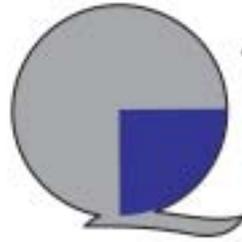


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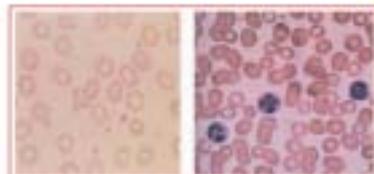
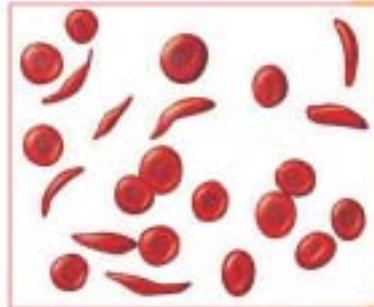


# QUARTERLY MEDICAL REVIEW

Vol. 60, No. 2

April - June 2009

## *Review : The Anaemic Women*



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## The Anemic Woman

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# QUARTERLY MEDICAL REVIEW

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## The Anemic Woman

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## NUTRITION AND WOMEN

The nutritional requirements of women differ in different stages of life. An individual's nutritional health starts to take shape while he/she is in-utero and remains the basic template through out life. Hence to give the children a well nourished body, a mother must start when she is pregnant. A healthy mother makes a healthy baby who makes a healthy adult and the circle goes on!

**FOOD TO BE EATEN IN ABUNDANCE: Vegetables, fruits, high fibre grains like oats, wheat bran, bajra, jowar.**

**FOOD TO BE EATEN IN MODERATION: Milk and milk products (rich in calcium), breads, some fruits like banana, mango, chikoo, nuts (contain minerals), sea-food.**

**FOODS TO BE RESTRICTED: Red meats (lamb, beef, pork), butter, cheese, ghee, fast food, junk food, processed & canned foods**

**NUTRITION IN PREGNANCY:** The Institute Of Medicine (IOM) recommendations for weight gain during singleton pregnancy are [1] are -

12.5-18 kg for underweight women	- BMI < 19.8 kg/sq m
11.5-16 kg for normal weight women	- BMI 19.9-26.0 kg/sq m
11.5 kg for over-weight women	- BMI 26-29.0 kg/sq m
Atleast 6.8 kg for obese women	- BMI > 29.0 kg/sq m

Dietary components – Specific dietary components do not appear to have a significant effect on birthweight.

### Macronutrients

Calories are the single most important nutritional factor in determining birthweight. Balanced energy/protein supplements-compared with no supplementation, energy supplementation during pregnancy (300-850 kcal/day with less than 25% of that energy coming from protein) is associated with small increases in maternal weight gain and birthweight, and a greater reduction in the risk of small for gestational age (SGA) infants and stillbirths. Women fed a diet low in cholesterol and saturated fat had a marked decrease in preterm deliveries.-The Cardiovascular Risk Reduction Diet in Pregnancy Trial(CARRDIP).

Docosahexaenoic acid (DHA, omega -3 polyunsaturated fatty acid) appears to be essential for early brain development during gestation and infancy. Some studies have demonstrated better mental growth of offspring of mothers who had taken cod-liver oil. Other studies have reported similar benefits and also improvement in visual acuity and decrease in risk of allergic disorders. Fish oil supplements or fish is recommended to improve neurological, immunological or physical development in the offspring.

### **Micronutrients**

In developing countries, consumption of multivitamins may improve birthweight and infant mortality.

### **Calories**

Calories are the single most important nutritional factor in determining birth weight. The recommended intake is 340kcal/day in the second trimester and 452kcal/day in the third.

The United States Department of Agriculture provides a free internet site to help pregnant women choose appropriate foods from a food pyramid (“My Pyramid for Moms”) based on their personal characteristics.

### **Protein**

The fetal/placental unit consumes approximately 1kg of protein during pregnancy, with the majority of this requirement in last 6 months. To fulfill this need the gravida should ingest 1.1g/kg/day protein, which is moderately higher than the 0.8 g/kg/day recommended for non-pregnant adult women. Animal proteins are considered complete or high quality proteins because they contain all 9 essential amino acids that the body needs for growth and repair of body tissues. Plant based foods are usually incomplete. The deficient amino acids can be obtained from soy products, consumption of foods with complementary amino acids and increased intake of dairy products.

### **Carbohydrates**

The RDA for carbohydrates in pregnancy is 175 g/day, up from 130g/day in non-pregnant women.

### **Iron**

This will be discussed in detail in the chapter on anemia. 1000 mg iron is lost in pregnancy & lactation. Experts recommend an increase in iron consumption by about 15-30mg / day, an amount readily met by most prenatal iron supplements.

### **Calcium**

Fetal skeletal development requires about 30 gm of calcium during pregnancy, primarily in the third trimester. This much is easily mobilized from maternal stores. The RDA for calcium is 1000 mg / day in pregnant & lactating women 19 to 50 years of age (1300 mg for girls aged 14-18yrs). The dietary recommendation is the same for lactating & non-lactating women of the same age. Calcium supplementation has been used to prevent Hypertensive disorders of pregnancy.

### **Vitamins and Minerals**

Women at risk for deficiency include those carrying twins, heavy smokers, adolescents, strict vegans, substance abusers, women with lactose deficiency. Content varies depending on product used. A supplement that contains: Iron-30mg, Zinc-15mg, Copper-2mg, Calcium-250mg, Vitamin B6-2mg, Folate-0.6mg, Vitamin C-50mg, Vitamin D-5 mcg (200IU) is useful.

Folic Acid requirements are higher in pregnancy, between 400-600mcg/day, best started in the periconceptual period.

**Breast-feeding Women**

Breast feeding women should increase their daily caloric intake by 300-500 kcal above pre-pregnancy levels and consume 1000mg/day of calcium. Theoretically, this level of caloric intake should promote post partum weight loss as caloric demand at this time is 640kcal/day.

**Nutrition & PMS**

Up to 40% of women experience PMS (Premenstrual Syndrome) in some form or the other. Symptoms include bloating, irritability, food craving, insomnia, mood swings, depression etc. Most women seek relief from the symptoms. Evaluation of the diet and its modification can mitigate some symptoms. Caffeine and alcohol should be avoided. Carbohydrate intake must be reduced to decrease mood swings & anxiety. Overall a well-balanced diet with fiber, dark green leafy vegetables, a wide selection of fresh fruits and regular exercise are helpful. Minerals like zinc and calcium may help.

**Nutrition and the Middle Aged Women**

Middle adulthood refers to the years between the adolescent and the golden years i.e. between 25-50yrs. This is the time when the body is not growing and the slowing down of old age has not started. Sadly, this is the time when 'lifestyle disorders' like diabetes, obesity, heart disease start acting up. This is the time that the 'middle-age spread' starts. Mainly because, the calorie needs decrease due to stopped growth, calorie intake increases. Due to stress from starting and maintaining career & family peaks, exercise decreases. One way to break this vicious cycle is to increase activity. At this time it is advisable to eat low calorie diet rich in fiber, fruits and vegetables. Sometimes the patient can reduce weight just by reducing stress. Sleeping well fine tunes the metabolism so that what is eaten is burnt and very little is stored.

**Nutrition and Menopause**

Again weight gain is common at this stage in life as metabolism decreases further due to decreasing sex steroids and activity declines even further. Diets rich in phyto-estrogens like soy products and plant products can help make the transition more tolerable. Calcium and zinc containing supplements are helpful. Green tea has a mild diuretic effect and can reduce bloating. Diets rich in protein, fiber, vegetables, fruits are advised. Fish containing omega fatty acids can increase estrogen levels and ease symptoms. The lady must avoid red meats which are difficult to digest and rich in calories. A well-balanced diet, exercise, stress control, busy lifestyle are the key to keep going in this difficult transitional phase of a woman's life.

