Anemia in Pregnancy.

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***Abstract**: Anemia is one of the most commonly encountered medical disorders during pregnancy. In developing countries it is a cause of serious concern as, besides many other adverse effects on the mother and the fetus it contributes significantly high maternal mortality. According to world Health Organization estimates, up to 56% of all women living in developing countries are anemic . In India, National Family Health Survey -2 in 1998 to 99 shows that 54% of women in rural and 46% women in urban areas are anemics. Iron deficiency anemia (IDA) is the commonest type of anemia in pregnancy. As most women start their pregnancy with anemia or low iron stores, so prevention should start even before pregnancy. . The Ministry of Health, Government of India has now recommended intake of 100 mg of elemental iron with 500 mg of folic acid in the second half of pregnancy for a period of at least 100 days. Women who receive daily antenatal iron supplementation are less likely to have iron deficiency anemia at term . This review is an effort to appraise about the various types of anemia in pregnancy, their implications on the maternal and fetal outcome, and long-term effects on the woman.*

INTRODUCTION

Anemia is one of the most commonly encountered medical disorders during pregnancy. In developing countries it is a cause of serious concern as, besides many other adverse effects on the mother and the fetus it contributes significantly high maternal mortality. According to United Nation declaration 1997, anemia is a major public health problem that needs total elimination. It is estimated that globally two billion people suffer from anemia or iron deficiency [1].

PREVALENCE OF ANEMIA IN PREGNANCY

According to world Health Organization estimates, up to 56% of all women living In developing countries are anemic [2]. In India, National Family Health Survey -2 in 1998 to 99 shows that 54% of women in rural and 46% women in urban areas are anemics[3]

The relative prevalence of mild, moderate, and severe anemia are 13%, 57% and 12% respectively in India (ICMR data).

According to WHO, hemoglobin level below 11gm/dl in pregnant women constitutes anemia and hemoglobin below 7gm/dl is severe anemia. The Center for Disease Control and Prevention (1990) defines anemia as less than 11gm/dl in the first and third trimester and less than 10.5gm/dl in second trimester[4,16]. Serum Ferritin of 15 micro gm/L is associated with iron deficiency anemia.[8,16]

ERYTHROPOIESIS IN PREGNANCY[8]

The various factors required for erythropoiesis are proteins (erythropoietin), minerals (iron), trace elements (including zinc, cobalt and copper), vitamins (particularly folic acid, vitamin B_{12} [cyanocobalamin], vitamin C, pyridoxine; and riboflavin), and hormones (androgens and thyroxine).

In addition to the common deficiencies of iron and folate, there is a growing body of evidence to implicate vitamin A (important for cell growth and differentiation maintenance of epithelial integrity and normal immune function) and Zn (important in protein synthesis and nucleic acid metabolism) in nutritional anemias.[7,8]

Anemia is a condition of low circulating haemoglobin (Hb) in which concentration has fallen below a threshold lying at two standard deviations below the median of a healthy population of the same age, sex and stage of pregnancy. The WHO definition for diagnosis of anemia in pregnancy is a Hb concentration of less than 11 g/dl (7.45 mmoL/L) and a hematocrit of less than 33%.[9]

***Table 1:** Prevalence of anemia globally and in South-East Asian countries[2,8]*

Region	No. of Countries		Year	Prevalence (%)
	Total	Included		
Europe	50	4	1992	20
Americas	36	3	1992	29
Western Pacific	26	3	1992	39
Africa	46	14	1992	44
Eastern Mediterranean	22	14	1992	61
South-East Asia	11	3	1992	79
			1993	74
Bangladesh			1995	68
Bhutan			1993	87.5
India			1995	51.0
Indonesia			1995	68.0
Maldives			1995	52.0
Myanmar			1996	40.0
Nepal			1995	40.0
Sri Lanka			1995	13.4
Thailand				

***Table 2:** The Indian Council of Medical Research Categories of anemia [5]*

Category	Anemia severity	Haemoglobin level (g/dl)
1	Mild	10.0 - 10.9
2	Moderate	7.0 - 10.0
3	Severe	< 7.0
4	Very severe (decompensated)	< 4.0

TYPES OF ANEMIA

The types of anemia are delineated In Fig 1

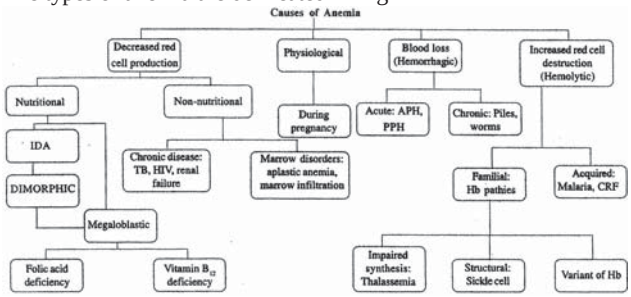

***Fig 1:** Classification of Anemia*

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PHYSIOLOGICAL ANEMIA

During pregnancy there is a disproportionate increase in plasma volume, RBC volume and haemoglobin mass. As plasma volume increase more than the RBC mass hemodilution occurs called as physiological anemia of pregnancy.

Criteria are:

a. RBC 3.2 million/cumm
b. Hemoglobin 10 gm%
c. RBC morphology on peripheral smear is normal i.e. normocytic, normochromic.
d. PCV 30%

IRON DEFICIENCY ANEMIA

About 1000 mg of iron is required during pregnancy[10]. 500-600 mg for RBC expansion. 300 mg for fetus and placenta and the rest for the growing uterus. As a result of amenorrhea there is a saving of about 150 mg of iron and therefore, about 850 mg of extra iron is required during pregnancy. Diet alone can not provide the extra iron and stores which have around 500 mg of iron get depleted. But if iron stores are already deficient, iron deficiency anemia manifests.

