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Management of Anaemia in Pregnancy

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1. Introduction

Obstetric practice in developing countries is known for unacceptably high maternal morbidity , mortality and perinatal deaths. Factors contributory to these include poor health care delivery system, cultural beliefs, poor nutrition, illiteracy, gender inequality, teenage pregnancies and high parity. Other factors such as infections and infestations ultimately cause anaemia and increase morbidity and mortality in pregnant women and their offspring. Anaemia during pregnancy is a well-known risk for unfavourable pregnancy outcomes.

Globally, anaemia has been found to be the most common complication in pregnancy. The World Health Organization (WHO) estimates that more than 40% of non-pregnant and over 50% of pregnant women in developing countries are affected. The majority of the cases occur in sub-Saharan Africa and South East Asia. In 1993, the World Bank ranked anaemia as the 8th leading cause of disease in girls and women in the developing world. Apart from maternal morbidity and mortality, neonatal mortality is high among the babies of anaemic mothers.

2. Hematological changes in pregnancy

Pregnancy is associated with normal physiological changes that assist fetal survival and prepares the mother for labour, delivery and breastfeeding. The changes start as early as 4 weeks of gestation and are largely as a result of progesterone and oestrogen. The total blood volume increases steadily from as early as 4 weeks of pregnancy to reach a maximum of 35-45 % above the non-pregnant level at 28 to 32 weeks. The plasma volume increases by 40-45 % (1000mls). Red blood cell mass increases by 30- 33 % (approximately 300mg) as a result of the increase in the production of erythropoietin. Erythropoietin levels increase throughout pregnancy, reaching approximately 150% of their prepregnancy levels at term.

The increase is steady until term. The greater increase in plasma volume than the increase in red blood cell mass results in a modest reduction in haematocrit, with peak haemodilution

occurring at 24-26 weeks. This is termed physiological anaemia of pregnancy (see Fig 1). This dilution picture is often normochromic and normocytic. Occasionally physiologic anaemia can also be associated with a physiologic macrocytosis, MCV increases to 120fl although average at term is 104 fl.

In pregnancy, there is an additional demand of about 1000 mg iron equivalent to 60 mg elemental iron or 300 mg ferrous sulphate daily. While the transferrin and total iron binding capacity rises, the serum iron falls . Thus women who enter pregnancy in an iron deficient state are then unable to meet the demands of pregnancy by diet alone and require supplementation. It takes approximately 2-3 weeks after delivery for these haematologic changes to revert to pre-pregnancy status.

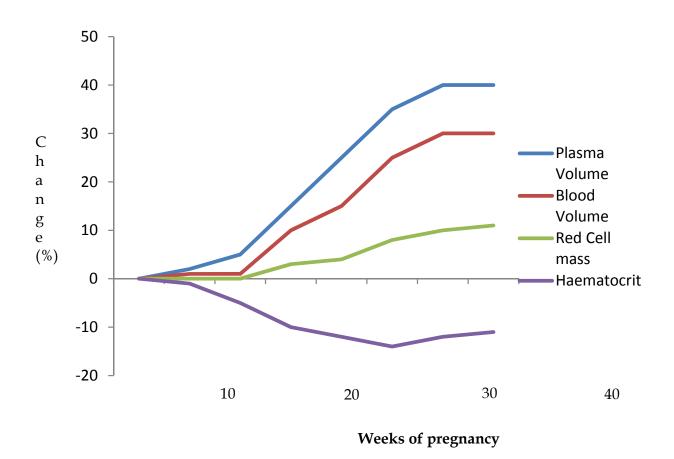


Fig. 1. Graphical representation of haematological changes in pregnancy.

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3. Epidemiology of anaemia in pregnancy

Anaemia has been found to be associated with poverty and underdevelopment and is one of the most common disorders globally. The incidence of anaemia varies from place to place even within the same country and depends on the socioeconomic status and level of development. The World Health Organization reports anaemia among the top ten most important contributors to global ill health and deaths. It estimated that about a third of the world's population of 7 billion have haemoglobin levels below the WHO criteria for diagnosis of anaemia. The majority of these persons reside in Sub-Saharan Africa and South East Asia.