Total fat should be restricted in all age groups, particularly saturated fat found in butter, ghee, red meats. High cholesterol foods like egg yolk must be avoided. Egg white contains only high quality protein and should be encouraged. Sodium intake should be less than 300mg/day.

Total daily calorie intake depends on age, sex (more in males), height and level of activity. Even reduction of few calories below required calories can help to maintain a steady weight throughout life.

## **THE ANEMIC WOMEN**

If a patient has **anemia**, people may say, “You have tired blood”. A physician may explain to a patient – “Anemia is a condition in which there aren’t enough healthy red blood cells (RBCs) to carry adequate oxygen to your tissues and that can make you feel tired.”

There are many causes of anemia, each with its own reasons. Anemia can be temporary or long-term and it can range from mild to severe.

Anemia is a common blood disorder. Women and people with chronic diseases are at increased risk. Anemia can be a sign of serious illness.

If a woman thinks she has anemia, she must visit her physician. Treatment can range from taking supplements to undergoing medical procedures.

One may even be able to PREVENT some types of anemia.

### **Causes:**

Blood consists of liquid, plasma and formed elements including, red cells, white cells and plasma. The red blood cells (RBCs) carry oxygen from the lungs to the rest of the body including brain. A good supply of oxygen is required for each and every cell in the body to function and hence the RBCs provide the basic life source to all cells, namely oxygen.

RBCs are produced in the bone marrow.

They contain hemoglobin which binds oxygen and carries it to cells. To make hemoglobin, the marrow requires iron, protein and multivitamins including minerals. A deficiency in any of these can cause anemia.

### **Anemia in women of different age groups**

The commonest cause of anemia is Iron deficiency. About 1 in 5 women and almost 50% of pregnant women are suffering from iron deficiency. Its causes are different in different age groups.

In adolescents, growth poses a huge demand and if not met can cause anemia. If the diet is deficient due to anorexia, then it sows the seeds for a life-time of suffering from anemia. Further, excessive bleeding during menses as in puberty, menorrhagia and blood dyscrasias can be a culprit. Treatment varies as per the cause.

In the reproductive age group, pregnancy, is the main source of demand and it stands to reason, that repeated and too frequent pregnancies stress an already anemic women. This is also the age group in which women have regular menses and heavy bleeding from causes like fibroids, DUB (Dysfunctional uterine bleeding) etc. Hormonal imbalances, infections, intra-uterine devices etc. can also cause anemia in this age group.

Anemia can also be looked upon as a legacy that a mother passes on to her daughters, in that anemic women produce anemic daughters and the cycle perpetuates. Somewhere, the cycle has to be broken.

The menopausal age group may also be fraught with anemia, due to chronic conditions like malignancies, concomitant medical disorders like diabetes, uterine structural and functional abnormalities, endocrine disorders like hypothyroidism, auto-immune conditions like SLE (Systemic Lupus Erythematosus), Gastro-intestinal disorders like polyposis, cancers, diverticulosis etc.

The body is completely dependent on the diet for its source of iron and a poor diet is the leading cause of anemia in poor countries like India.

Along with iron, multiple vitamins and minerals like vitamin B<sub>12</sub>, Folic acid, selenium, copper, zinc are necessary for adequate hemoglobin formation and good red cell function. Eggs and meats remain good sources of protein needed for globin formation. Vegetarians must look to soy, cottage cheese, pulses as sources of protein.

Other less common causes include aplastic anemia, hemoglobinopathies, hemolytic anemia, both acquired (the ubiquitous malaria) and inherited.

### **Abnormal and excessive uterine bleeding**

A normal menstrual blood loss is 50-80 ml and does not exceed 100 ml. If the quantity of menstrual loss increases and remains persistent, it can lead to anemia. The underlying cause is difficult to detect.

Menorrhagia is cyclical bleeding at normal intervals which is excessive in amount or duration, for example 5/28 or 8/28. It occurs in uterine tumours such as leiomyoma or adenomyosis, or it can be a manifestation of a coagulation disorder.

Polymenorrhoea is cyclical bleeding which is normal in amount but which occurs at too frequent intervals of less than 21 days, for example 5/21. It occurs when pituitary – ovarian relationships are upset, and when there is alteration of ovarian function associated with vasomotor disturbance, pelvic infection and ovarian endometriosis.

Polymenorrhagia is cyclical bleeding which is both excessive and too frequent, for example 9/20-12/20. It implies a disturbance in the hypothalamic-pituitary-ovarian-uterine-axis plus the uterus itself and the endometrium and is seen particularly in the presence of pelvic infection and sometimes under high pressure stress situations.

Metrorrhagia is bleeding of any amount which is acyclical and which occurs irregularly or continuously between normal cycles. It is caused by a surface lesion of the genital tract – a benign or malignant growth with ulceration. It is also a feature of abnormal pregnancy states like abortion and ectopic pregnancy.

Menometrorrhagia is prolonged and irregular bleeding.

There is increased tendency nowadays to use the patient's own words regarding abnormal bleeding. The major causes include local causes like uterine fibroids, fibroid polyp, chocolate cyst, ovarian feminizing tumors, PCOD (Polycystic ovarian disease), endometriosis, pelvic inflammatory disease, immediate puerperal and post abortion periods, IUDs (intra uterine contraceptive devices), oestrogen and progesterone administration etc.

The management may be conservative initially. Pronounced anemia may be produced by the continuous bleeding. The anemia caused may demand blood transfusion and hematinic treatment. Hormone therapy, danazol, clomiphene, ethamysylate may be used. Surgery is advocated for severe cases.

### **Incidence of Anemia in Women**

Anemia is a problem of gigantic proportions. Some statistics are worth considering:

- Anemia, particularly, iron deficiency affects 2 billion people world-wide.
- Affects 44-56% of pregnant women in developing countries.
- Affects 18% of pregnant women in industrialized nations.
- In India, out of a pregnant population of 22 million women, it affects 13 million pregnant women.
- About 0.5 million women die annually, in India as a result of pregnancy and its complications. Anemia is the leading contributor to this appallingly high maternal mortality rate. It is directly responsible for 20% of maternal deaths and another 20% die due to indirect consequences of anemia like obstetric hemorrhage, sepsis etc.
- Anemia is present in 82.9% of school going girls in India.
- Anemia is even more common in non-school going girls in India, affecting a whopping 92.7%.

There are many reasons why anemia is so common in the Indian woman. Some of them are:

- poverty
- illiteracy and ignorance
- religious taboos

#### **Superstitions and unfounded beliefs**

- gender discrimination
- early marriage
- early and frequent child-bearing
- poor contraceptive acceptance
- social dependence
- poor ante, intra and post natal care
- inadequate obstetric health services

There is an interesting study by Awasthi et al (13) clearly showing how maternal and perinatal hazards increase due to maternal anemia.

## ANEMIA

The centers for disease control and prevention (1990) defined anemia as haemoglobin less than 11g/dl in the first and third trimesters and less than 10.5g/dl (grams per deciliter) in the second trimester.

Hemoglobin less than 12 g % (or g/dl) in adult non pregnant female and less than 11 g/dl in children should be considered as evidence of anemia.

Cases with mild anemia usually don't have clinical manifestations. Symptoms associated with moderate anemia include fatigue, loss of stamina, breathlessness, tachycardia.

With chronic anemia intracellular levels of 2, 3-bisphosphoglycerate rise, shifting the oxy- Hb (hemoglobin) dissociation curve to right. This compensatory mechanism can only maintain normal tissue oxygen delivery in the face of 2-3gm/dl deficit in Hb concentration. Further protection to vital organs is done by shunting blood away from organs that are relatively rich in blood supply, particularly kidney, gut, skin.

