the need for **blood transfusion, preeclampsia, placental abruption, cardiac failure, and related death.**

- **Physiologic anemia** of pregnancy reflects an expansion of plasma volume of 50% relative to the increase in the red blood cell (RBC) mass of 25%.

- Globally, the most common cause for anemia of pregnancy is iron deficiency, arising from maternal-fetal transfer of iron, frequently aggravated by decreased maternal iron reserves.

Iron requirements in pregnancy

- In a typical pregnancy, maternal iron requirements include 300 to 350 mg for the fetus and the placenta, 500 mg for the expansion of the maternal RBC mass, and 250 mg associated with blood loss during labor and delivery.

- The requirement for iron increases gradually from 0.8 mg per day in the first trimester to 7.5mg per day in the third.

- **the average daily absorption of iron from western diets is only 1 to 5 mg**

Extra Iron Requirement & Loss During Pregnancy

During pregnancy Total 800-1000 mg extra iron is required		
300 mg for Fetus & 50 mg for Placenta	400-500 mg for increased red cell mass	250 mg iron lost during delivery 220 mg basal losses

Due to cessation of menses & contraction of blood volume after delivery conservation of iron is around 400 mg

Factors Required for Erythropoiesis

- Proteins for synthesis of Globin
- Mineral – Iron for synthesis of heme
- Hormones – Erythropoietin (produced from Kidney, stimulates stem cells in Bone Marrow), Thyroxine, Androgens
- Trace elements – Zinc (also important for protein synthesis & Nucleic acid metabolism), Cobalt, Copper
- Vitamins –
  - Vit B12 required for synthesis of RNA in early stage,
  - Folic acid (Vitamin 9) required in later stage for DNA synthesis
  - Vitamin C necessary for conversion of folic acid to folinic acid, it enhances absorption of iron from small intestine
  - Pyrodoxine B6 useful adjuvant in erythropoeisis
  - Vitamin A required for cell growth, differentiation & maintenance of integrity of epithelium, immune function

- The **CDC** recommends that all pregnant women begin **a 30 mg per day iron supplement at the first prenatal visit**, the **WHO suggests 60 mg per day for all pregnant women**, whereas British guidelines do not recommend any routine iron supplementation in pregnancy

Diagnosis of iron-deficiency anemia

- Hemoglobin level
- Ferritin
- Mean corpuscular volume
- Iron, transferrin, and transferrin saturation

- Maternal Hb declines progressively during pregnancy due to hemodilution and may be accentuated by iron-deficient erythropoiesis, **with a nadir reached at 24 to 32 weeks' gestation.**

- Due to considerable variation in Hb level, **it cannot be used as a single parameter to estimate iron status.**

- **Ferritin is a more sensitive and specific marker** for iron deficiency than serum iron, transferrin saturation, and erythrocyte protoporphyrin values and is the best test for iron deficiency in pregnancy if low.

- In the absence of active comorbidity, **ferritin values >100 ng/mL indicate** adequate iron stores and a low likelihood of iron-deficiency anemia.

- MCV is an unreliable marker of iron deficiency in pregnancy.
- Stimulation of erythropoiesis leads to a physiologic increase in MCV during gestation that counterbalances the microcytosis of iron deficiency.
- A low MCV, defined as an MCV ,80 fL, is highly sensitive, but not specific, for iron-deficiency anemia.

- Serum iron circulates bound to its transport protein, transferrin. **The serum iron reflects both iron recycling from macrophages and iron absorbed from the diet**.

- It demonstrates diurnal variation, with a rise in the morning and fall at night; serum iron is also influenced by recently ingested meals.

- Therefore, no single value is diagnostic of iron deficiency. **Serum iron should be drawn after an overnight fast**. Total iron-binding capacity (TIBC) and transferrin are measurements of iron transport proteins that increase in iron deficiency.

- **Inflammation, chronic infection, malignancies, liver disease, nephrotic syndrome, and malnutrition can lower TIBC, whereas pregnancy can raise it, in the absence of iron deficiency.**

- **Plasma transferrin saturation** is the ratio of plasma iron to transferrin.

- A saturation of ,15% suggests an inadequate supply of iron, either because of low total body iron (iron deficiency) or due to trapping of iron in macrophages (anemia of inflammation).