Iron deficiency anemia (IDA) is the commonest type of anemia in pregnancy[16]. Iron nutritional status depends on long-term iron balance and is favoured by ingestion of adequate amounts of iron in the diet (native or fortified) or through iron supplementation as shown in Table-3. The balance is adversely affected by the loss of Iron through intestinal mucosal turnover and excretion, skin desquamation, menstruation and lactation[18]. Iron absorption is 15-30% (haem iron) and up to 50% in the iron deficiency state reduce to 5-8% with an excessive haem diet. Its absorption is usually not affected by inhibitors. The non haem iron pool is made of all other sources of iron such as cereals, seeds, vegetables, milk and eggs. Its absorption can be increased by enhancers (haem, proteins, ascorbic acid and fermentation) and decreased by inhibitors (phytic acid, fibres, calcium, tannins, tea, coffee, chocolate and herbal infusion)[8,21.] On the basis of type of food, iron bio-availability can be characterized as follows.

Table 3: *Factors affecting the iron status of a pregnant woman[8,13]*

Iron absorption	Iron Loss
Dietery iron (haem and non-haem)	Physiological factors Basal losses from desquamation from intestines and skin
Enhancers of absorption ***Haem iron*** Proteins Meat Ascorbic acid Fermentation Ferrous iron Gastric acidity Alcohol Low iron stores Increased erythropoietic activity (high attitude, haemolysis, bleeding)	***Menstruation*** Delivery Lactation **Pathological factors** ***Hookworm and other helminthes*** Haemorrhage from GIT Allergies Occult blood losses
Inhibitors of iron absorption ***Phytates*** Calcium Tannins Tea and coffee Herbal drinks Fortified iron supplements	

DIET IN RELATION TO NUTRITIONAL ANEMIA[8,13]

Low bio-availability diets

Simple diet of beans, whole wheat flour and sorghum with negligible amounts of meat, fish and ascorbic acid. In non-industrialised countries, a very low-bio-available iron, vegetarian diet low in ascorbic acid and high in biological proteins composed almost entirely of cereals is consumed with excess of inhibitors of iron absorption (phytates); thus, absorption may be as Low as 3.4%[21.]

Intermediate bio-availability diet

Diets in this category are mainly comprised of cereals, roots or tubers, but include some animal foods like meat, fish and ascorbic acid which increase the iron absorption.

High bio-availability diet

This is a varied diet rich in meat, poultry, fish and foods with a generous amount of ascorbic acid, as found in industrialized countries.

Worm infestation[8,15,19]

Prevalence of amoebiasis and giardiasis is around 40%.Increased iron loss due to hookworm infestations, schistosomiasis, chronic malaria, excessive sweating and blood loss from the gut due to haemor-rhoids are important causes of anemia in pregnancy.

Multiple pregnancies

Most women enter pregnancy with little or no iron reserve, which is further compounded by repeated and closely spaced pregnancies and prolonged periods of lactation.

Prevention of iron deficiency

- ***Prophylaxis of non-pregnant women***

As most women start their pregnancy with anemia or low iron stores, so prevention should start even before pregnancy. As a public health approach, prolonged oral supplementation beginning before the woman becomes pregnant may be a better strategy to benefit the majority of the population. Twelve by twelve initiative is one such initiative aiming to have Hb of 12 g/ dl by 12 year of age using prophylactic iron therapy and advising consumption of iron rich food. Iron supplementation by 30 doses administered weekly over 7 months was as effective as 90 doses consumed daily for 3 months. Hence, women of child-bearing age in developing countries should receive a 2-4 months course of 60 mg of iron daily. In addition, concomitant use of folate will prevent neural tube defects in the new-born.

- ***Iron supplementation during pregnancy***

The Ministry of Health, Government of India has now recommended intake of 100 mg of elemental iron with 500 mg of folic acid in the second half of pregnancy for a period of at least 100 days. Women who receive daily antenatal iron supplementation are less likely to have iron deficiency anemia at term[26]. Even two injection of iron dextran (250 mg each) given intramuscularly at 4 week intervals along with tetanus toxoid injection have been recommended for better compliance and adequate results[25].

- ***Treatment of hookworm infestation[15]***

As worm infestation is very common and given the safety of the deworming drugs, oral antihelminthic treatment can also be given to pregnant and lactating women. Single albendazole (400 mg) or mebendazole (100 mg) doses twice daily for 3 days with iron supplementation should be given to all anemic pregnant; women in the second and third trimesters for better results.

- **Improvement of dietary habits and improving the bio-availability of food iron[13].**

Those pregnant should eat foods rich in iron (jaggery, green leafy vegetables like spinach, mustard leaves, turnip green, cereals, and sprouted pulses) cook their food in iron utensils. Too much of cooking should be avoided.

- ***Social Services***

Improvement of sanitation, personal hygiene, better education and

alleviation of poverty are not easy tasks and need political will also.

- ***Food fortification***

Iron fortification of foods is a preventive measure that aims at improving and sustaining iron nutrition on a permanent basis.. Even common salt, which is often fortified successfully with iodine in deficient areas, can be fortified with iron as has been successfully done in various South -East Asian and Latin American countries. Production of iron' fortified salt on a commercial scale has been approved by the Government of India and is in the process of manufacture[20].