### Approach To Patient

A detailed history must be elicited including –

- Nutritional history including drugs and alcohol intake
- Family history of anemia
- Geographic background and ethnic origins

Symptoms like bleeding, fatigue, malaise, fever, weight loss and night sweats, blood in stool may be complained of. On examining the patient, signs like forceful heartbeat, strong peripheral pulses, systolic flow murmur, lymphadenopathy, splenomegaly or petechie may be present.

Skin and mucous membrane are pale if Hb is less than 8-10gm/dl.

If the palmar creases are lighter in colour than the surrounding skin, it indicates hemoglobin below 8gm/dl.

The investigations carried out give the following results -

Microcytosis (MCV<80fL), macrocytosis (MCV>100fL)

<b>Changes in Hemoglobin (Hb) and hematocrit (crit) according to age</b>		
<b>Age</b>	<b>Hb</b>	<b>Hematocrit</b>
Birth	17	52
Child	12	36
Adolescent	13	40
Adult	13	40
Pregnancy	12	37
Postmenopausal	14	42

**Normal Values**

MCV-(crit X 10)/red cell count X 106 = 90 +- 8fL

MCH-(HbX 10) / (red cell count X 106)=30 + - 3 pg

MCHC — (HbX 10)/crit = 33 + - 2%

Reticulocyte count=1-2%

Serum iron= 50-150mcg/dl

TIBC= 300-360 mcg/dl

Transferrin saturation = 25-50%

Serum ferritin in adult male= 100 mcg/dl - most convenient lab test to estimate iron stores

Serum ferritin in adult female 30mcg/dl

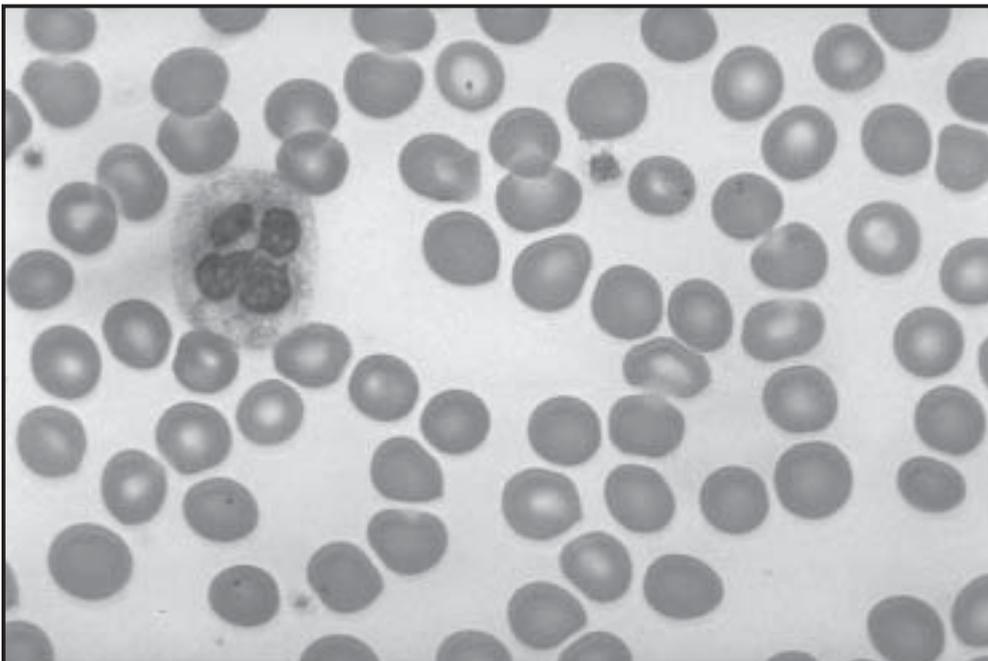
Marrow- diagnose fibrosis, infiltrative disease, leukemia, marrow can be stained for iron reserve, which is stored in the form of ferritin or hemosiderin, ringed sideroblast

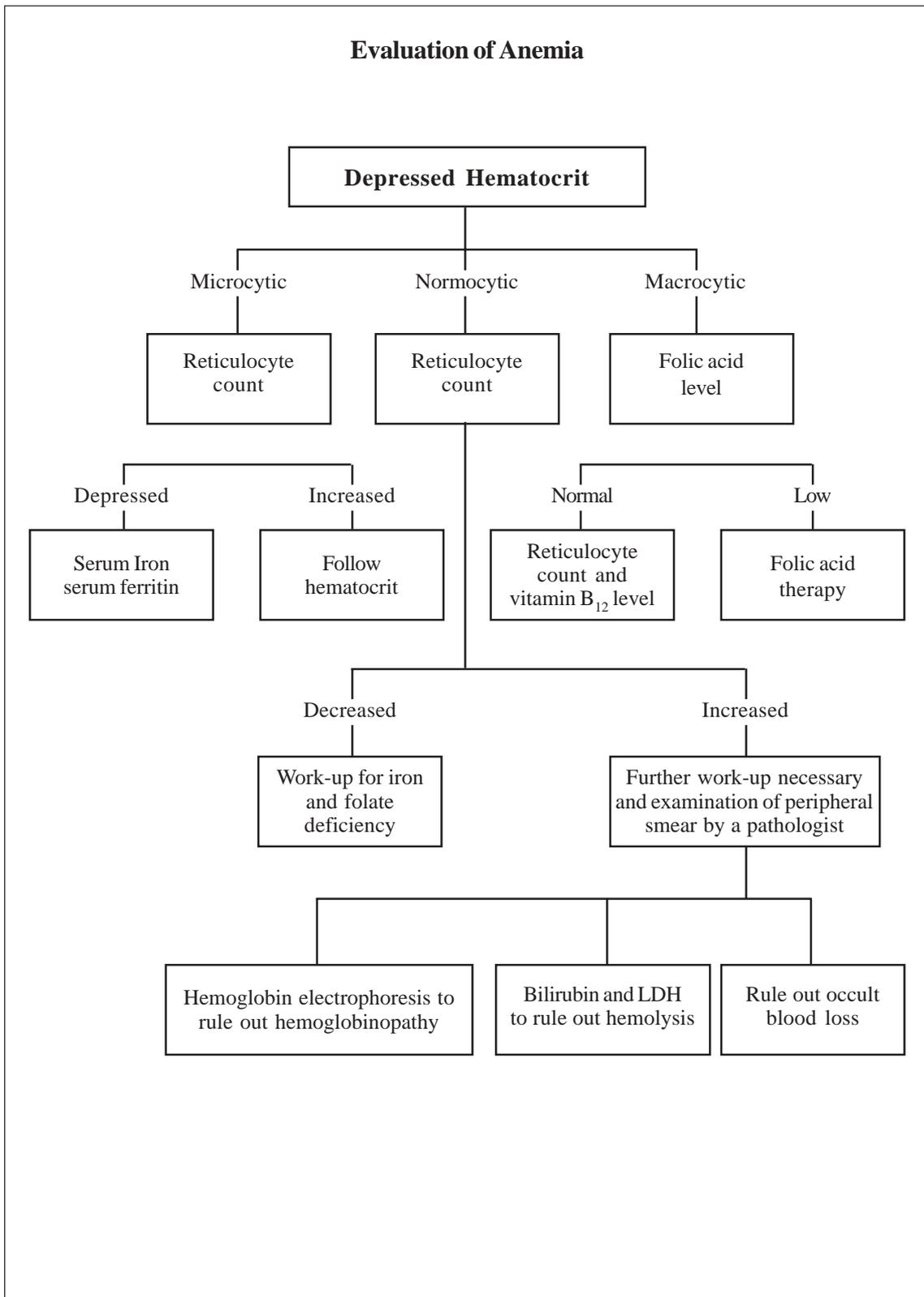
Red cell protoporphyrin-<30mcg/dl (increased in absolute or relative iron deficiency, lead poisoning)