Pregnant women are particularly considered to be the most vulnerable group because of the additional demands that are made on maternal stores during pregnancy. The average global prevalence of anaemia in pregnancy is reported to be 51%. Like anaemia in the general population the prevalence of anaemia in pregnancy varies from 17% in Europe to 52% and 60% respectively in Africa and Asia. In sub-Saharan Africa it is estimated that 20% of maternal deaths are associated with anaemia. It is also a major risk factor for infant iron deficiency which has been shown to be associated with adverse behavioural and cognitive development of children and low birth weight, which is one of the main risk factors for infant mortality.

4. Definition of anaemia

The term anaemia refers to the reduction in the oxygen-carrying capacity of the blood due to fewer circulating red blood cells than normal or a reduction in the concentration of haemoglobin. The deficiency may occur as a result of a reduction in the production or an increased loss of erythrocytes.

Anaemia is said to occur when the haemoglobin content of blood is below the normal range expected for the age and sex of the individual, provided that the presence of pregnancy, the state of hydration of the individual and the altitude have been taken into account. While several authorities and experts accepts the lower limits of normal haemoglobin concentration as 12g/dl in women and 14g/dl in men, WHO accepts up to 11gm percent as the normal haemoglobin level in pregnancy. Thus any haemoglobin level below 11gm in pregnancy by WHO standard should be considered as anaemia. However in most of the developing countries the lower limit is often accepted as 10 g/dl because a large percentage of pregnant women in this setting with haemoglobin level of 10 g/dl tolerate pregnancy, labour and delivery very well and with good outcome.

The centre for disease control, USA defined anaemia as a hemoglobin (Hgb) or hematocrit (Hct) value less than the fifth percentile of the distribution of Hgb or Hct in a healthy reference population.

5. Classification of anaemia

Anaemia can be classified as physiological (eg pregnancy), according to the aetiology (Table 1) and red blood cell morphology (Table 2).

Classification based on red cell morphology classifies anaemia based on the size and shape of the red blood cell,(normocytic MCV80-90fl, macrocytic MCV>100fl, microcytic MCV<80fl), as well as .pigmentation (hypochromic, normochromic, hypochromic) (Table 2).

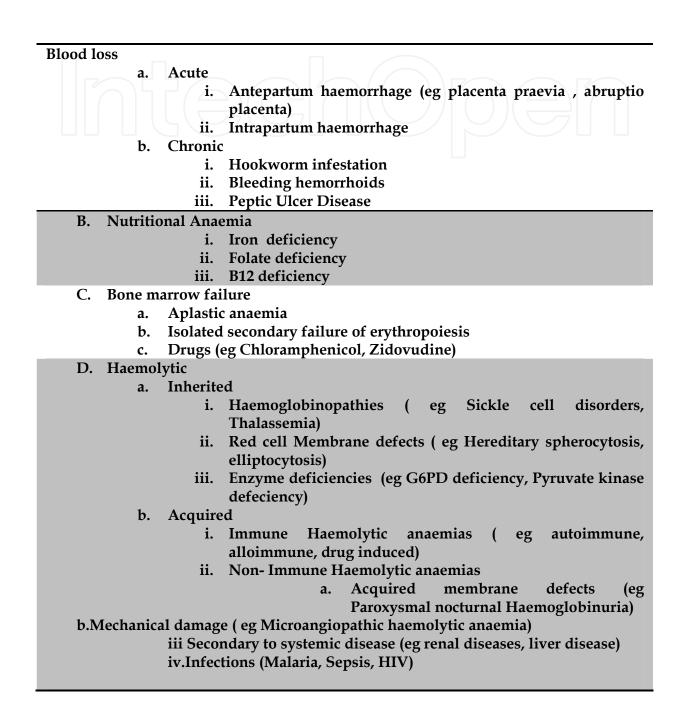


Table 1. Classification of anaemia based on aetiology.