EFFECTS OF ANAEMIA ON PREGNANCY

Maternal effects [8,14]

Mild, anemia may not have any effect on pregnancy and labour except that the mother will have low iron stores and may become moderately-to-severely anemic in subsequent pregnancies. Moderate anemia may cause increased weakness, lack of energy, fatigue and poor work performance. Severe anemia, however, is associated with poor outcome. The woman may have palpitations, tachycardia, breathlessness, increased cardiac output leading on to cardiac stress which can cause de-compensation and cardiac failure which may be fatal [5,8]. Increased incidence of pre-term labour (28.2%), pre-eclampsia (31.2%) and sepsis have been associated with anemia.[5]

Fetal effects[8]

Irrespective of maternal iron stores, the fetus still obtains iron from maternal transferrin, which is trapped in the placenta and which, in turn, removes, and actively transports iron to the fetus. Gradually, however, such fetuses tend to have decreased iron stores due to depletion of maternal stores. Adverse perinatal outcome in the form of pre-term and small-for-gestational-age babies and increased perinatal mortality rates have been observed in the neonates of anemic mothers. Iron supplementation to the mother during pregnancy improves perinatal outcome. Mean weight, Apgar score and haemoglobin level 3 month after birth were significantly greater in babies of the supplemented group than the placebo group.

CLINICAL FEATURES OF IRON DEFICIENCY ANAEMIA

Symptoms

There may be no symptoms, especially in mild and moderate anemia. Patient may complain of feelings of weakness, exhaustion and lassitude, indigestion and loss of appetite. Palpitation, dyspnoea, giddiness, oedema and, rarely, generalized anasarca and even congestive cardiac failure can occur in severe cases.

Signs

There may be no signs especially in mild anemia. . There may be pallor, glossitis and stomatitis. Patients may have edema due to hypoproteinaemia. Soft systolic murmur can be heard in mitral area due to hyper dynamic circulation.

Diagnosis

Haemoglobin estimation is the most practical method of diagnosis as it is cost effective and can be easily performed by trained technician. The Taliquist's method of Hb estimation has simplicity and easy applicability, but is not very -accurate. Sahil's methods is reliable and accurate when done by expert, and is the most communally used method, although the cyanomethaemoglobin, method appears to be the most accurate.

Peripheral blood film is another bed.-side indicator for diagnosis of anemia which will also differentiate between iron deficiency anemia, megaloblastic anemia and haemolytic anemia. In iron deficiency anemia, there is microcytosis, hypochromia. Anisocytosis, poilkilocytosis and target cells in the blood film. Iron deficiency anemia must be differentiated from thalassemia as shown in table 4[22,23].

Table 4: *Red cell indices in iron deficiency and thalassemia* [22,23]

Characteristics	Calculation	Normal rage	Iron deficiency	*Thalassaemia*
MCV*(fl)	PCV/RBC	75 –96	Reduced	Very reduced
MCH(pg)	Hb/RBC	27 –33	Reduced	Very reduced
MCHC**(g/dl)	Hb/PCV	32 –35	Reduced	Normal or slightly receded
Hb (%)	HbF/HbAx100	< 2%	Normal	Raised
HbA_2 (%)	HbA_2x100	2-3%	Normal or reduced	Raised
FEB (microgram/dl)		< 35	> 50	Normal
Red cell width			High	Normal

*Mean corpuscular volume (MCV) is the first to get reduced and is the most sensitive indicator of iron deficiency.
**Mean corpuscular haemoglobin concentration (MCHC) Is reduced in more severe cases of iron depletion.

Serum ferritin level below 12 m/l is taken to indicate to iron deficiency. It is stable, unaffected by recent iron intake, reflects iron stores accurately, and is the first abnormal laboratory test in iron deficiency. Serum iron varies from 60-120 mg/dl while TIBC is 300-350 mg/dl, (increased to 300-400 mg/dl in pregnancy). Serum iron of less than 60 mg/dl, TIBC of more than 350 mg/dl and transferring saturation of less than 15% indicates deficiency of iron during pregnancy table 5.

Table5: *Categorization of women using haemoglobin and ferritin estimations*[19]

Categories	Serum ferritin (µg/l	Haemoglobin (g/dl)	Diagnosis
Category I	> 12	> 11	Normal, iron deficiency excluded
Category II	< 12	> 11	Storage, iron depletion
Category III	< 12	< 11	Iron deficiency anemia
Category IV	> 12	< 11	Other cause of anemia

Free erythrocyte protoporphyrin (FEP) is the third estimation of Iron status rising with defective iron supply to the developing red cells and takes 2-3 weeks to become abnormal after depletion of iron stores. It also helps in differentiation between iron deficiency anemia and thalassaemia.[22]

Serum transferrin receptor appears to be specific and sensitive marker of iron deficiency in pregnancy. Its levels are increased in iron deficiency anemia Bone marrow examination by staining with potassium ferrocyanate to see characteristic blue granules of stainable iron in, erythroblasts is the most accurate method for iron stores, but is not practical in most cases as the test is invasive, Bone marrow, examination is only dated in cases where there is no response to iron therapy after 4 weeks or for diagnosis of Kala-azar or in suspected aplastic anemia[11]. As worm infestations are common causes of anemia, stool examination for ova and cysts should be done consecutively for 3 days in all cases. In areas where schistosomiasis is prevalent, urine examination for occult blood and schistosomes should be performed. As malaria is an important cause of anemia peripheral blood should be examined for malarial parasites in the case. Significant bacteriuria should also be ruled out. If the clinical scenario demands, other tests can be done, such as sputum examination and chest X-ray for pulmonary tuberculosis (abdominal shielding should be done), renal function tests in suspected renal disease and serum proteins in hypoproteinemia.[22]

MANAGEMENT OF IRON DEFICIENCY ANEMIA

In developing countries, it is common to see patients of moderate and severe anemia late in pregnancy. They have had nil or inadequate antenatal care and did not take iron supplements in pregnancy. If the woman presents in mild-trimester or early third trimester, oral iron is started.