Serum levels of transferrin receptor protein-4-9 mg/l

**NORMAL PERIPHERAL BLOOD SMEAR**

Note the RBCs full of Hb





### **Functional Classification of Anemia**

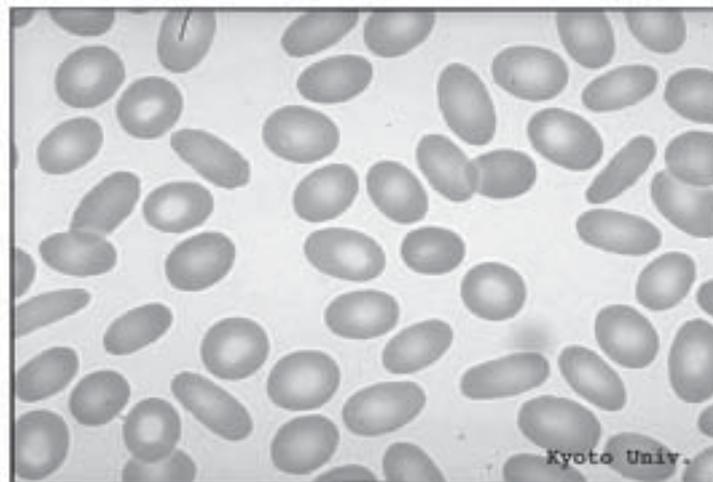
- Hypoproliferative anemia
- Maturation disorder
- Hemolysis/ hemorrhage

### **Hypoproliferative anemia**

At least 75% anemias are HYPOPROLIFERATIVE, the majority of it is because of mild to moderate iron deficiency or inflammation. The aetiology is as follows-

1. Marrow damage
  - a. Infiltration/fibrosis
  - b. Aplasia
2. Iron deficiency(mild- moderate)
3. Decreased stimulation
  - a. Inflammation producing IL-1
  - b. Metabolic defect like hypothyroid
  - c. Renal disease

### **VARIATIONS OF RED CELLS : ELLIPTOCYTES**



### **Maturation Disorder**

The aetiology includes

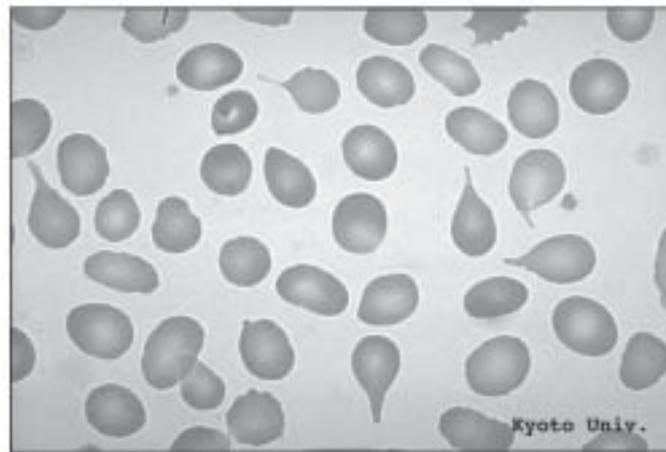
Cytoplasmic defects (microcytosis)

- a. Iron deficiency(severe)
- b. Thalassemia
- c. Sideroblastic anemia

2. Nuclear defect (macrocytosis)
  - a. Folate deficiency
  - b. Vit B<sub>12</sub> deficiency
  - c. Drug toxicity (methotrexate)
  - d. Refractory anemia (myelodysplasia)

Marrow Myeloid/erythroid <1:1

#### VARIATION OF RED CELL : TEAR DROP CELL

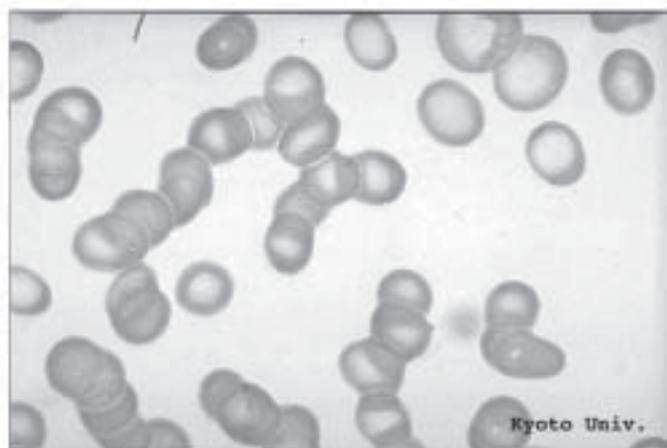


#### Blood loss / hemolytic anemia

The aetiology is as follows

1. Blood loss
2. Intravascular hemolysis
3. Metabolic defect
4. Membrane abnormality
5. Hemoglobinopathy
6. Autoimmune defect
7. Fragmentation hemolysis

#### HEMOLYTIC ANEMIA Rouleaux formation, clumped RBCs



## IRON METABOLISM

Body iron distribution in adult female is as follows

Hemoglobin	1700mg
Myoglobin/enzyme	300mg
Transferrin	3mg
Store	0-300mg

Females in child bearing age group will need to absorb 1.4 mg of iron daily because approximately the same amount is lost per day. In the last two trimesters in pregnancy daily requirement is increased to 5-6 mg/day.

Iron is found in a variety of foods. Heme iron is found in meat, poultry, and fish. Nonheme iron is found in fruits, vegetables, grains, nuts, legumes, and iron-enriched foods. The body absorbs heme iron better than nonheme iron.

Dietary iron intake is closely related to calorie intake (approximately 6 mg of elemental iron per 1000 calories). About 10% of the dietary intake is absorbed. Vegetarians have disadvantage because certain foods contain phytates and phosphates that reduce absorption by 50%.

<b>Iron requirement (mg)</b>	
Females 14 to 18 years old	15
Males 14 to 18 years old	11
Females 19 to 50 years old	18
Females over 50 years old	8
Pregnant females	27
Breast – feeding females 14 to 18 years old	10
Breast – feeding females 19 to 50 years old	9

Iron absorption takes place largely in the proximal small intestine. It is facilitated by the acidic content of the stomach, which maintains the iron in solution. At the brush border of the absorptive cell, the ferric iron is converted to the ferrous by ferrereductase.

There is no excretory path for iron and the only mechanisms by which iron is lost from the body are blood loss and loss of epidermal cells from the skin and gut. Non menstruating women lose about 1 mg of iron per day. Menstruating women lose from 0.6 to 2.5 percent more per day. An average 132-lb (60-kg) woman might lose an extra 10 mg of iron per menstruation cycle, but the loss could be more than 42 mg per cycle depending on how heavily she menstruates. A pregnancy takes about 700 mg of iron, and a whole blood donation of 500 cc contains 250 mg of iron.

Because iron requirements are slight during the first 4 months of pregnancy, it is not necessary to provide supplemental iron during this time. Withholding iron in the first trimester of pregnancy avoids the risk of nausea and vomiting. Ingestion of iron at bed time or on an empty stomach facilitates absorption and appears to minimize the possibility of an adverse gastrointestinal reaction.

