A STUDY OF IRON DEFICIENCY ANAEMIA IN PREGNANCY IN IBADAN WITH REFERENCE

To

TREATMENT WITH PARENTERAL IRON

By

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INDEX

INTRODUCTION

Anaemia in pregnancy is a major obstetric problem in most places including Ibadan, Nigeria, where it is common (Ojo, 1965) and it is associated with a high maternal mortality, particularly when the haematocrit level is 26 per cent or less (Harrison, 1975).

Iron deficiency is the commonest cause of anaemia in many tropical countries, occuring either alone or in association with folate deficiency (Pitney, 1971). For example, iron deficiency is rife in the hot damp river valleys of Assam; in the coastal regions of Kenya and Mozambique (Foy et al, 1952, Foy and Kondi, 1957); in Mauritius where an incidence of 64% was found by Stott (1961), in Gambia (Woodruff & Schofield, 1957,, Topley, 1968a) and in Uganda (Vanier, 1966).

In Nigeria, however, until recently, the main causes of anaemia in pregnancy in Ibadan have been stated to be red cell haemolysis due to malaria (Gilles et al, 1969, Fleming, 1969) dietary deficiency of folates (Fleming et al, 1969) and haemoglobinopathies (Hendrickse 1966, and Harrison, 1973). As a result of these reports, the antenatal routine at the University College Hospital (U.C.H.) and in most maternity centres that follow the University College Hospital practice is to give prophylactic antimalarial of 25 mg. pyrimethamine weekly and folic acid 5 mg. daily to expectant women (Appendix 1).

The only detailed study of iron status of anaemic Nigerian women was by Fleming (1969). Patients studied had severe anaemia with packed cell volume 23 per cent or less. This group was studied then because severe anaemia in pregnancy was very common and was associated with an alarmingly high maternal and foetal mortality. In Fleming's group (1969) 18% of the patients studied showed possible evidence of iron deficiency but only one out of the 221 bone marrows examined contained no stainable intracellular iron. Anaemia in all the other patients was the result of haemolysis (probably related to plasmodium falciparum infection) folate deficiency, haemorrhage, haemoglobinopathies and various miscellaneous causes. Anti malarials and folic acid supplement were therefore considered more important than iron supplements during pregnancy in Nigeria.

We now see less number of patients with severe anaemia, and from the literature reviewed (section 1) it is clear that the iron status of pregnant women with mild to moderate degree of anaemia has not been fully determined. Besides, there has, over the past 10 - 15 years, been a change in the dietary habits of the urban population. The traditional clay cooking pots which are known to contribute to the iron content of foods have almost been completely replaced by modern aluminium

utensils. Imported polished rice has largely taken the place of the traditional native unpolished variety, and the rice is fast becoming a common item of food in many homes. Absorption of the dietary iron may be reduced by the increasing consumption of eggs now occuring among people living in the city. There is thus the possibility of depressed absorption of iron that may be present in our foods not only by the nature of our habitual diet which contains high carbohydrate and much vegetables but also by the big change in our dietary habits brought about by the influx of western civilization.

The present study was therefore undertaken to evaluate the prevalence of iron deficiency anaemia especially in the more common milder anaemias which have so far been inadequately investigated.

Definition of Anaemia

There has been much controversy in the past concerning the values of haemoglobin which should be considered normal for indigenous tropical populations. A World Health Organisation report (1959) concluded that inhabitants of the tropics who are free from disease should have haemoglobin values similar to people in the temperate zone, and this opinion has been confirmed by a more recent report from the same source (1968). The latter recommended for women the following haemoglo-