Although for prophylaxis the Government of India, Ministry of Health recommends 100 mg of elemental iron with 0.5 mg folic acid, for treatment more than 180 mg of elemental iron per day is required. Three tablets of ferrous sulphate (available free of cost in most Indian hospitals) per day are required. This may cause increased incidence of side-effects and some recommend 120 mg elemental iron per day, which is more suitable for supplementation rather than treatment. Ferrous ascorbate is the most favorable iron for Indian Diet which have high content of inhibitor for iron absorption [12]. One needs to change a brand only when the patient cannot tolerate it. Addition of folic acid, but not vitamin B_{12} helps in improving the results in supervised supplementation. Up to 10% of women may have side-effects with oral iron in the form of gastrointestinal symptoms such as nausea, vomiting, constipation, abdominal cramping and diarrhoea which are dose-related. The treatment of choice is to reduce the dose. If this does not work, another preparation (carbonyl) iron or haemoglobin preparations may be better tolerated.

Response to therapy

Feeling of well, improved look and better appetite. Haematologically, there is reticulocyte response in 5-10 days with a rise in Hb concentration from 0.3 g to 1.0 g per week and haematocrit subsequently. If there is no significant clinical or haematological improvement within 3 weeks, diagnostic re-evaluation is needed.

Reasons of failure to respond to oral therapy are inaccurate diagnosis (non-iron) deficiency microcytic anemia, such as thalassaemia, pyridoxine deficiency and lead poisoning), non-compliance, continuous loss of blood through hook worm infestation or bleeding haemorrhoids, co-existing infection, faulty iron absorption and concomitant folate deficiency.

Table 6: *Iron content of different salts is as follows* [19,24]

Salt	Dose of salt in mg	Elemental iron in (mg)
Ferrous fumarate	200	65
Ferrous gluconate	300	35
Ferrous glycine sulphate,	225	45
Ferrous succinate	100	35
Ferrous sulphate	300	60
Ferrous sulphate dried	200	65

NEWER IRON PREPARATIONS

• *Iron Amino Acid Chelates*

These are conjugates of ferrous or ferric ions with amino acids. Ferrous glycine sulphate is the only iron amino acid chelate available in India. Its main advantage is its relatively high bioavailability in the presence of dietary inhibitors. The chelates prevents iron from binding inhibitors in food or precipitating it as an insoluble complex in the gut.

Sustained release preparations like Iron polymaltose complex (IPC) and Iron hydroxide polysucrose complex are available. These have nonionic iron in a stable complex. Absorption is not affected by food or milk and these can be given with food. It has better absorption and lesser side effects than ferrous salt.

• *Carbonyl Iron*

It is pure form of elemental iron which has low toxicity and is tolerated in larger does when compared to ferrous salts. Carbonyl iron refer to manufacturing process whereby pentacarbonyl iron is reduced by heating to very fine microsphere of less than 5 microns in diameter which are better absorbed and associated with lesser gastrointestinal side effects. It is available as modified release preparations.

While selecting iron preparations for therapy, it is important to bear in mind that modified release formulations release iron gradually as they pass along the gut hence, a part of the iron is released beyond the most actively absorbing regions of the intestines, that is the first part of the duodenum, thereby reducing overall absorption of iron. Of all the iron preparations ferrous sulphate, ferrous fumarate and ferrous ascorbate are the preferred formulations.

Parenteral iron therapy

- The rise in Hb concentration is the same, as with oral iron (up to l g per week).

Indications

- Poor tolerance to oral therapy.
- Poor absorbtion of iron like in chronic diarrhea, ulcerative colitis, coeliac disease or inflammatory bowel disease.
- Non compliance
- Oral iron is not effective
- Women near term with severe anemia.
- Presence of concurrent disease like chronic renal failure when patient is on hemodialysis or being treated with erythropoietin.

Preparations

- Parenteral iron is available as iron dextran complex (Imferon) which can be given intramuscularly or intravenously
- Iron sorbitol citrate (Jactofer) which can only be given, intramuscularly.
- Iron sucrose complex (Venofer) each ml has 20 mg of elemental iron. Jectofer plus contains folic acid and vitamin B_{12} along-with elemental iron. Iron
- Iron gluconate is available as sodium ferric gluconate (ferrlecit).

Deficit is calculated as

Elemental iron needed (mg) =

(Normal Hb - Patient's Hb) x Weight (kg) x 2.21 + 1000

Here normal hemoglobin is taken as 14% and 2.21 is standard coefficient. To the value calculated by above formula 1000mg is added for the stores.

Technique of giving parental iron

- **Intravenous route:** Before giving test dose it is essential to have all the resuscitation equipment and drugs ready.

Iron dextran (Imferon) is diluted in normal saline or 5% dextrose and given slowly initially [22]. If there is no reaction, it can be given faster. If the calculated dose is more than 2500 mg, it should be even in 2 doses on two consecutive days. One should look for any reaction in the form of chest pain, rigor, chills, fall in blood pressure, dyspnoea and anaphylactic reaction.[22] For any such reaction, infusion should stopped and anti-histaminic, corticoids and epinephrine given.