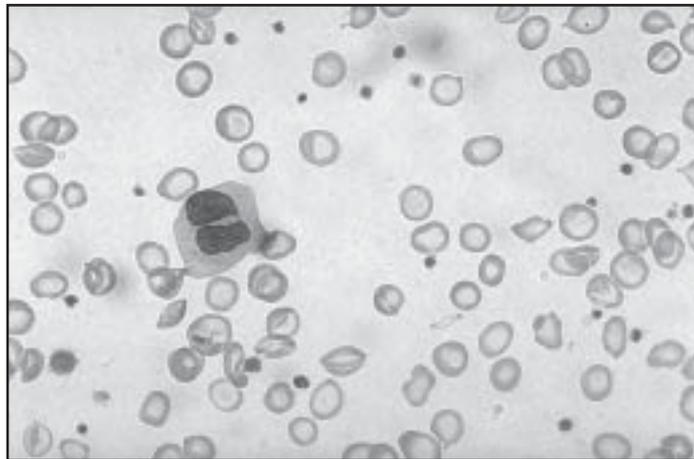
Since 1997, the FDA has required that iron preparations containing 30mg or more of elemental iron per tablet be packaged as individual doses, such as in blister packages.

Iron deficiency anemia - causes

1. Increased demand
  - a. Rapid growth in infancy / adolescence
  - b. Pregnancy
  - c. Erythropoietin therapy

### **IRON DEFICIENCY ANEMIA**

Note the pale cells, empty of Hb in centre, schistocytes, poikilocytes, a large multi-lobate precursor



2. Increased iron loss
  - a. Chronic blood loss
  - b. Menses
  - c. Acute blood loss
  - d. Blood donation
  - e. Phlebotomy as treatment of polycythemia vera
3. Decreased iron intake or absorption
  - a. Inadequate diet
  - b. Malabsorption (sprue, Crohn's disease)
  - c. Surgery (postgastrectomy)
  - d. Acute / chronic inflammation

### **Effects of anemia on pregnancy**

Klebanoff and coworkers (1991) studied nearly 27, 000 women and found a slightly increased risk of preterm birth with midtrimester anemia. Lieberman & colleagues (1987) found an association with low hematocrit and preterm birth. Anemia may lead to fetal growth restriction that may lead to adult cardiovascular disease. Kadyrov and colleagues (1998) have provided evidence that maternal anemia influences placental vascularisation by altering angiogenesis during early pregnancy. Anemia contributes to approximately 40% maternal deaths in third world countries.

Kadyrov compared trophoblast invasion into spiral arteries in pregnancies with maternal anemia or related these findings to trophoblast apoptosis. Trophoblast invasion into the placental bed in early-onset preeclampsia/intrauterine growth restriction is limited by increased apoptosis, resulting in narrower spiral arteries, which is in contrast to findings in anemia.

### **Physiologic Compensatory Mechanisms for anemia**

The five main physiologic compensatory responses to anemia vary in prominence, depending on rapidity of onset and duration of the anemia and the condition of the patient. First, in acute-onset anemia with severe loss of intravascular volume, peripheral vasoconstriction and central vasodilation preserve blood flow to vital organs. Second, over time and with increasingly severe anemia, systemic small vessel vasodilation results in increased blood flow to ensure better tissue oxygenation.

These vascular compensations lead to decreased systemic vascular resistance, increased cardiac output, and tachycardia, which result in a higher rate of delivery of oxygen-bearing erythrocytes to tissues. Third, an increased level of 2, 3-diphosphoglycerate accumulates in RBCs and interacts with hemoglobin molecules to cause a rightward shift of the hemoglobin oxygen dissociation curve, which in turn enhances the release of oxygen to tissues at any given partial pressure of oxygen. Fourth, in chronic anemias there is a compensatory increase in plasma volume that maintains total blood volume and enhances tissue perfusion. The fifth compensatory response in otherwise normal individuals is stimulation of EPO (Erythropoetin) production, which in turn stimulates new erythrocyte production. The latter occurs if the stem cells and erythroid precursors are normal, the erythroid precursors are able to respond normally to EPO, and the developing normoblasts are normal.

The two most common causes of anemia during pregnancy and the puerperium are iron deficiency anemia and acute blood loss. In a typical singleton pregnancy, the maternal need for iron averages to 800mg - 300mg for the fetus and placenta and 500 mg if available, for maternal Hemoglobin mass expansion. Approximately 200 mg more are shed through the gut, urine and skin. The total amount (1000 mg) considerably exceeds the iron stores of most women and results in iron deficiency anemia. With rather rapid expansion of blood volume during the second trimester, iron deficiency is often manifested. Because the amount of iron diverted to the fetus is similar in a normal and in an iron deficient mother, the newborn infant of a severely anaemic mother doesn't suffer from iron deficiency anemia.

If at the time of delivery, the newborn is placed at or below the level of the vaginal introitus for 3 minutes and the fetoplacental circulation is occluded after that, an average of 80ml of blood may be shifted from placenta to newborn ( Yao and Lind, 1974). This provides about 50mg of iron,

which reduces the frequency of iron deficiency anemia later in infancy. But there is theoretical risk of circulatory overload in preterm and growth restricted neonates. Infant social-emotional behavior appears to be adversely affected by Iron deficiency with or without anemia. Infant social-emotional behavior can profoundly influence the care-giving environment, with repercussions for overall development. (3)



**Chronic anemia.** Pallor of the hand in anemia is obvious in this patient, especially when compared with the physician's hand on the right (From Forbes CD, Jackson WF: Color Atlas and Text of Clinical Medicine, 3rd ed. London, Mosby, 2003.)

### Diagnosis of Iron Deficiency Anaemia

Erythrocyte - hypochromic and microcytosis ( D/D- thalassemia, chronic inflammation, sideroblastic anemia)

Serum ferritin level is below normal (less than 15mcg confirms the diagnosis)

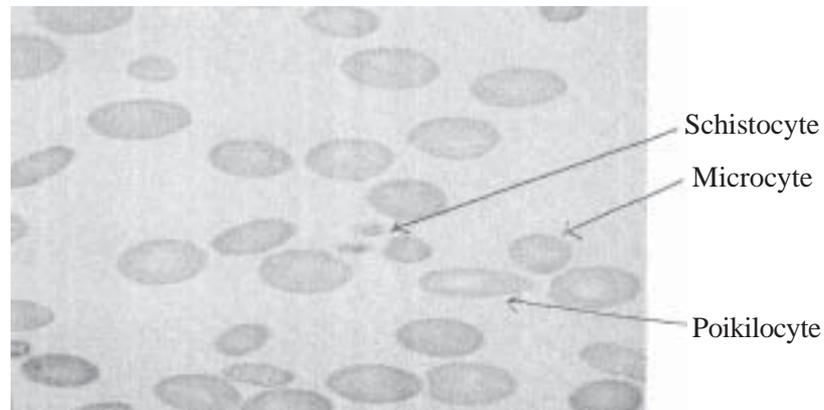
No stainable bone marrow iron

Iron deficiency anemia in pregnancy is primarily the consequence of expansion of plasma volume without normal expansion of maternal hemoglobin mass.

When cases with moderate iron deficiency anemia are treated with adequate iron therapy, response is detected by an elevated reticulocyte count. The rate of increase of Hb concentration is typically slower than in non pregnant women due to the differences in blood volume.

The use of Doppler ultrasound evaluation to measure the peak systolic velocity of the fetal middle cerebral artery (MCA) has been a major breakthrough in the noninvasive detection of fetal anemia. An elevated peak MCA velocity of >1.5 multiples of the median is useful in the timing of the initial intrauterine transfusion (IUT).

The peak MCA velocity has also proved useful in the detection of other anemic states that include Kell alloimmunization, fetal parvovirus infection, fetomaternal hemorrhage, alphathalassemia, and after-laser therapy for twin-twin transfusion. (4)



### Screening and Primary Prevention

The U.S. Preventive Services Task Force (USPSTF) recommends screening pregnant women for IDA.