bin values below which people at sea level should be considered to be anaemic: adult non-pregnant females, 12g/100 ml and pregnant women, 11g/100ml. These values are in agreement with those considered normal for populations in temperate zones (Dacie & Lewis, 1968) and are probably achieved in the tropics in individuals who consume an adequate diet and are free from parasitic disease. It is difficult, however, to find unselected population in the tropics who satisfy these requirements, so that information on optimal haemoglobin values is inadequate. For practical purposes, a haemoglobin level below which the maternal and foetal prognosis is seriously impaired has to be selected in tropical countries, In most parts of the tropical world a haemoglobin of 60% (8.7g%) will have to be accepted; indeed, in many parts of Africa and Asia the haemoglobins of more than half the pregnant women, when unsupervised and untreated, fall below this level (Lawson, 1967). At present Nigerian pregnant women who have a haemoglobin value of 10g/100ml (P.C.V.30%) or less are considered anaemic.

Degree of Anaemia

In this presentation - the degree of anaemia has been classified as mild, moderate and severe, Anaemia

was classified as 'severe' when the packed cell volume (P.C.V.) was less than 19%. Packed cell volume of 18% or less (Haemoglobin 6.5%) has been shown to be the critical level at which both maternal and foetal mortality rises (Harrison, 1975). A "moderate" anaemia was diagnosed when patients presented with packed cell volume of 19 - 25%. Such patients were admitted to the hospital for investigations and treatment. Except for patients near term, they were discharged from the wards as soon as the P.C.V. attained the level of 26%. Patients first seen with packed cell volume of 27-30% were classified as "mild" anaemias. Such patients were not usually admitted to hospital. It is our practice to treat them on out-patient basis with anti-malarials and haematinics after the routine investigations of blood grouping, haemoglobin genotype determination and Venereal disease Research Laboratory tests.

IRON DEFICIENCY IN PREGNANCY

Iron deficiency anaemia has long been recognised as a very common complication of pregnancy in Europe and North America (Davidson et al, 1935, Elliot, 1944 & Donald, 1974).

Physiological Concepts

This has been well documented by Nhonoli (1974).

The uptake of iron in immature red cells per unit time depends largely on the degree of saturation with iron of the protein vector transferrin, all other things being equal, i.e. cell membrane status, total quantity of transferrin, oxygen and carbon dioxide concentration in the environment. At over 60% saturation iron, red cell uptake is increased, while below 20% saturation attachment of iron to immature cells is diminished. Thus in iron deficiency states in spite of bone marrow medullary erythroblastosis there is little or no increase in the rate of haemoglobin synthesis but promotes intestinal iron absorption and the flow of iron from storage sites to the plasma. In this way in early deficiency the plasma iron levels tend to remain relatively high while the total iron binding capacity (total amount of transferrin) rises, transferrin saturation reduces with iron stores depleted and haemoglobin levels falling.

Plasma and red cell volume in pregnancy

Accurate measurements of red cell and plasma volumes became possible with the introduction of various techniques, which have been reviewed critically by Hytten and Leitch (1964). The most usual method of estimating red cell volume is by labelling the patient's own red cells with radioactive chromium (^{51}Cr), injecting these back

into the circulation, and calculating the dilution of the labelled cells in the body after sufficient time has elapsed for mixing. Plasma volume may be measuured satisfactorily by the dilution of Evan's blue dye injected into the circulation.

The most acceptable figures are a normal plasma volume in the non-pregnant of about 2,600 ml, and an increase in primiparae of 1,250 ml, the maximum increase being at about the 34th week of pregnancy. In multiparous patients the increase is about 1,500ml (Hytten and Paintin, 1963), and it is is further increased in multiple pregnancies. The normal red cell volume is about 1,400 ml in the non-pregnant, and increases by about 250 ml at term in patients not receiving iron supplemtns (Paintin,1962). When patients do receive iron supplements the increase is greater, 400-450 ml. Hytten and Leitch (1964) and Paintin et al. (1966) consider the increase following iron therapy to be unphysiological, but other workers think that a smaller increase of red cell mass during pregnancy is the first response to iron deficiency, before the development of hypochromic anaemia (Anon, 1964).