Soluble transferrin receptor

- **The soluble transferrin receptor (sTfR)** is a truncated fragment of the membrane receptor.
- In iron deficiency, synthesis of transferrin receptors, and sTfR, is increased. Unlike TIBC and ferritin, **sTfR concentrations are not affected by inflammation.**
- **A meta-analysis of 10 studies of sTfR showed that the assay had a sensitivity of 86%and a specificity of 75%.**
- However, the assay is not standardized and is not used in routine diagnosis of iron-deficiency anemia.

Hepcidin

- **Hepcidin is the master regulator of systemic iron bioavailability**.

- **Hepcidin** decreases as pregnancy progresses, with the lowest hepcidin levels seen in the third trimester.

- **Pregnant women with undetectable serum hepcidin transfer more maternally ingested iron to their fetus than women with detectable hepcidin, indicating that maternal hepcidin in part determines the iron bioavailability to the fetus.**
- Hepcidin is currently being evaluated as a biomarker in pregnancy.
- In summary, Hb, the percentage of transferrin saturation, and plasma ferritin are adequate to assess iron status in the majority of pregnant women, and the combination of anemia and ferritin ,15 to 30 ng/mL is diagnostic of iron deficiency.

Differentiation between iron deficiency anemia & Thalassemia diminished synthesis of Hb b chains in Thalassemia)

Investigations	Normal values	Fe Def Anemia	Thalassemia
MCV	75-96 fl	reduced	reduced
MCH	27-33pg	reduced	reduced
MCHC	32-35 gm/dl	reduced	N or reduced
HbF	<2 %	normal	Raised
HbA2	2-3%	N or reduced	Raised >3.5%
Serum Iron	60-120 ug/dl	reduced	Normal
Serum Ferritin	15-300 ug/L	reduced	Normal
TIBC	300-350 ug/dl	Raised	Normal
Bone iron stores		reduced	Normal
Free erythrocyte protoporphyrin (FEP)	<35 ug/dl	>50	Normal

Management

- **The choice of therapy depends** on the degree of anemia, the stage of pregnancy, and factors that influence gastrointestinal absorption of iron.

- **Oral iron is the frontline therapy** for iron-deficiency anemia. It is inexpensive, readily available, and effective.
- However, **up to 70% of patients experience significant gastrointestinal side effects** (nausea, constipation, diarrhea, indigestion, and metallic taste) that prevent adherence to treatment.

- In pregnancy, decreased bowel motility caused by elevated progesterone and the enlarging uterus pressing on the rectum is made worse by oral iron

- Recommendations for dosing oral iron vary from **60 to 200mg of elemental iron per day.**
- This can be achieved with 325-mg tablets (each containing 50-65 mg of elemental iron) **given once to 3 times daily.**
- The acid pH of the stomach favors solubility of iron by the conversion of ferric (Fe3+) to ferrous (Fe2+) iron for duodenal uptake.
- Iron absorption is facilitated by ascorbate (which facilitates Fe3+ to Fe2+), amino acids, and iron deficiency, and is retarded by phytates, tannins, antacids, and iron overload.
- The most commonly prescribed iron preparations are ferrous sulfate, ferrous gluconate, and ferrous fumarate.

- Prolonged-released ferrous sulfate (ferrous sulfate–polymeric complex) is the best tolerated oral preparation, and is associated with good compliance, although delayed release compromises absorption.

- An iron-deficient patient absorbs up to 28% of oral iron, if taken without food.

- The total iron absorbed increases with increasing doses to a maximum of 160 mg per day.

- **However, oral iron acutely increases hepcidin and recent data suggest that twice and thrice daily supplementation may have little added benefit over once daily dosing.**

- Two weeks after starting oral iron, a Hb increase of 1 g or more suggests adequate absorption.

- **Replacement should be continued until iron stores are replenished (generally 2-3 months),and 6 weeks postpartum**.

- **IV iron** circumvents gastrointestinal absorption and is therefore the preferred agent for patients with gluten sensitivity, inflammatory bowel disease, gastrointestinal malabsorption, after gastric bypass surgery, hyperemesis gravidarum, or a history of oral iron intolerance.