- **The intramuscular route**: it is more popular and is associated with less side--effects. For giving intramuscular injection it is important to test for hypersensitivity. Full dose of iron can be given daily on alternate buttocks by deep intramuscular injection by Z technique. Oral iron should be stopped before, giving iron sorbitol as it is associated with toxic reaction such as headache, nausea and vomiting. Disadvantages of intramuscular route are pain, sterile

abscess formation nausea, vomiting, headache, fever, lymphadenopathy, allergic reactions and rarely anaphylaxis.
Blood transfusion is required in patients with severe anemia beyond 36 weeks, associated infection, to replenish blood loss due to ante-partum or post-partum hemorrhage and in patients not responding to oral or parenteral iron therapy. Packed cells are preferred for transfusion. Blood: transfusion can cause transfusion reaction, precipitated preterm labour and, rarely, overloading of the heart [17,22].

- ***Iron Dextran***

It is stable parenteral iron product with a molecular weight of 100 to 500 kDa. The stability of iron dextran complex allows administration of high single does in total does therapy.

- ***Iron Gluconate***

This is labile type of iron compound with fast degradation kinetics and iron is released directly to the plasma proteins like apotransferrin, apoferrtin and others. About 80% of the iron supplied as iron gulconate is delivered to transferring in 24 hours.

- ***Iron Sucrose Complex***

It is a smaller molecule than iron dextrin being only 36 to 60 kDa and hence, carries no risk of anaphylaxis .The iron released is partially taken up by plasma protein like apoferritin and partially by reticuloendothelial system.
We have performed studies on role of parenteral iron (iron Sucrose) alone or in combination with Erythropoietin at AIIMS and found a rise in Hb of 1.5g with parenteral iron alone as compared to 3.0g in combination with parenteral iron with erythropoietin.

One single regimen is as follow;

Inj. Iron Sucrose (FerriS, Hemfer) 200mg i.v injection every alternate day for 5 -10 injections depending upon the deficit in hemoglobin. Usually there is no reaction with iron sucrose but still it is better to keep injection of adrenaline, hydrocortisone and oxygen etc.
Inj. Iron Sucrose plus Inj. Erythropoietin (Epofer) 4000-6000unit subcutaneously every other day for 3 doses (total about 18000 units).
Alternatively for postpartum anemia a bolus of 1000mg iron sucrose intravenously over 2 hr in saline along with 18000 unit of erythropoietin in one day.

Recombinant Erythropoientin :

The stimulation of erythropoiesis with rhEPO is highly promosing alternative to blood transfusion.

Dosage regimen Erythropoetin (Epofer)

• Inj erythropoetin can be given subcutaneously or iv 100-150 IU/ kg. On day 1 ,3 &5 along with parenteral iron or day 1,3&5 6000units s/c erythropoietin and iron dextran 100mg deep im daily for 5 day. Dose should be given after subcutaneously sensitivity test. Adrenaline, hydrocortisone and oxygen to be kept ready

ANTENATAL CARE

The antenatal management is like any other case, but more frequent visits are required. One should be vigilant to detect and manage complications of anaemia, such as heart failure or preterm labour, as early as possible. Fetal monitoring for growth and well-being should be done as these fetuses tend to be small. Prognosis is good if anaemia is detected and treated in time. Management of a case of severe anaemia is given in Figure 2.

MANAGEMENT OF LABOUR IN ANAEMIC PATIENT

In the first stage, the patient should be in a comfortable position.

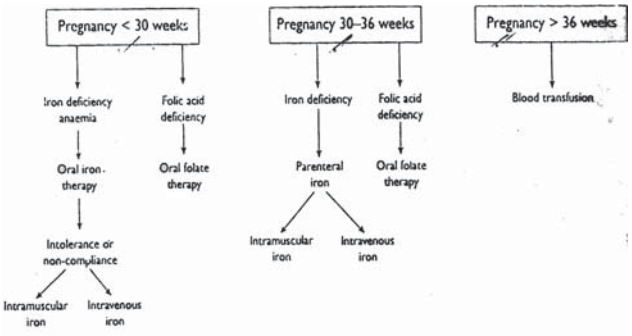

Fig. 2 :*Summary protocol of severe anaemia in pregnancy* [22]

Sedation and pain relief should be given. Oxygen should be kept ready and is given in dyspnoea. In cases of preterm labour, betamimetics and steroids should be given with caution to avoid the risk of pulmonary oedema. Digitalisation may be required in cardiac failure due to severe anaemia. The aim is to deliver the baby vaginally. Antibiotic prophylaxis is preferred. The second stage is the most stressful, when the patient can go into cardiac failure. A tendency for prolongation of the second stage can be curtailed by forceps. Active management of the third stage should be done except in very severe anaemia for fear of cardiac failure. However, any post-partum haemorrhage must be frenetically treated as these patients tolerate bleeding very poorly[17,22] Maternal mortality in severe anaemia can occur in the last trimester, during labour, immediately after delivery and during puerperium due to cardiac failure or pulmonary embolism.

DURING PUERPERIUM

The mother should have adequate rest; iron and folate therapy should be continued for least 3 months. Any infection must be treated. Puerperal sepsis, failing lactation, subinvolution of uterus and thrombo-embolism are more common in these patients and should be carefully watched for. Maternal mortality in severe anaemia can occur in the last trimester, during labour, immediately after delivery and during puerperium due to cardiac failure or pulmonary embolism.