The haemoglobin concentration and PCV of peripheral blood falls to a minimum about the 34th week as a result of the greater increase of plasma volume than red cell volume. The average lowest haemoglobin concentration

has been about 12.0± 1.0 g/100 ml, whatever their environment and race.

Dietary Intake of Iron

The iron content of diet is 12 - 18 mg. per day in Europe (Anon,1964) and 15-18mg. per day in the United States (Moore, 1965 & White,1968) but in other countries it may be considerably different. In Mauritius the average intake is 5 - 10 mg. per day (Stott, 1961) while in the Gambia the soil is very rich in iron (Topley 1968) and in Western Nigeria the daily dietary iron has been reported to be 40mg. (Gilles et al 1964).

Absorption

Many factors interact to determine the amount of iron absorbed from the gastrointestinal tract. These include (1) The amount and source of dietary iron; (2) Intraluminal factors such as normal gastrointestinal anatomy, gastric acidity, and gastric, billiary and pancreatic secretions and (3) rate of iron absorption by the small intestinal mucosa, particularly that of the duodenum and jejunum.

A composite of the available studies permits certain general statements. Normal subjects absorb approximately 5 - 10% of dietary iron compared with 20% in iron deficient patients (Moore 1965). Absorption is better from muscles, liver haemoglobin and enriched bread

than from green vegetables and eggs.

Iron Loss

Body iron is located mainly intracellularly, either firmly chelated in the porphyrin ring of haemoglobin, myoglobin, and various intracellular enzymes or bound as the iron-protein complexes ferritin and haemosiderin. Plasma iron is tightly bound to transferin and is not normally lost into the urine or into the intestinal lumen.

Obligatory loss of iron occurs with sloughing of epithelial cells from the gastro-intestinal tract, skin, urinary tract, and lungs. Blood loss from the gut, measured by the 51 Cr technique, is usually less than 1 ml. (0.5 mg. iron) daily (Jones, 1958). Although physiologic regulation of iron excretion probably does not occur, iron deficiency results in decreased loss and excessive body iron content results in increased iron loss (Dubach et al, 1955 and Crosby et al, 1963). As much as 5 mg. of iron per day may be lost through the normal channels (Crosby et al, 1963).

Iron Demands in Pregnancy

Iron content of the full-time foetus and the placenta together is 200 to 300 mg (Nhonoli, 1974). Most of this is taken by the foetus in the third trimester. The total iron demands by the expectant

mother are just over 1 g. disbursed thus:

200 mg. lost by maternal excretion

300 mg. taken by foetus and placenta

500 mg. when available utilized to increase maternal haemoglobin mass

150 mg. lost in blood at delivery.

It should be remembered that during this 9-month amenorrhoea she has saved 600 to 800 ml of blood, i.e., 250 to 270 mg. of iron. Thus the extra iron needed is just under 1 g. which must be made available from external sources in those 280 days.

Iron Deficiency States

Iron stores are the basic regulators of the total iron binding capacity (TIBC), hence this TIBC has a significant negative correlation to the iron stores saturation (Garby, 1973). In iron deficiency states the high TIBC is accompanied by low iron stores; replenishing the iron stores reduces the TIBC level. Bainton and Finch (1964) also showed that failure of iron supply to the normoblast occurs when the saturation of transferrin falls below 16%, and figures of less than this are invariably associated with iron-deficient erythropoiesis. Iron deficient erythropoiesis is defined as a state in which the supply of iron is inadequate to support optimal erythropoiesis in the

developing red cell mass. This may occur as a result of depletion in total body iron or through inadequate supply of plasma iron which may be due either to a block in iron discharge from the reticulo-endothelial cells as occurs in infections or to absence of circulating transferrin.

The American Medical Association (Committee on Iron Deficiency, 1968) had the following as the classification of iron deficiency states, i.e., stages of iron deficiency;

(1) Iron depletion: decreased or absence of marrow haemosiderin.