- A. Hypochromic Microcytic
- Iron deficiency
- Thalassemia
- Sideroblastic anemia
- Anaemia of chronic disorders
- Lead poisoning
- B. Macrocytic
- Folic acid deficiency
- Vitamin B12 deficiency
- Liver disease
- Myxoedema
- Chronic Obstructive Pulmonary Disease
- Myelodysplastic syndromes
- Blood loss anemia
- C. Normocytic Normochromic
 - Autoimmune haemolytic anaemia
 - Systemic Lupus Erythomatosis
- Collagen vascular disorders
- Hereditary spherocytosis
- Haemoglobinopathies
- Bone marrow failure
- Malignancies
- Myelodysplasia
- Blood loss anemia
- Anemia of chronic disease

Table 2. Morphological Classification of Anemia and causes.

The classifications are not necessarily independent of each other as the cause of the anaemia could be multifactorial.

Anaemia can be classified according to severity as mild, moderate, severe and very severe (Table 3). Following the diagnosis and possible cause(s) of anaemia in the pregnant woman, management as regards the need for blood transfusions or not will depend on the severity as well as rapidity of development of anaemia.

Degree of Severity	Haemoglobin level (g/dl)
Normal haemoglobin level	>11g/dl
Mild Anaemia	9-11g/dl
Moderate	7-9g/dl
Severe	4-7g/dl
Very severe	<4g/dl

Table 3. Classification of Anaemia by degree of severity.

6. Aetiology

The causes of anaemia in the general population are generally same for anaemia in pregnancy. The causes of anaemia in pregnancy are often multifactorial. In developing countries, the major causes of anaemia in pregnancy are nutritional deficiencies, infections and infestations, haemorrhage and haemoglobinathies. Anaemia is also seen also in some chronic medical disorders like renal and hepatic diseases.

6.1 Nutrition

In many regions of the world nutritional deficiency is the major cause of anaemia in pregnancy. The World health Organization ((WHO) estimates that about half of all pregnant women globally suffer from nutritional anaemia. Nutritional anaemia is mainly due iron and folate deficiency in diet. Diseases that cause poor dietary intake or malabsorption of these nutrients will also result in nutritional anaemia.

Iron deficiency is the commonest cause of nutritional anaemia in both developing and industrialized countries and is usually as a result of poor diet. Sources of iron include meat(liver in particular) vegetables and dairy products. The demand for iron increases in pregnancy as it is required by both mother and fetus for growth and development. In developing countries the already depleted iron stores as a result of poor diet, too early, too many and too frequent pregnancies are unable to cope with the requirement of 1000mg of iron required during a normal pregnancy. The resultant effect is iron deficiency anaemia. Hook worm infestation is another cause of iron deficiency anaemia in the tropics.

The folic acid requirement is also increased two fold in pregnancy. Normal body stores can only last for 3- 4 months. Folate deficiency in pregnancy often develops as a result of poor dietary intake which is often the case in developing countries as well as excess utilization. Sources of folate include liver, egg yolk, and leafy green vegetables. Folate deficiency results in ineffective erythropoesis.

Folate deficiency can be further exacerbated in pregnant women with hemoglobinopathies as well as in those residing in areas of high malaria endemicity as increased haemolysis leads to high red cell turnover and increased folate demand.

Vitamin B12 is rare during pregnancy as the daily requirement is as low as 3- $5\mu g$ and liver stores last for as long as 2 years.

6.2 Infections

Pregnant women are more prone to infections as a result of depressed immunity. Anaemia due to infections is usually as a result of products from the infecting organisms causing ill health, fever, red cell destruction and/ or reduced red cell production. Bacterial infections used to be a leading cause of anaemia, however in the tropics and developing countries, malaria and more recently, HIV/AIDS are leading contributors to anaemia in pregnancy.