Encouraging mothers to breastfeed their infants and to include iron-enriched foods in the diet of infants and young children also is recommended. Although the USPSTF found insufficient evidence to recommend for or against the routine use of iron supplements in healthy infants or pregnant women, a recent study showed a significant decline in the number of newborns weighing less than 5 lbs 8 oz (2.5 kg) (number needed to treat = 7) when the mothers used routine prenatal iron supplementation. This supports prescribing prenatal vitamins with iron to all pregnant women, which is the current standard of care in the United States. Essential amino acids are necessary for the formation of hemoglobin. Hence, adequate protein in the diet is essential for formation of hemoglobin.

Dietary Reference Intakes (DRI) for many vitamins and minerals, including iron must be considered. DRI replaced Recommended Daily Allowance. The DRI for iron is 8 mg per day for healthy, non menstruating adults; 18 mg per day for menstruating women; and 16 mg per day for vegetarians because of their differential absorption of nonheme iron. For blood donors, a daily dose of 20 mg of elemental iron is recommended.

Transfusion of blood is seldom indicated unless hypovolemia from blood loss coexists, there are severe symptoms of anemia, continued and excessive blood loss from whatever source or an emergency operative procedure must be performed on a severely anemic woman.

In the patient with established iron deficiency anemia who is asymptomatic, treatment with oral iron is adequate. Typically, for iron replacement therapy, up to 300mg of elemental iron per day is given as 3-4 tablets each containing 50-65mg elemental iron over one day in empty stomach. A dose of 300mg should result in the absorption of 50mg/day. Typically, the reticulocyte count should begin to increase within 4-7 days. The absence of a response may be due to poor absorption, noncompliance or confounding diagnosis.

To replenish iron stores, oral therapy should be continued for 6-12 months after anemia has been corrected to provide stores of at least 0.5 to 1 gm of iron.

Gastrointestinal distress is the most prominent side effect of iron supplementation and may be manifested as abdominal pain, nausea, vomiting, constipation etc.

<b>Iron content of oral iron salts</b>	
<i>Oral Iron Therapy</i>	<i>Iron content (mg)</i>
Ferrous sulfate	325(107)
Ferrous fumarate	325(107)
Ferrous gluconate	325(39)
Polysaccharide Fe	150 (150)

### **Parenteral Iron Therapy**

Parenteral iron is indicated in those who are unable to tolerate oral iron, whose needs are relatively acute or who need iron on an ongoing basis as in persistent gastrointestinal blood loss. The maximum increase of hemoglobin was observed 2 weeks after the start of intravenous iron treatment, indicating that administration of intravenous iron 2-3 weeks before surgery may be optimal.

Calculation of Parenteral iron dosage

Need = body wt in Kg X 2.3 X ( 15 - Hb) + 500 or 1000 for the stores

### **Preparations available**

- Iron dextran
- Iron sucrose
- Sodium ferric gluconate

Adverse drug reactions to parenteral iron include anaphylactic reactions, arthralgia, skin rash, low grade fever (may occur several days after infusion).

If a large dose (>100mg) has to be given, the preparation should be diluted in 5% dextrose or 0.9% NaCl solution. It can be infused over 60-90 minutes. Early in the infusion if chest pain, wheezing, hypotension or other systemic features develop, the infusion should be interrupted immediately.

### **Blood Loss Anemia**

The gastrointestinal tract is a major site of chronic blood loss. Malignancies, gastritis, peptic ulcer disease, inflammatory bowel disease, diverticulitis, proctitis, hemorrhoidal bleeding, angiodysplasia, arteriovenous malformations, and hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) are among the major causes of chronic or intermittent gastrointestinal blood loss.

Chronic excessive menstrual blood loss, chronic urinary tract bleeding and recurrent epistaxis can also lead to iron deficiency and anemia.

With acute blood loss, estimation of the loss is notoriously inaccurate by inspection. Signs of vascular instability appear with acute blood loss of 10-15% of the total blood volume. When more than 30%

of the blood is lost suddenly, patients are unable to compensate with the usual mechanisms of vascular contraction and changes in regional blood flow. The patient will show postural hypotension and tachycardia when upright. If the volume of blood lost is more than 40% (i.e. 2 litres in an average sized adult), signs of hypovolemic shock including confusion, dyspnoea, diaphoresis, hypotension and tachycardia in supine posture appear. After about 1000ml blood loss the hematocrit typically falls only 3 % in the first hour. During an episode of acute significant hemorrhage, the initial hematocrit is always the highest. When resuscitation is given with rapid infusion of intravenous crystalloids, there is rapid equilibration. Urine output is one of the most important vital signs to follow in the bleeding patients. In the absence of diuretics, the rate of urine formation, when carefully measured reflects the adequacy of renal perfusion and in turn perfusion of other vital organs, because renal blood flow is especially sensitive to changes in blood volume. Urine flow of at least 30ml and preferably 60ml per hour should be maintained. The cause of acute blood loss should be addressed first like treatment of DUB (Dysfunctional uterine bleeding), PPH (post partum hemorrhage) etc.

### **Fluid replacement**

Crystalloid solution typically is used for initial volume resuscitation. Such solutions rapidly equilibrate into the extravascular space and only 20% solution remains in the circulation after 1 hour. Because of this, initial fluid infusion should involve about 3 times as much crystalloid as the estimated blood loss. Schierhout and Roberts (1998) found a 4% excessive mortality in non pregnant patients resuscitated with colloid compared with that with crystalloid. Cardiac output does not substantially decrease until the Hb concentration falls to about 7gm/dl.

For the woman acutely bleeding, if crit < 25%, blood infusion should be given or if Hb < 8gm% and there is any imminent surgery. Mortality rates were lowest when hematocrit values were maintained between 27 and 33 %.

Compatible whole blood is ideal for treatment of hypovolemia from catastrophic acute hemorrhage. It has a shelf life of 40 days and 70% of the transfused red cells function for at least 24 hours following transfusion. One unit raises the hematocrit by 3-4 volume percent. Whole blood replaces many coagulation factors, especially fibrinogen and its plasma expands hypovolemia from hemorrhage. For women who are more stable and do not have massive blood loss, packed red cell transfusions are more suitable.

Because some RBCs are invariably transfused along with the platelets, only platelets from D-negative donors should be given to D-negative recipients.

Cryoprecipitate is an ideal source of fibrinogen if levels are dangerously low and there is oozing from surgical incisions. Erythrocytes stored for 3 weeks are as efficacious as are erythrocytes stored for 3.5 hours in reversing the neurocognitive deficit of acute anemia. Requiring fresh rather than stored erythrocytes for augmentation of oxygen delivery does not seem warranted. (5)

Packed RBC	250ml, crit=55-80%	RBC only	Increase Hct 3-4 volume%
FFP	250 ml, 30 min thaw needed before use	Colloid, 600-700mg fibrinogen, no platelets, all stable and labile clotting factors present	Restores TBV and fibrinogen  Indicated if fibrinogen level <100mg/dl or with abnormal PT, PTT
Cryoprecipitate	15 ml frozen Prepared from FFP*	200 mg fibrinogen, other clotting factors, no platelets	3000-4000 mg total is needed to restore maternal fibrinogen to > 150 mg/dl
Platelets	50 ml at room temperature	5.5X 10 <sup>10</sup> (10) platelets Single donor preferred but can't be stored <5days. Donor plasma must be compatible with recipient erythrocytes.	6-10 units usually transfused, each increases platelets 5000 / mcl
Whole blood	500 ml, crit = 40%	RBC, plasma, 600-700 mg of fibrinogen, no platelets	Restore total blood volume and fibrinogen Hct increase by 3-4 volume %
Packed RBC	250 ml, crit = 55-80%	RBC only	Increase Hct 3-4 volume%

When blood loss is massive, replacement with crystalloid solutions and packed red blood cells usually results in a depletion of platelets and soluble clotting factors, leading to a dilutional coagulopathy that clinically is indistinguishable from disseminated intravascular coagulopathy. This impairs blood loss and further contributes to blood loss. The most frequent coagulation defect found in women with blood loss and multiple transfusions is thrombocytopenia. Stored blood is deficient in factors V, VIII, XI and platelets and all soluble clotting factors are absent from packed red blood cells. Component replacement is rarely necessary with acute replacement of 5 to 10 units of packed red blood cells or less. When loss exceeds this amount, consideration should be given to evaluation of platelet count, clotting studies and fibrinogen concentration. In the bleeding women, the platelet count should be maintained above 50,000/mcl. A fibrinogen level of less than 100 mg/dl or sufficiently prolonged prothrombin or partial thromboplastin time in a woman with surgical bleeding is an indication for fresh frozen plasma in doses of 10 to 15 ml/kg.