(2) Iron deficiency without anaemia: Absence of iron in stores and a saturation of transferrin of 15% or less.

(3) Iron deficiency anaemia: Findings as in (2) above plus a reduction of haemoglobin level below the normal levels.

AETIOLOGY OF IRON DEFICIENCY

There are five main causes of iron deficiency, and more than one cause can contribute in any one patient.

(1) Low dietary intake

(2) Increased requirements

(3) Blood loss

(4) Malabsorption

(5) Disturbed iron metabolism.

Low Dietary Intake During Pregnancy

Before the work of Lucy Wills (1931) few clinicians attached much importance to the role of diet in causing anaemia in pregnancy. Since then, many workers have stressed that their anaemic patients had diet poor in meat and green vegetables (Forshaw, 1957; Pritchard, 1962 and Gilles, 1966). Even without accurate figures, it is obvious that the disease is much more common in countries with improverished populations including India, Macedonia and Africa. The iron content of food may be wholly inadequate: For example, intake in Mauritius is on the average only 5 mg. per day (Stott 1961). The foods in most part of the world, however contain more than sufficient iron and the problem usually is with inadequate intake of foods rich in iron. The iron content of many Nigerian diets where meat is scarce and expensive may be deficient. During pregnancy the dietary intake could be further depressed by nausea and vomiting of early pregnancy. Forgetfulness or non-motivation to take iron tablets may also contribute to iron deficiency. Nutritional deficiency of iron occurs even in prosperous countries because of food fads, individual poverty, loss of appetite old age and in infancy (Davis et al, 1960).

Increased Iron Requirements During Pregnancy

That pregnancy often results in iron deficiency

anaemia has been well presented by Mcfee (1973) from an extensive review of the literature. In a detailed study deLeeuw, Lowenstein and Hsieh 1966 showed that iron supplemented patients in the last trimester had higher haemoglobins, haematocrits, M.C.H.C. red cell volumes, haemoglobin masses, serum irons, and stainable marrow iron than did unsupplemented control patients. Although plasma volume augmentation was the same in both groups, the increase in red cell volume and haemoglobin mass in supplemented patients was approximately twice that of the controls. Many of the unsupplemented groups were iron deficient during latter pregnancy as demonstrated by low haemoglobins, low serum iron, low transferrin saturation, lack of stainable iron in the marrow, and the observation that much of this was uncorrected by 6 weeks postpartum. Similar studies of Holly (1953) and Lawrence (1962) have shown the same findings.

Thus many gravidas can develop an iron deficient state because iron requirements of pregnancy are high and often cannot be met by diet alone. Additional iron, over the normal, is needed during pregnancy for augmentation of maternal red blood cell mass, for formation of foetal haemoglobin and for the placenta. In considering these necessary iron requirements various workers have derived the iron requirement of a normal pregnancy which are summarized in Table 1. For practical purposes

the total iron requirement of pregnancy is about 1 gram (1000 mg.).

If these iron requirements of pregnancy, the availability of iron stores and the normal consumption of iron from the diet are all considered, certain conclusions are apparent. If iron stores (1000 mg.) and dietary iron (about 1.5 mg. daily for 280 days or 420 mg.) are adequate, the iron requirement of pregnancy will be met (total available iron 1420 mg.). However, this is unusual. As Holly (1959, 1965) and others (Hunter, 1960; Deleeuw et al 1966 and Hellman and Pritchard 1971), have pointed out, if stores are low or absent a deficit exists (1000 mg. requirement minus 420 mg. dietary iron). If, in addition, the daily dietary iron intake is reduced (as in nausea or poor diet) the deficit is even greater (perhaps as much as the entire 1 gram requirement). If such a patient is unsupplemented iron deficiency anaemia will ensue.