6.3 Malaria

Malaria infection is a leading cause of anemia in the tropics both in pregnant and nonpregnant individuals. Malaria induced anaemia is more profound in pregnancy as the susceptibility to malaria is greater in the primigravidae. Anaemia resulting from malarial infection is caused by the destruction of infected and uninfected red blood cells as well as bone marrow suppression. Red blood cells infected with malaria parasites also accumulate

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and sequester in the placenta. Macrophages and cytokines(e.g.Tumor necrosis factor α , Interferon γ and interleukin 1),enhance red cell destruction, splenic clearance capacity,and depress bone marrow erythropoesis. Concurrent micronutrient deficiencies, infection with HIV, hookworm infestation or other chronic inflammatory states will worsen anaemia in these persons.

6.4 HIV/AIDS

Anaemia is the most common haematological complication of the Human Immunodeficiency Virus (HIV) infection and may be consequent upon the effects of the virus itself or treatment with various drugs. The mechanisms of HIV induced anaemia occur through three mechanisms of decreased red blood cell production, increased red cell destruction and ineffective production of red blood cells. The aetiology of HIV associated anaemia is multifactorial and may include the infiltration of the bone marrow by tumour or infection, bone marrow suppression by the virus itself, the use of myelosuppressive drugs like Zidovudine or drugs that prevent the utilization of folate like cotrimoxazole. Other aetiologies include decreased production of erythropoietin , red cell destruction as a result of autoantibodies to red blood cells, and nutritional deficiencies. Nutritional deficiencies could occur as a result of reduced intake due to difficult in swallowing as a result of oropharnygeal thrush, malabsorption or increased catabolism as a result of ill health and associated fever from various infections. Apart from iron and folate deficiency, other reported vitamin deficiencies in HIV infection include vitamin B12, vitamin B6 and vitamin A.

6.5 Haemoglobinopathies

Haemoglobinopathies are inherited disorders affecting haemoglobin structure (Sickle cell disorders) or synthesis (thalassemias). They are usually seen in individuals from Africa, the Middle East, the Mediterranean, Asia and the Far East. The haemoglobinopathies that cause anaemia in pregnancy are sickle cell disorders- HbSS, HbSC and HBS- β thalassemia. Haemoglobinopathies cause a chronic haemolytic anaemia. In sickle cell disorders, the abnormal haemoglobin S sickles in hypoxic states, predisposing the structurally damaged cells to early destruction hence affected persons are chronically anaemic. Folate demands are increased and concurrent infections will worsen anaemia.

6.6 Haemorrhage

Acute blood loss as result of ectopic pregnancy, antepartum haemorrhage and abortions are common causes of anaemia in pregnancy. Chronic blood loss from worm infestations, gastrointestinal ulcers and hemorrhoids results in depletion of iron stores and ineffective erythropoesis.

6.7 Red cell aplasia

This is a rare cause of anaemia in pregnancy and results from a selective failure of erythropoesis. In most cases, the cause is unknown The identified causes of pure red cell aplasia include autoimmune diseases (e.g. SLE,) drugs, and infection with parvovirus B19.

7. Risk factors for anaemia in pregnancy

Pregnant women in developing countries of sub-Saharan Africa, South America and South East Asia are at particular risk of anaemia in pregnancy as a result of poverty, malnutrition

and depleted iron stores from too early, too many and too frequent pregnancies. Irrespective of race and economic situation, the prevalence of anemia in pregnancy is highest amongst teenage mothers. A recent report by Scholl estimates that in a low income setting, rates of iron deficiency anemia are 1.8% in the first trimester, 8.2% in the second trimester, and 27.4% in the third trimester.

In all regions of the world, the risk factors for iron deficiency anemia include a diet poor in iron-rich foods, a diet poor in iron absorption enhancers, a diet rich in foods that diminish iron absorption, gastrointestinal disease affecting absorption, heavy menstrual bleeding and postpartum bleeding.