CONTRACEPTION

The anemic patient must use an effective method of contraception and should not conceive for at least 2 years giving time for Iron stores to recover. Sterilization is preferred if the family is completed. If there is no history of menorrhagia, an intra-uterine device can be inserted. Levonorgestrel intrauterine device (Mirena) can be used in presence of menorrhagia for contraception. It reduces blood loss but is expensive. Barrier methods can be safely given, but their higher failure rate is a disadvantage

MEGALOBLASTIC ANEMIA IN PREGNANCY

The low incidence of megaloblastic anemia during pregnancy is because of the abundance of both folic acid and vitamin B_{12} (Cyanocobalamine) in the vegetarian and non vegetarian diet .In the developing world the incidence is considerably higher approximately 25% of women with anemia during pregnancy.
In Megaloblastic anemia, DNA replication is affected .There is derangement of red cell maturation with production of abnormal precursors known as megaloblasts which can due to deficiency of Folate or Vit B_{12} [22,23].
Usually has an insidious onset with gradually progressive symptoms and signs which are usual of anemia i.e. weakness, easy fatigability,

tiredness etc. GI symptoms like anorexia, nausea, vomiting, diarrhea and glossitis more common. Hyper pigmentation of Skin and oral mucosa, palpable liver and spleen, petechial rash due to thrombocytopenia may be present and in such case leukemia and aplastic anemia should be ruled out.

Nail changes do not occur in megaloblastic anemia. Occurs more commonly in multiple pregnancies, develops late in pregnancy around 20-28 weeks, develops immediately postpartum or up to fifth month, in OC pill users or in anti-epileptic drug users.

The cause of megaloblastic anemia in pregnancy is nearly always due to for the deficiency which leads to ***folate deficiency*** and wasting. ***Hematological symptoms*** are more marked. If post-delivery hemoglobin level falls rapidly and there is no history of excessive blood loss then suspicion of folic acid deficiency is aroused first. Folic acid in pregnancy is not always accompanined by significant hematological changes. In the absence of changes, megaloblastic hematopoiesis is suspected when expected response to adequate iron therapy is not achieved. Ultimately diagnosis is dependent on marrow examination and the finding of large erythroblasts and giant abnormally shaped metamyelocytes.

As such ***vitamin* B_{12} deficiency** takes years to develop anemia and its deficiency causes infertility so megaloblastic anemia due to B_{12} deficiency is very rare in pregnancy. ***Neurological features*** are more pronounced and if any autoimmune disease exists in the body with anemia then suspicion of B_{12} megaloblastic anemia arises.

Criteria for Megaloblastic Anemia

At least two of the following criteria must be present:

a. More than 4% of neutrophil polymorphs have five or more lobes
b. Orthochromatic macrocytes must be present with diameter > 12 mm.
c. Howell Jolly bodies are demonstrated.
d. Nucleated red cells.
e. Macro polycytes may be present.

DIMORPHIC ANEMIA

This is due to deficiency of both iron and folate with dominance of one in finding of both pre-dominance of that type whose deficiency is more.

FOLATE DEFICIENCY

Effects on pregnancy

There is increased incidence of abortion, growth retardation, abruption placentae and pre-eclampsia in 'folate deficiency in some, but not all, studies[23]. Folate supplements during pregnancy have resulted in increased' birth weight in cases of malnutrition.

Effects on fetus

Neural tube defects can be prevented in most cases by periconceptional folic acid in dosage of 0.4 mg/day in low-risk cases and 5 mg/day in high-risk women. Incidence of neural tube defects is very high in India and periconceptional folate supplementation is strongly recommended in all cases. There is some evidence that the incidence of abortion, premature babies, small-for-date babies and folate deficiency in the neonates is higher in babies born to mothers with folate deficiency.[22,23]

Investigations

Laboratory findings consist of a fall in Hb concentration to generally <10 g/dl, MCV > 96 fI, MCH >.33 pg, and normal MCHC. There is macrocytic anaemia: with hypersegmentation of neutrophils, neutropenia and thrombocytopenia on peripheral blood film. A combination of low serum folate (<3 mg/ml) and red cell folate (< 150 ng/ml is diagnostic of folic acid deficiency. Serum iron is usually normal or high. Increased formiminoglutamic acid (FIGLU) in urine following a loading dose of histidine is found in folate deficiency, but the test is rarely done these days.[23] Serum lactic dehydrogenase (LDH) and homocysteine levels are elevated in folate deficiency. The deoxyuridine suppression test helps in -differentiating between folate and vitamin B_{12} deficiency. Bone marrow will show a megaloblastic picture, but is rarely required.

Prophylaxis

The WHO recommends a daily folate intake of 800 µg in the antenatal period and 600 µg during lactation. However, 300-500 µg present in most iron preparations is enough for prophylaxis[23,27]. Pregnant women should eat more green vegetables (e.g. spinach and broccoli) offal (e.g. liver and kidneys). Folate is destroyed by cooking. Even food fortification with folic acid is recommended and is already in use in Western countries.

Treatment

Treatment of established folic acid deficiency by giving 5 mg oral folate per day which should be continued for at least 4 weeks in puerperium.

By 4-7 days of therapy the reticulocyte count is appreciably increased.

VIT B_{12} DEFICIENCY

Pernicious anaemia caused by lack of intrinsic factor resulting in lack of absorption of vitamin B_{12} is rare during pregnancy as it usually causes infertility. Women with gastrectomy and ileal disease and resection can have vitamin B_{12} deficiency. Acquired vitamin B_{12} deficiency causing megaloblastic anaemia is also uncommon, as the daily requirement of vitamin B_{12} is only 3.0 µg during pregnancy which is easily met with a normal diet.[28] Only vegans who do not eat any animal-derived substance may have a deficiency of vitamin B12 and they should have their diet supplemented during pregnancy. Infestations with Diphyllobothrium latum in some countries can cause megaloblastic anaemia due to competitive utilization of ingested vitamin B_{12} by the parasite

Investigations

Findings are the same as in folate deficiency. Vitamin B_{12} levels are lower in blood (<90 µg/l). Serum methyl malonic acid is elevated in vitamin B_{12} deficiency. Serum homocysteine is elevated in both folate and vitamin B, deficiency. The deoxyuridine suppression test can differentiate between vitamin B12 and folate deficiency. Schilling Test is done to diagnose pernicious anaemia.