### **Red Cell Substitutes**

- perflurochemicals
- liposome encapsulated Hb
- Hb based oxygen carriers

Flouridated hydrocarbons are biologically inert liquids with relatively high oxygen solubility, which allows oxygen to be transported and delivered to tissues by simple diffusion. Fluosol must be stored frozen and thawed within 24 hours of use. One formulation of a Hb based oxygen carrier, diaspirin cross linked Hb (DCLHb) is proven dangerous. Polymerised bovine Hb (HBOC-201) has been successfully used.

The potential advantages of hemoglobin substitutes include their availability without need for cross-matching, a long shelf life, the ability to store the products at room temperature and a reduced risk of disease transmission. Disadvantages include their relatively short half-life after administration (24-48 hours), their interference with laboratory hemoglobin measurements, renal toxic effects and adverse effects on vascular tone and blood pressure.

Anemia commonly affects critically ill patients. The causes are multifactorial and include acute blood loss, blood loss from diagnostic testing and blunted red blood cell production. Although blood transfusion is a life-saving therapy, evidence suggests that it may be associated with an increased risk of morbidity and mortality. A number of blood conservation strategies exist that may mitigate anemia in hospital patients and limit the need for transfusion. These strategies include the use of hemostatic agents, hemoglobin substitutes and blood salvage techniques, the reduction of blood loss associated with diagnostic testing, the use of erythropoietin and the use of restrictive blood transfusion triggers. Lowering the hemoglobin threshold at which blood is transfused will reduce the need for transfusions and is not associated with increased morbidity or mortality among most critically ill patients without active cardiac disease. (6)

### **Anemia associated with Chronic Disease**

Chronic infection, neoplasm, chronic renal failure, chemotherapy, HIV infection, chronic inflammation are the most common causes. Others are IBD, SLE, Rheumatoid arthritis. Renal disease causes decreased erythropoietin secretion and infection causes acute red cell destruction from endotoxin mediated sepsis. Erythropoietin is required for the maintenance of the committed erythroid progenitor cells that, in the absence of the hormone undergo apoptosis.

Erythropoietin is a glycoprotein hormone secreted by the peritubular capillary epithelium and hepatocytes. The fundamental stimulus for EPO is availability of oxygen for tissue metabolic needs. The normal level is 10-25U/L. When the Hb concentration falls below 10-12gm/dl EPO level increases.

Bone marrow picture is not altered, serum iron concentration is decreased, serum ferritin levels increased. There is slight hypochromic microcytic anemia, increased red cell protoporphyrin, hypoproliferative marrow and transferrin saturation is 15-20%.

Treatment is with recombinant erythropoietin.

Adverse Drug Reactions include hypertension, placental abruption, pure red cell aplasia and antierythropoietin antibodies.

Although use of erythropoietin analogues has decreased the need for red-blood-cell transfusions, patients assigned the analogues received, on average, just one unit of blood less than controls—a difference that is highly unlikely to be life-threatening in most cases.

The Lancet Oncology called for erythropoietin analogues to be reassessed urgently to define the exact settings for their use.(7)

Iron supplementation is essential for the treatment of patients with anemia of chronic kidney disease (CKD). For patients with CKD, there was a small but significant difference in Hemoglobin level favoring the Intravenous (IV) iron group. Review shows that patients on hemodialysis therapy have better Hb level response when treated with IV iron. For patients with CKD, this effect is small. (8)

### **Metabolic Conditions causing Anemia**

Testosterone and anabolic hormones augment erythropoiesis. Liver disease, protein starvation, Hypothyroidism, Hypopituitarism, Addison's disease and Hyperparathyroidism also can lead to development of anemia.

Treatment of the underlying cause is important and in whom this is not possible, transfusion and erythropoietin are the recommended therapies.

### **Megaloblastic Anemia**

In megaloblastic anemia, there is derangement in red cell maturation with the production in the bone marrow of precursors known as megaloblasts (due to impaired DNA synthesis) due to deficiency of either Vitamin B<sub>12</sub> or Folic acid or both. Cells primarily affected are those having rapid turnover especially hematopoietic precursors and gastrointestinal epithelial cells. The daily requirement of Vit B<sub>12</sub> is 2mcg in nonpregnant and 3 mcg in pregnant females, which is met with by any food containing animal product. Only strict vegans may need supplementation. Vit B<sub>12</sub> is attached to gastric R binder found in saliva, gastric juice and bile. On entering the duodenum, the cobalamine - R binder complex is digested and the B<sub>12</sub> is attached to intrinsic factor secreted by parietal cells of gastric mucosa and the complex is absorbed in the distal ileum, hence cases with gastrectomy or ileal resection or pernicious anemia develop Vit B<sub>12</sub> deficiency.

### **Causes of megaloblastic anemia**

Megaloblastic anemia of pregnancy - temperate climate

Nutritional megaloblastic anemia- tropical countries

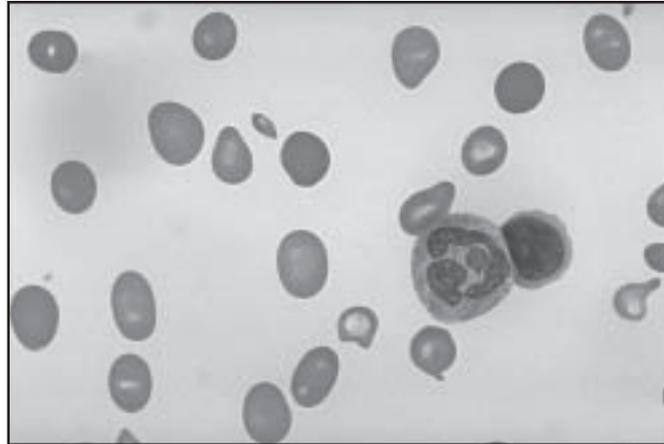
Addisonian pernicious anemia

Malabsorption Syndrome.

In pregnancy, the cause is increased requirement. Other causes include vegan diet, chronic use of antacids, fish tapeworm, alcohol intake, malabsorption syndromes, use of dihydrofolate reductase inhibitors like methotrexate, trimethoprim, chemotherapy etc.

### MEGALOBLASTIC ANEMIA Vit B<sub>12</sub> DEFICIENCY

Note the poly-lobate nucleus and huge RBC.



#### Addisonian Pernicious Anemia

This is considered the most common cause of cobalamine deficiency

It is an autoimmune disease causing deficiency of intrinsic factor hence Vit B<sub>12</sub>. If it occurs earlier it causes infertility hence it's rarely encountered in pregnant patients. Treatment with glucocorticoids may reverse the disease.

#### Folic Acid Deficiency

Folate deficiency can cause anemia. The presentation typically consists of macrocytosis and hypersegmented polymorphonuclear leucocytes (PMNs). Fruits and vegetables constitute the primary dietary source of folic acid. The minimal daily requirement is about 50 mcg, but this may be increased several fold during periods of enhanced metabolic demand such as pregnancy.