8. Consequences of anemia in pregnancy

8.1 Fetal

The fetal consequences of anaemia in pregnancy are well established and depend not only on the severity of anaemia but also on the duration of the anaemic state. A fall in maternal haemoglobin below 11.0 g/d1 is associated with a significant rise in perinatal mortality rates. The rate of perinatal mortality triples at maternal haemoglobin levels below 8.0 g/d1 and increase by ten fold when anaemia is very severe. Similar findings have also been noted for both infant birth weight and preterm delivery rates. A significant fall in birth weight as a result of increase in preterm rate and intrauterine growth restriction has been reported with maternal haemoglobin levels below 8.0 g/d1.

8.2 Maternal

The presence of, severity and duration of anaemia affect maternal as well as fetal well being. Women whose means of livelihood involve manual labour may find it difficult to earn a living as tolerance and capacity for exercise is reduced. This is worse if the onset of anaemia is acute. When anaemia is of gradual onset and is chronic, adequate compensatory mechanisms enable the women to go through pregnancy and labour without any adverse consequences.

Where anaemia is moderate, there is a substantial reduction in work capacity and she may be unable to cope with household chores and child care. Women with moderate anaemia tend to experience higher rates of morbidity during pregnancy as compared to those with mild anaemia. Evidence has shown that a large percentage of maternal deaths due to antepartum haemorrhage, pre-eclampsia and infections occur in women with moderate anaemia.

The maternal outcomes in severe anaemia depend on level of decompensation. If not recognized early and corrected, the heart is unable to compensate for the severity of anaemia and eventual circulatory failure occurs leading to pulmonary oedema and death. The women are unable to tolerate third stage of labour and blood losses associated with delivery. When the anaemia is very severe, there is a steep rise in maternal deaths.

9. Clinical features

The clinical features of anaemia in pregnant or non pregnant states are dependent on rapidity of onset and severity of anaemia. In general, symptoms occur with moderate to severe anaemia and are more severe when anaemia has been rapidly progressive. In presence of anaemia the body initiates a number of compensatory mechanisms. The symptom (s) that is subsequently felt by the individual is dependent on whether the compensation is sufficient or insufficient. As such, a pregnant woman with anaemia may be asymptomatic body systems adjust to reduced haemoglobin mass. Where the patient is symptomatic, symptoms may be those of vague ill health, headaches, light headedness, tinnitus, intermittent claudication, or symptoms of angina. However, as decomposition ensues, there may be palpitations, easy fatigability and patients can present in heart failure.

The signs of anaemia can be general or specific. General signs of anaemia include pallor of the mucous membranes, hyperdynamic circulation with tachycardia, a bounding pulse, cardiomegaly and a apical systolic flow mummur (haemic mummur). The specific signs are associated with particular types of anaemia e.g painless glossitis, angular stomatitis,ridged or spoon shaped nails, unusual dietary cravings for non-food substances(pica) in iron deficiency, jaundice in haemolytic and megaloblastic anaemias, neuropathy, widespread melanin pigmentation in B12 deficiency. Hepatoslenomegaly (may be difficult to elicit when pregnancy is advanced) may be features of chronic hemolytic disorders, megaloblastic anaemia, or other haematologic pathologies. The findings of anaemia with fever and spontaneous bruising may be indicative of bone marrow failure.

10. Diagnosis of cause(s) of anaemia

A detailed history, physical examination and appropriate investigations are necessary for the identification of the cause(s) of anaemia. Except in very severe anaemia where there is an urgent need to treat the pregnant woman to avoid death, the cardinal rule is to establish the cause of anemia before commencing treatment.

10.1 History

A detailed history including diet, gynaecological, obstetric,drug and social history should be taken. As nutritional anaemia is common in developing countries, a detailed enquiry into the person's and diet and feeding habits should be made. Knowledge of the dietary and food habits will be necessary to plan strategies to prevent reoccurrence after management of the present anaemic state. It is also important to enquire in detail about duration and symptoms of anaemia (if any), symptoms of decompensation and possible predisposing factors. Other specific symptoms like a beefy red painful tongue, discoloured nails, parasthesias can also be sought. Previous history of postpartum haemorrhage or abortion, drug ingestion should be sought. Ideally, the history should address all possible aetiology of anaemia, features and its complications.