- IV iron is superior to oral iron in achieving a sustained Hb response, reducing the need for packed RBC transfusions and improving quality of life for chronic heart failure, inflammatory bowel disease, chronic kidney diseases and hemodialysis, and cancer-related anemia

- **In the first trimester, we treat iron deficiency with oral iron, reserving IV iron for after the 13thweek.**

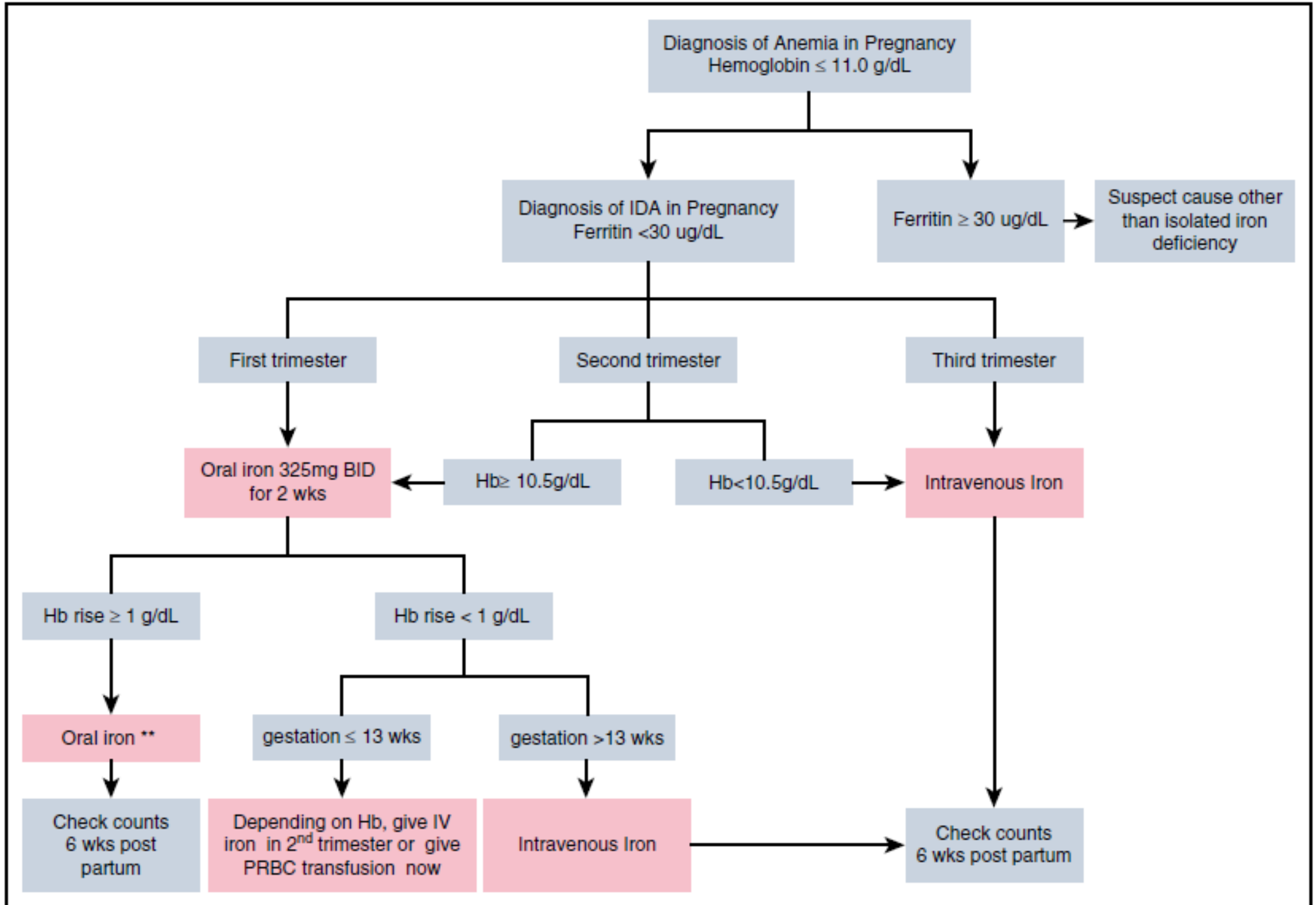
- The US Food and Drug Administration (FDA) does not explicitly restrict the use of IV iron until after the first trimester.

- Because IV iron has been shown to improve Hb more rapidly than oral iron, **we preferentially treat patients with IV iron in the second half of pregnancy.**

- Some investigators report additional advantages of IV over oral iron beyond the more rapid increase in Hb.

Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U,Gafter-Gvili A. Intravenous versus oral iron supplementation for the treatment of anemia inCKD: an updated systematic review and metaanalysis.Am J Kidney Dis. 2016;68(5):677-690

- We recommend that pregnant women with any degree of iron deficiency be treated to **correct anemia and replete ferritin as early in pregnancy as possible**.


Diagnosis of Anemia in Pregnancy
Hemoglobin ≤ 11.0 g/dL
Diagnosis of IDA in Pregnancy
Ferritin <30 ug/dL
Ferritin ≥ 30 ug/dL
Suspect cause other than isolated iron deficiency
First trimester
Second trimester
Third trimester
Oral iron 325mg BID for 2 wks
Hb≥ 10.5g/dL
Hb<10.5g/dL
Intravenous Iron
Hb rise ≥ 1 g/dL
Hb rise < 1 g/dL
Oral iron **
gestation ≤ 13 wks
gestation >13 wks
Check counts 6 wks post partum
Depending on Hb, give IV iron in 2nd trimester or give PRBC transfusion now
Intravenous Iron
Check counts 6 wks post partum

Folic acid and vitamin B12 (cobalamin) deficiency

- Folate and cobalamin are involved in tetrahydrofolate metabolism, and are **necessary for DNA synthesis for fetal growth and maternal tissue growth.**

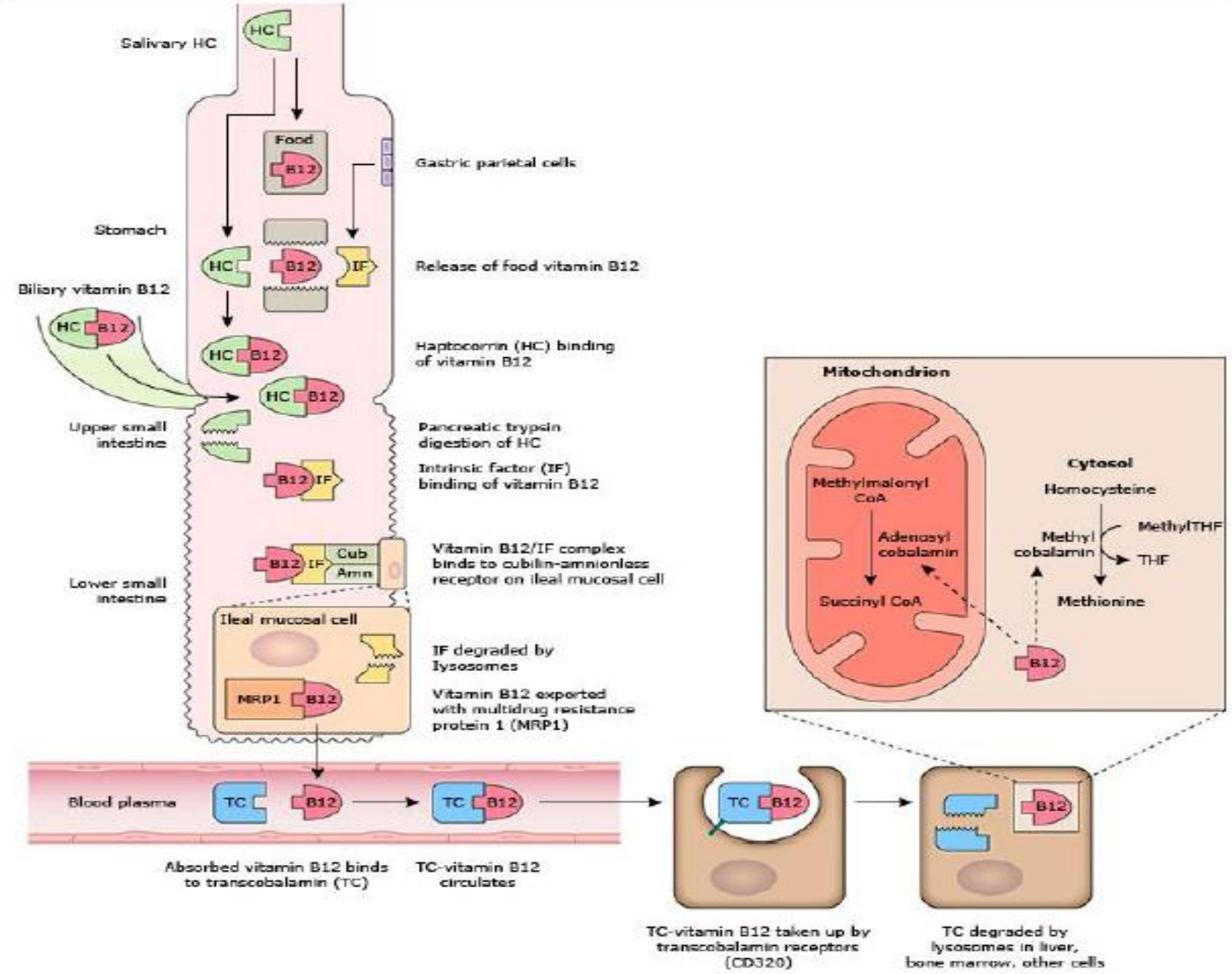
- **Dietary folate is absorbed in the jejunum. Poor nutrition, intestinal malabsorption, and increased requirements for fetal growth may contribute to folate deficiency**