#### Causes of Folic Acid Deficiency

- Dietary deficiency is common in the elderly people eating a poor diet. In rare cases, it is found in teenagers living on junk-food. Alcohol consumption may aggravate the deficiency.
- There is an increased need for folic acid when there are periods of rapid growth in childhood and during pregnancy. Folic acid also helps to protect the foetus against spina bifida. In pregnant females the requirement of folic acid is 400 mcg. Increased demand may be seen in twin pregnancy. Folic acid deficiency is more common in multipara.
- Haemorrhagic states such as peptic ulcer, hookworms, haemorrhoids and hemolytic states like chronic malaria, some kinds of hereditary anemia such as haemolytic anaemia (sickle cell anaemia, thalassemia) may lead to folic acid deficiency.
- Some drugs or medicines such as anti-epileptic drugs and some antibiotics can interfere with the body's normal metabolism of folic acid. Pregnant women should always check with their doctor before taking any kind of medication during pregnancy.
- Diseases of the small intestine that cause a reduced absorption of nutrients, for example gluten intolerance (coeliac disease).

Some symptoms are unique to folic acid deficiency and include a red, irritated and possibly shiny, tongue, a reduced sense of taste, indigestion, changed bowel movements etc. In addition to complications of anemia, folic acid deficiency in pregnancy could contribute to abortion, dysmaturity, prematurity, abruption placentae, fetal malformations etc. This can be prevented if women of reproductive age group at risk are given 400 mcg folate daily. Additional 4 mg can be given in cases of high demand like multiple pregnancy, patients on anticonvulsant therapy, hemoglobinopathies, Crohn's disease, alcoholism etc. Patients already having infants with neural tube defects should be given 4 mg folic acid per day beginning 1 month preconceptionally till 12 weeks. Several observational and controlled trials have shown that neural tube defects can be reduced by 80% or more when folic acid supplementation is started before conception.

### **Dimorphic Anemia**

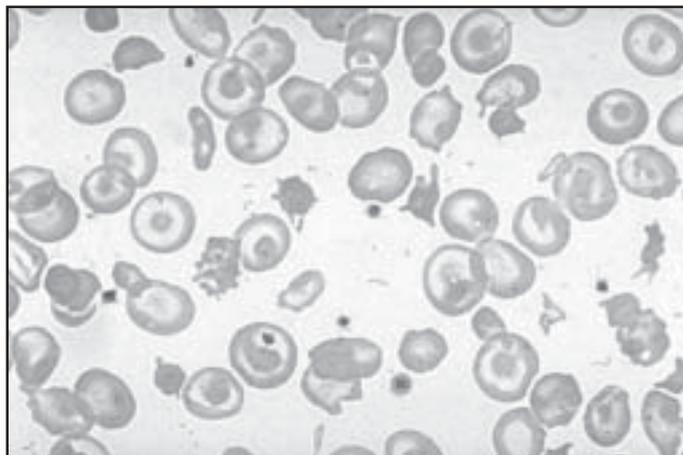
This is the commonest type of anemia in underprivileged sections of the society in tropics wherein there is both deficiency of iron, folic acid or Vitamin B<sub>12</sub>. It is related to dietary inadequacy and intestinal malabsorption and requires supplementation of iron, folic acid and Vitamin B<sub>12</sub>.

### **Haemoglobinopathies**

**Hemoglobinopathy** is a genetic defect that results in abnormal structure of one of the globin chains of the hemoglobin molecule. Common haemoglobinopathies include sickle-cell disease and thalassemia. They cause hemolytic anemia.

The hemoglobin molecule is composed of four separate polypeptide chains of amino acids, two alpha chains and two beta chains, as well as four iron-bearing heme groups that bind oxygen. The alpha chains are coded for by two similar genes on chromosome 16; the beta chains by a single gene on chromosome 11. Mutations and deletions in these genes cause one of the many hemoglobinopathies. Sickle cell disease is inherited structural abnormality involving primarily the beta chain of HbA. Thalassemia is an inherited defect in the synthesis and production of globin in otherwise normal HbA.

#### **THALASSEMIA – Note the target cells**



Hemoglobinopathies, including sickle cell disease and thalassemia, present unique health care challenges during pregnancy. Sickle cell disease can increase the incidence of abortion, prematurity, IUGR (intrauterine growth retardation) and fetal loss. Women with sickle cell disease need access to coordinated high-risk obstetrical and hematological care. Transfusion support does not improve maternal or fetal complications, even if used to correct severe anemia, but does lessen the incidence of sickle cell events, and should be reserved for women with severe anemia (hemoglobin < 6.0 gm/dl), frequent severe pain crisis or other sickle cell complications. (15). The reproductive performance in beta thalassemia minor patients is usually normal. They require oral iron and folate supplementation during pregnancy.

Preconceptional counselling of hemoglobinopathies is essential to make the parents aware of the potential risks to the offspring.

### **Conclusion**

If a woman complains of feeling unusually tired at any stage in her life, it warrants a trip to the doctor and a check on her hemoglobin. Anemia transcends age, sex and class barriers. Everyone is at risk and everyone should be tested. Simple dietary measures and supplements in the form of tablets can cure most forms of this deadly disease. Complicated therapies like bone marrow transplant are required for an occasional patient. Anemia, like convulsion, then is a sign of an underlying disorder and the physician must ascertain, the degree of anemia and its cause. The treatment is tailored both to correcting the anemia and eradicating its root cause, whatever that be.

Anemia is a very common disorder, with many causes and easy therapies. It can be a miracle to see the improvement in the patient's basic quality of life if her anemia can be cured. She can almost be made to feel like a new woman.

### **References**

- 1) Gabbe: Obstetrics; Normal and Problem pregnancies, 5<sup>th</sup> ed.
- 2) Kadyrov M- Am J Obstet Gynecol- 01- Feb-2006; 194(2) : 557-663
- 3) Lozoff B-J Pediatr-01-May- 2008;152(5):696-702, 702 31-3
- 4) Moise KJ Jy-Am J Obstet-Gynecol -01-Feb -2008;198(2)
- 5) Weiskopf RB – Anesthesiology-01-May-2006;104(5):911-20
- 6) Alan T Tinmouth, Lauralynn A.McUntyre, Robert A.Fowler, Canadian Medical Association Journal-Volume 178, Issue1 (Jan 2008)
- 7) Erythropoietin analogues: an unnecessary class of Drugs: The Lancet Oncology Volume 9, Issue 2 (Feb 2008)
- 8) Benaya Rozen-zvi, Anat Gafter- Givli, Mical Paul Leonard Leibovici, Ofer Shpilberg, Uzi Gafter- American Journal of Kidney diseases-volume 52, Issue 5 (November 2008)
- 9) Practical Guide to High-Risk Pregnancy & Delivery, A South Asian Perspective, 3<sup>rd</sup> Edition, Fernando Arias et al: Chapter 18; page 484-486.

- 10) William's Obstetrics: 7<sup>th</sup> edition.
- 11) Nutrition During Pregnancy: Obstetrics & Gynecology Clinics, Vol 35, issue 3, Sept 2008.
- 12) Textbook of Nutrition and Dietetics: Kumud Khanna.
- 13) Awasthi A, Thakur R, Dave A, et al. Maternal and perinatal outcome in case of moderate and severe anemia complicating pregnancy. J Obstet Gynecol India 2001;51:45
- 14) WHO, UNICEF and UNFPA 2004. Maternal mortality in 2000.
- 15) Hemoglobinopathies in Pregnancy, Current Women's Health Reviews, Volume 2, Number 1, February 2006, pp. 41-49(9)
- 16) Jeffcoate's Principles of Gynaecology, 7<sup>th</sup> ed

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