Treatment

Parenteral cyanocobalamin (250 µg) is given intramuscularIy every month.

CONCLUSION

Nutritional deficiency anemia during pregnancy continues to be a major health problem in India. To eradicate it certain steps can be taken at individual and community level like education of the women as regards anemia, its causes and health implication. Imparting nutritional education, with special emphasis on strategies based on locally available food stuffs to improve the dietary intake of proteins and iron, administration of appropriate iron supplements and ensuring maximum compliance, deworming, treatment of chronic disease like malaria and universal antenatal care to pregnant women will help in combating this serious problem. Long term policies by government, non-government agencies and the community can be directed to formulate effective plans like eradicating anemia in children and adolescent girls.

Hemolytic Anemias

Hemolytic anemias may occur because of erythrocyte defects such as abnormalities of hemoglobin structure metabolic disturbances, or membrane abnormalities[29]. Almost all erythrocyte defects causing hemolysis are hereditary in nature. Hemolysis may also occur due to the presence of substances in the plasma that attack and destroy the erythrocyte such as is the case in autoimmune hemolytic anemia. A normal red cell lives for about 120 days. This life span is shortened in the case of hemolytic anemias because of premature destruction of red cells, which may occur extravascularly (i.e acquired immune hemolytie anemia or intravascularly (i.e., microangiopathic hemolytic anemia of preeclampsia). Although classifications of anemias according to the site of hemolysis is important for an adequate interpretation of the laboratory tests for differential diagnosis, in many hemolytic process destruction occurs in both compartments and laboratory tests are ambiguous.

Extravascular hemolysis is the most common hemolytic anemia. The red cell are destroyed in the reticuloendothelial system, liberating which is converted to bilirubin. An increase in indirect bilirubin is apparent in the patient's serum. The products of bilirubin metabolism, fecal and urinary urobilinogen, also increase. Erythropoiesis increases markedly, and reticulocytosis occurs. Thus, elevated unconjugated bilirubin, increased urinary urobilinogen, and reticulocytosis are the laboratory hallmarks of extravascular hemolysis.

Intravascular and extravascular hemolysis both causes bone marrow response characterized by marked erythroid hyperplasia and reticulocytosis. In some cases the erythroid poiesis is so active that there is passage of immature cells into the bloodstream. Also, in all cases of accelerated red cell destruction, plasma- lactic dehydro (LDH) increases as a consequence of the liberation LDH isoenzyme from the red cells.

The most common form of hemolytic anemia seen during pregnancy is the intravascular microangiopathic hemolysis, which is a part of the HELLP Syndrome. More infrequently the Obstetrician sees the hemolytic anemia associated with defects in hemoglobin structure, particularly sickle cell disease (SCD). The World Health Organization (WHO) estimates that globally at least 5% of adults are carriers for a haemoglobin condition: approximately 2.9% for thalassemia and 2.3% for sickle cell disease.

Microangiopathic Hemolytic Anemia

Microangiopathic hemolytic anemia occurs during pregnancy in patients with a severe form of preeclampsia, HELLP syndrome. The differential diagnosis in pregnant women can be thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome. All of these show fragmented red cell, schistocytes, and burr cells. Thrombocytopenia is always present. Delivery improves clinical and laboratory in HELLP but not in HUS.

Hemolytic Anemias Associated with hemoglobinopathies

Sickle cell disease (SCD) is the most common hemoglobinopathy encountered during pregnancy because of the severity of the applications associated with this condition. Pregnency with sickle cell disease is a high risk pregnancy and management should be multidisciplinary to give optimal maternal and neonatal outcome. SCD is an autosomal recessive condition caused by the substitution of a valine for glutamine in position 6 in the beta-globin chain of the hemoglobin molecule, resulting in the proteins on of sickle cell hemoglobin, or HbSS. The condi-tion affects 0.2 % of the African-American population of USA. In India it is common in the tribal population of central India [29]. The disease is characterized by chronic hemolytic anemia and by the occurrence of acute, life-threatening **occlusive** crisis.It is associated with increased maternal and perinatal morbidity and mortality.

Sickle-Cell Trait

The heterozygous inheritance of the gene for hemoglobin S results in sickle-cell trait, or AS hemoglobin. The trait is not associated with increased abortion, perinatal mortality, low birth weight, or pregnancy-induced hypertension. Sickle-cell trait therefore should not be considered a deterrent to pregnancy on the basis of increased maternal risks.[29,30]

In SCD when HbS is oxygenated, its solubility is similar to that of normal hemoglobin (HbSS) but in the deoxy form sol-ubility decreases and in a reduced oxygen environment the HbSS will polymerize into long tube-like fibers, which causes morphological changes characterized by sickling of the erythrocytes. The abnormal erythrocytes are removed and destroyed in the reticuloendothelial system, resulting in chronic extravascular hemolysis. HbF inhibits the poly-merization of HbSS and patients with elevated levels of HbF have milder forms of the disease.

In certain situations such as increased deoxygenation, acidosis, fever, dehydration ,prolonged capillary transit time. Concentration of corpuscular hemoglobin and clusters of sickle cells occlude the microvasculature, producing **ischemic** infarction and severe inflammatory reactions that clinically translate into a painful sickle cell crisis. Around 14.2% of all pregnancies in patients with SCD end with the delivery of stillborn infants and neonatal morality is approximately 84.5 per 100 live births. Another study shows a perinatal mortality as low as 11.0% .The frequency of infants with birth weights less than 2500 g in patients with SCD is increased.