- **Cobalamin** is present in animal protein and absorbed **in the terminal ileum.**

- R-protein (haptocorrin), secreted by salivary glands, binds cobalamin in the stomach and **transports cobalamin to the duodenum where pancreatic proteases degrade the R-protein.**

- Cobalamin is then released and binds to intrinsic factor released from gastric parietal cells. The cobalamin intrinsic factor complex subsequently binds to receptors on ileal enterocytes.

- **Atrophic gastritis, proton pump inhibitors, and malabsorption all increase the risk of cobalamin deficiency**


Salivary HC
HC
Food
B12
Gastric parietal cells
Stomach
HC
B12
IF
Release of food vitamin B12
Biliary vitamin B12
HC B12
HC B12
Haptocorrin (HC) binding of vitamin B12
HC B12
Upper small intestine
Pancreatic trypsin digestion of HC
B12 IF
Intrinsic factor (IF) binding of vitamin B12
B12 IF Cub Amn
Vitamin B12/IF complex binds to cubilin-amnionless receptor on ileal mucosal cell
Lower small intestine
Ileal mucosal cell
IF degraded by lysosomes
MRP1 B12
Vitamin B12 exported with multidrug resistance protein 1 (MRP1)
Blood plasma
TC
B12
TC B12
Absorbed vitamin B12 binds to transcobalamin (TC)
TC-vitamin B12 circulates
Mitochondrion
Methylmalonyl CoA
Adenosyl cobalamin
Succinyl CoA
Cytosol
Homocysteine
Methyl cobalamin
MethylTHF
THF
Methionine
B12
TC B12
TC-vitamin B12 taken up by transcobalamin receptors (CD320)
B12
TC degraded by lysosomes in liver, bone marrow, other cells

Diagnostic tests

- Most pregnant women with folate or cobalamin deficiency do not exhibit macrocytosis, which may be masked by iron deficiency or by an underlying minor thalassemic phenotype.

- Furthermore, 2% to 5% of pregnant women with normocytic anemia have mild megaloblastic changes in the bone marrow that resolve with folic acid supplementation

- Serum cobalamin measures cobalamin bound to **2 circulating binding proteins, haptocorrin and transcobalamin.**

- In **nonpregnant patients**, serum cobalamin ,200 pg/mL (,148 pmol/L) is diagnostic of cobalamin deficiency, whereas levels above 300 are considered normal. Levels in the range of 200 to 300 pg/mL are borderline, and cobalamin deficiency is possible

- Notably, there is no difference in levels of the **metabolites homocysteine and methylmalonic acid in pregnant women** with subnormal cobalamin levels when compared with pregnant women with normal levels, suggesting that low cobalamin in pregnancy may not reflect true tissue deficiency.

- **A "physiologic" decline in cobalamin is seen in up to 20%of pregnant women that is indistinguishable from frank deficiency using routine laboratory studies**

- Holotranscobalamin (biologically active cobalamin bound to transcobalamin) does not decline in pregnancy and has been suggested as a marker for cobalamin deficiency in pregnancy.

- Holotranscobalamin is not available for clinical use.

- Serum folic acid concentrations <2 ng/mL are diagnostic of folic acid deficiency, whereas levels above 4 ng/mL effectively rule out deficiency.

- Although **RBC folate is not so influenced**, **serum folate is more readily available** and, in most instances ,RBC folate measurement could be reserved for patients with borderline low serum values

- The **WHO recommends** folate supplementation for pregnant women**, 400 mg per day from early pregnancy to 3 months postpartum**.