10.2 Physical examination

A good physical examination should confirm the presence of anaemia, possible aetiology and signs of decompensation. Where anaemia has been chronic, physical examination may reveal cardiomegaly, bounding pulses and a systolic flow murmur (hemic murmur). In acute blood loss the patient can present in shock. On examination the presence of pallor, jaundice, spleen and liver size should be documented.

10.3 Investigations

Investigations for anaemia are general and specific. A full blood count is required as part of the general investigation and includes the haemoglobin levels, packed cell volume, white cell and platelet counts. Red cell indices include mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC). These indices will in the classify anaemia into either microcytic (MCV <80 fL), macrocytic (MCV >100fL) and normocytic (MCV80-100fL) or hypochromic or normochromic (MCH and MCHC)., A peripheral blood smear and reticulocyte count are also mandatory. While peripheral blood smear provides information about red cell morphology, variations in size, and shape, the reticulocyte count provides information on the marrow response. In the presence of anaemia a reticulocyte count less than 2-3 times normal indicates inadequate bone marrow response. Elevated neutrophil counts may suggest an infection.and peripheral smears that reveal a pancytopenia is suggestive of marrow failure. Stools should also be examined for colour, consistency, occult blood, ova and parasites. It is also important to note that in the tropics most of the causes may coexist. Other specific tests are often dictated by suspected cause of the anaemia. In the tropics, it is usual to screen for malaria as it is a well documented cause of anaemia in pregnancy. Some specific tests necessary to confirm some common causes and features of anemia is shown in Table 4.

 Iron deficiency a. Serum ferritin b. Total iron binding capacity c. Transferrin saturation d. Marrow iron stain 	 Haemoglobinopathies a. Hb electrophoresis 3. HIV infection a. Detection of antibody to HIV using ELISA or Western blot assays.
4. Chronic medical disorders a. Liver function tests b. Serum electrolyte, urea and creatinine c. Screening for autoimmune diseases	 Antepartum haemorrhage a. Ultrasonography

Table 4. Specific investigations for some common causes of anaemia.

11. Treatment

It is of utmost importance to establish the cause of anaemia prior to definitive management. However, features of decompensation, very severe anaemia and acute blood loss require immediate red cell transfusion as soon as the required samples have been collected. The only caveat is that we must ensure that all necessary samples have been collected before transfusion.

The goal of treatment of anaemia in pregnancy is therefore to maintain wellbeing, identify and correct the underlying cause(s) and correct anemia within shortest time possible and improve patient quality of life and survival. The definitive management of anaemia depends on the cause. The identified causes must be treated appropriately otherwise the anaemia becomes recurrent.

By and large, the management of anaemia in a pregnant woman depends on the duration of pregnancy, severity of the anaemia and complication (obstetric, medical or both).

Mild and moderate anaemia in pregnancy as a result of iron deficiency should be carefully assessed for the cause and the patient placed on iron therapy apart from the treatment of the aetiology. The preferred route of iron replacement is oral route as there is no benefit in giving parenteral iron as opposed to oral iron. Ferrous sulphate (200mg per tablet containing 67mg elemental iron) is the least expensive and best absorbed form of Iron. Ferrous glutamate (300mg per tablet containing 37mg elemental iron) and fumarate can also be used where iron sulphate is not tolerated. The optimal doses are 120-200mg daily of elemental iron in divided doses. Oral iron should be given for long enough to correct the anaemia and to replenish iron stores which usually means for at least 6 months. Haemoglobin should rise at the rate of approximately 2g/dl every 3 weeks. Side effects of oral iron include gastrointestinal symptoms such as diarrhea, nausea, constipation, abdominal pain.