Acute chest syndrome are most common cause of mortality in patients with SCD. It is characterized by chest pain, respiratory distress with tachypnea, coughing and wheezing, fever, decreased oxygen saturation. Infection is a frequent-cause of sickle cell crisis but diagnosis is diffucult because many of the signs and symp-tom of a **vaso-occlusive** crisis are similar to those of infection. Fever, leukocytosis, elevated bilirubin, and LDH are also components of crises. Relief of the severe pain, reduction in HbSS concentration and to increase oxygen supply to the tissues are the tenets of management. Treatment usually involves pain management, oxygen, antibiotics, incentive spirometry, bronchodilators, and most case transfusion therapy.

Prenatal Diagnosis

Women with sickle cell trait should have preconception counseling, and the male partner should be examined to determine whether or not he also carries the trait. The father is a carrier, there is a 25% chance that the infant will be homozygous and have SCD. In this situation early prenatal genetic diagnosis is important because it will allow the possibility of pregnancy termination. Early prenatal diagnosis is possible with the use of polymerase chain reaction (PCR). Amniocentesis or Chorionic Villous Sampling.[30,31,32]

Antepartum Care

- Close Observation
- Folic Acid Supplementation
- Identify sickle cell crisis- Adequate hydration to be maintained
- Screening and treatment for bacteriuria.
- Assessment of Fetal Health- weekly ante partum fetal surveillance beginning at 32 to 34 weeks with serial ultrasonography to monitor fetal growth and amniotic fluid
- Prophylactic transfusions in women with a history of multiple vaso-occlusive episodes and poor obstetrical outcomes:

Patients with SCD do not require iron supplemental and during pregnancy unless laboratory evidence of iron deficiency is obtained. In contrast, they need adequate Folic acid supplementation to compensate for the increased consumption of folate secondary to the active process of cell replication that takes place in their bone marrow.

Labour and Delivery

- Adequate Analgesia

- Epidural Analgesia-Ideal
- Compatible blood should be available
- If hematocrit is less than 20% packed erythrocyte transfusions are administered
- Prevent circulatory overload and pulmonary oedema from ventricular failure.

Post partum management

- Early ambulation to prevent venous thrombosis.
- Adequate hydration
- Analgesic drugs should be given for pain relief.
- Cord blood should be sent for electrophoresis.

Contraception

Progesterone based contraception like Depot medroxy progestron acetate is safe and has beneficial effect of decreasing sickling due to stabilization of erythrocyte membrane. Barrier method is widely used but rate of failure is high. Permanent method is advised on completion of family.

THALASSEMIA IN PREGNANCY

There are many point mutations in the globin gene that may cause beta thalassemia minor, and this ,explains the clinical variability of the condition[33] In this condition HbA2 (á2 ä2) is increased more than 3.5 % HbF (á2 ã2) is usually increased to more than 2%. The anemia is microcytic and hypochromic, and there is basophilic stippling of the erythrocytes. The hemoglobin levels range from 8 to 10 g/dl. The diagnosis is frequently missed, and the patients are repeatedly treated with large doses of oral, and in some instances parenteral, iron with- out therapeutic response. This is dangerous because they may develop hepatic and cardiac hemosiderosis secondary to iron overload.

The diagnosis of beta thalassemia minor should be suspected when the MCV is 75 fl or less and the RBC is greater than 4.5 – 5.0 million cells/ µL. If doubts remain, measurements of serum ferritin and serum iron will clarify the dilemma.

Pregnant partner microcytic, hypochromic anemia who does not respond to oral iron by an elevation of her hemoglobin concentration after 4 weeks of treatment. Patients with beta thalassemia minor characteristically, show hemoglobin A2 (HbA2) concentrations greater than 3.5% and normal or increased serum iron concentrations. In 90% of the cases the HbA2 level is above 5%.Approximately 50% of women with beta thalassemia minor will exhibit a hemoglobin F concentration greater than 2%.

BETA THALASSEMIA MAJOR

This is a serious disease where both the beta chains are defective. The neonate with this condition is healthy at birth but become severely anemic as the HbF falls with failure to thrive. Such a child needs blood transfusion to survive and there is problem of iron overloading. In the past most children with Beta thalassemia major used to die, but are now reaching reproductive age group with blood transfusion and chelation therapy with deferoxamine. Such women are usually sterile with shorten life span. However, some women had successful pregnancy outcome under intensive maternal and fetal surveillance by an experienced team of hematologist and obstetrician. They need cardiac assessment for myocardial function. There anemia should be treated with blood transfusion , folic acid supplementation required. Iron supplementation is contraindicated.

IMMUNE HEMOLYTIC ANEMIA

In Immune hemolytic anemia, the patient makes autoantibodies of the immunoglobuli (lgG) type or "warm antibodies" against red cell antigents, causing premature destruction of these cells. In other cases the RBCs are sensitized with both an IgG antibody and complements, usually, C3, More rarely, the RBCs only exhibit complement and no IgG. This abnormality many occur in association with several disease (leukemia, lymphomas, viral infections) or as a consequence of an immune reaction to certain drugs (penicillin, sulfas, quinidine). The most frequent cause of this abnormality in pregnant women is an autoimmune disorder. On a few occasions, no cause can be discovered and the disorder is named "idiopathic immune hemolytic anemia."

The diagnosis of immune hemolytic anemia is made with the direct Coombs test. In this test, red cells of the patient are mixed with Coombs anti-human globulin antiserum, and since they are coated with IgG and complement, agglutination occurs immediately.

APLASTIC ANEMIA

Cause are as in non pregnant. Treatment option are Bone marrow transplant, antillymocyte globulin, cyclosporine, corticosteroids.

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