- The US Public Health Service and CDC recommend the same for all women of childbearing age (15-45 years of age) to prevent spina bifida and anencephaly.

- **A higher supplementation dose, 5 mg per day, is recommended in women who have increased demands for folate** (multiple pregnancies, hemolytic disorders, folate metabolism disorders) and in women who are at an increased risk of NTDs (personal or family history of NTD, pregestational diabetes, epilepsy on valproate or carbamazepine).

Cobalamin deficiency

- Owing to the relatively large amounts of cobalamin that are stored in the human body, **cobalamin deficiency in pregnancy is far less common than folate deficiency.**

- However, with more pregnant women **having undergone bariatric surgery, the risk of cobalamin deficiency is increased.**

- **The WHO and US National Institutes of Health (NIH) recommend a higher daily allowance of cobalamin in pregnant women than in nonpregnant women (2.6 vs 2.4 mg per day) to support fetal neurologic development. Growth retardation, general hypotonia, and loss of neuromotor skills have been described in infants of mothers with cobalamin deficiency.**
- Notably, hematologic abnormalities caused by cobalamin deficiency may respond to folate supplementation, leaving other consequences of cobalamin deficiency unchecked.

- Therefore, prompt recognition of cobalamin deficiency and rapid treatment are of great significance.

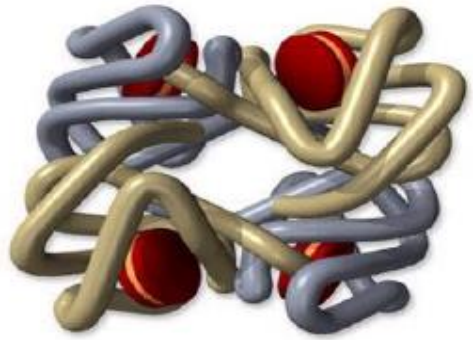
RBC transfusions in pregnancy

Table 11Indications of blood transfusion in pregnancy(197, 198, 199)

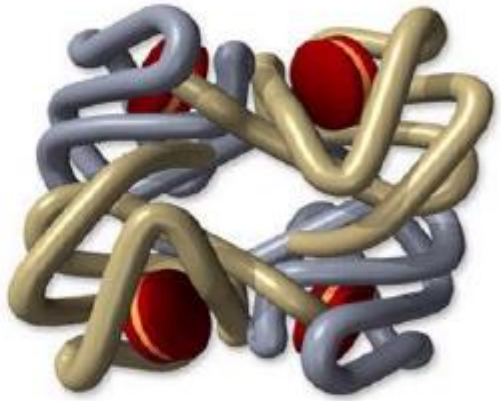
Antepartum Period
1. Pregnancy <34 weeks
a. Hb <5 g/dL with or without signs of cardiac failure or hypoxia
b. Hb 5-7 g/dL – in presence of impending heart failure
2. Pregnancy >34 weeks
a. Hb <7 g/dL even without signs of cardiac failure or hypoxia
b. Severe anemia with decompensation
3. Anemia not due to hematinic deficiency
a. Hemoglobinopathy or bone marrow failure syndromes
b. Hematologist should always be consulted
4. Acute hemorrhage
a. Always indicated if Hb <6 g/dL
b. If the patient becomes hemodynamically unstable due to ongoing hemorrhage
Intrapartum Period
a. Hb <7 g/dL (in labor)
b. Decision of blood transfusion depends on medical history or symptoms
Postpartum Period
a. Anemia with signs of shock/acute hemorrhage with signs of hemodynamic instability.
b. Hb <7g% (postpartum): Decision of blood transfusion depends on medical history or symptoms

HEMOGLOBINOPATHIES

- Normal adult hb is a conjugated protein with a molecular weight of about 68000,which contains a globin fraction bound to 4 haem molecules.
- Abnormalities of heme synthesis are responsible for porphyrias.
- The hemoglobinopathies are concerned with the disorders within polypeptide chains that comprise globin fractions.
- There are 4 possible chains,namely alpha,beta,gama&delta.



THERE ARE 4 POSSIBLE CHAINS,NAMELY ALPHA,BETA,GAMA&DELTA.