Parenteral iron may be indicated in cases of poor adherence, intolerable side effects or malabsorption of oral iron. In such situation parenteral iron such as iron dextran or sorbitol may be administered by the intravenous or intramuscular route. The hematological response to parenteral iron is not faster than adequate dosage of oral iron but the stores are replenished faster. Ferric hydroxide –sucrose (Venofer) is the safest form and is administered by slow intravenous injection or infusion usually 200mg in each infusion. Iron dextran (Cosmofer) can be given as slow injection or infusion in small doses or as a total dose infusion given in one day.

Total dose Intravenous infusion of iron with iron dextran in pregnancy (50mg iron per ml) Dose (mL) = 0.0442 (Desired Hb - Observed Hb) x Lean Body Weight (45.5 kg + 2.3 kg for each inch of patient's height over 5 feet.) + ($0.26 \times LBW$) + 1g.

The total dose of iron dextran is added to 500ml normal saline and infused over a period of 4 hours. The major drawback of parenteral iron is anaphylaxis which can occur within 30 mins of commencing the infusion and may prove rapidly fatal.

Intramuscular iron therapy can be given as iron sorbitol (Jectofer)(50mg/ml). Injections should be given deep into the gluteal muscle. The drawbacks of intramuscular iron include pain and staining of the skin at the injection site,myalgia, athralgia and injection abscess

Severe or very severe anaemia requires the immediate hospitalization of the woman, management of heart failure and transfusion of packed cells. Once the emergency is averted, the iron replacement is as in mild to moderate anaemia.

Treatment of anaemia from folate deficiency is with folic acid 5mg daily for 4 months and is usually given throughout pregnancy. Vitamin B12 deficiency is rare in pregnancy and is treated with intramuscular injections of hydroxocobalamin 1000ug. Initial doses are 6 injections over 2-3 weeks then 100ug every 3 months.

Erythropoietin is beneficial in patients -with marrow suppression . 100-200U/Kg 3times a week until normalization of the red cell and then once a weekly to maintain haemoglobin of approximately 12g/dl.

Treatment of malaria with artemisin combination therapy, bacterial infections with appropriate antibiotics, hookworm infestation with mebendazole or Albendazole and use of

highly active antiretroviral therapy according to treatment guidelines in HIV infection. Other co-morbidities e.g. diabetes, hypertension should also be managed.

12. Prevention

Approximately 1g of iron is required during a normal pregnancy. Up to 600mg of iron is required for the increase in maternal red cell mass, and a further 300mg for the foetus. These requirements exceed the iron storage of most young women and often cannot be met by the diet. Therefore, few women avoid depletion of iron reserves by the end of pregnancy. Folate requirements are increased approximately twofold in pregnancy (800ug/day vs 400ug/day because of transfer of folate to the growing fetus and if diet is insufficient, may exceed the body's stores of folate(5-10mg).

To prevent anaemia in pregnancy the following are necessary. Routine screening for anaemia in adolescence, nutritional education about foods rich in iron(meat, liver, leafy green vegetables, legumes) and folate (liver, egg yolk, yeast and leafy green vegetables) to encourage consumption, early as well as regular antenatal clinic attendances, iron, folate supplementation in pregnancy and early treatment of concomitant infections. In areas of high malaria endemicity, intermittent prophylactic therapy with pyrimethamine-sulphodoxine for malaria should also be given at 16-17 weeks and 4 weeks later. A third dose is given in HIV infection.

13. Conclusion

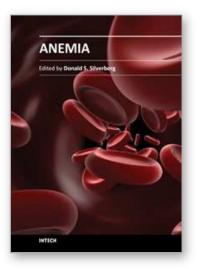
Anaemia in pregnancy is a major public health problem in developing countries and is associated with an increased risk of maternal and perinatal morbidity and mortality. Fortification of foods with iron and folate, routine screening for anaemia from adolescence, health education, and prompt treatment of infections and attendance of antenatal facilities by pregnant women can reduce this burden.

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This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

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