- HbA---97%, = 2 alpha +2 beta globin chains

  HbA2---(1.5-3.5%), = 2alpha+2 delta globin chains

  HbF --<1%. = 2 alpha+ 2 gamma globin chains

- Two classes of abnormality of Hb A synthesis can result in decreased portion of HbA
  - Quantitative defect(thalessemias)
  - Qualtitative defect(sickle cell disease)

THALESSEMIA

- The synthesis of globin chain is partially or completely suppressed resulting in reduced Hb. content in red cells, which have shortened life span
- Result is ineffective erythropoesis, haemolysis & varying degree of anaemia

  Incidence: 1 in 300 – 500 pregnancies
- TYPES
  - Alpha thalassaemia (impaired production of Alpha chain).
  - Beta thalassaemia: (impaired production of beta chains)
    - Major
    - Intermedia
    - Minor

THALESSEMIA INTERMEDIA AND MINOR

- Low MCV,MCHC.near normal or normal MCHC.
- Diagnosis is confirmed by a raised concentration of Hb A2.
- If Patient is found to have thalessemia partner should be tested if both have thalassemia trait the couple is offered prenatal diagnostic testing.
- pregnancy termination can be offered if fetus found to be Thalassemia major.
- In thalasssemia minor oral iron and folate prescribed but never parenteral preparations.

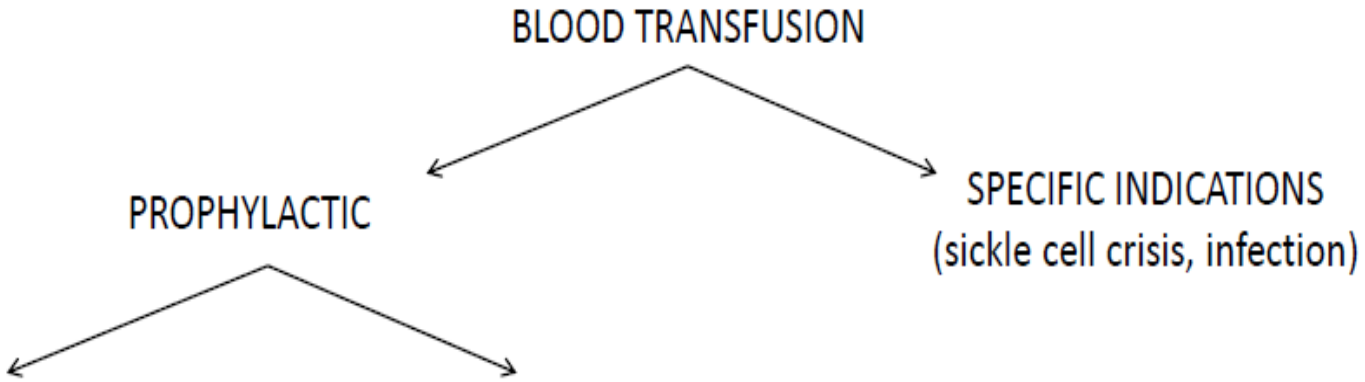
SICKLE CELL DISEASE

- Structural Hb variant
- substitution of Valine for glutamic acid at 6 position of b chain.
- Exists in homo(Hb-SS) & heterozygous forms(Hb-SA)
- Under hypoxic conditions, HbS polymerizes, gels or crystallizes.
- hemolysis of cells, & thrombosis of vessels in various organs
- In long standing cases, multiple organ damage.
- Constant sickling & desickling leads to membrane damage & cells may be irreversibly sickled
- Slow rbc transit through microcirculation contributes to vaso-occlusion

IN PREGNANCY

- Abortion and still birth
- Intra uterine growth restriction
- Premature birth
- Intrapartum fetal distress
- Increased perinatal mortality
  - Aplastic , megaloblastic sequestration & haemolytic crisis
- Diagnosis: Hb. Electrophoresis

TREATMENT OF SICKLE CELL ANEMIA



Partial iso volumetric exchange at 28 wks to achieve

* Hct 35%
* HbA1 40%

Repeated when

* Hct < 25%
* Hb A1 < 20%
* At 36-38wks

Packed red cell infusion as soon as dx of pregnancy is made. Then intermittently till term

iron is usually not required but folic acid should be given

MANAGEMENT OF SICKLE CELL CRISIS

- HOSPITALISATION
- HYDRATION AND OXYGENATION
- PAIN RELIEF
- TRANSFUSION
- IV ANTIBIOTIC