Blood Loss

This is an important cause of iron deficiency anaemia. For the purpose of estimating the effect of blood loss on iron balance, 1.0ml of blood may be considered to contain about 0.5 mg. iron (Wintrobe, 1974). Thus if an average diet is consumed, a steady loss of as little as 3 to 4 ml/day (1.5 to 2 mg. iron) that may occur from heavy hookworm infection can result in a negative iron balance.

In women, bleeding from the genital tract is the most single cause of iron deficiency. Excessive menstrual blood loss is an important factor but the effect of this is related to the nutritional status of the patient. In Swedish women with a dietary intake of about 10 mg iron per day, 67% of women with menstrual loss exceeding 80ml/period were anaemic (Halberg et al 1966). In contrast, however a better nourished Canadian population tolerated flows greater than 80ml. per period without overt anaemia or hypoferremia (Beaton, 1970).

A common source of blood loss in places with general undernutrition and poor antenatal care is bleeding during pregnancy or/and at delivery. The incidence of post partum haemorrhage at the University College Hospital, Ibadan over an eight year period (1962-1973) was 3.4%(Ogunbode 1976). Most of these women if not adequately treated would become iron deficient in the puerperium. Some of them may thus become iron deficient even before the next pregnancy.

Lactation results in a daily iron loss of about 0.5mg to 1mg. Since normal menstruation is usually inhibited while breast feeding continues, iron requirements in the lactating woman approximate those of menstruating women (Wintrobe 1974).

Malabsorption of Iron

Under normal circumstances is probably unusual although this is sometimes proposed as a cause of anaemia. Certain diseases do at times cause this. Patients who have had a partial or total gastrectomy often develop an iron deficiency anaemia which in part is due to malabsorption of iron (Turnberg, 1966 and Kimber et al, 1967). The sprues, idiopathic steatorrhea and coeliac disease which are common in the tropical countries also can result in impaired iron absorption (Wintrobe, 1967). Diets high in phosphorus (e.g. eggs) often result in the formation of insoluble iron complexes (Wintrobe, 1967). Phytates, present in cereals, also form insoluble and unabsorbable iron salts (Wintrobe, 1967; Goodman and Gilman; 1970 and Iyenger and Apte 1970). At least one antacid, magnesium trisilicate, has been observed to reduce iron absorption (Hall and Davis, 1969). The extensive use of various antacids during pregnancy for heartburn thus could be responsible for some degree of impaired iron absorption. Protein lack has also been noted to have adverse effect on iron absorption (Kroe et al, 1963).

Disturbed Iron Metabolism

Iron metabolism may be disturbed by a number of diseases. In the tropical countries the two important

factors are infections and exposure tc various drugs and chemicals.

Various systemic diseases have been recognised for many years as causes cf anaemia. Anaemia of bone marrow inadequacy or failure often accompanies chronic renal disease, chrcnic infection, collagen disease and rheumatic and arthritis, malignancy, chronic liver disease, endocrine deficiency and nutritional deficiency (Wintrobe,1974). During pregnancy the most common of these chronic conditions are infection and chronic renal disease. These should be ruled out in any pregnant patient whose anaemia fails to respond to the usual haematinics.

Anaemias are more often encountered in those with untreated urinary tract infections than in pregnancies unaccompanied by infections (Gilles and Brown,1962; and Robertson et al, 1968). The anaemia of infection is usually normocytic and normochromic although can occasionally be microcytic and hypochro ic. Serum iron levels are usually reduced. Regarding the cause of anaemia of infection, most evidence indicates that iron both absorbed from the gastro intestinal tract and from the red cell break down, is transferred primarily to tissue storage sites rather than being made available for erythropoiesis (Wintrobe 1967 & Barnett-Connor 1972).

Disturbed iron metabolism in pregnancy may also be due to exposure to various drugs and chemicals which have an adverse effect on the bone marrow and is like in the non-pregnant state Lachmann et al, 1954; Rovinsky, 1959; Figge et al, 1960; Rosner and Susmann, 1964; Fleming, 1968; and Taylor et al, 1968). Most of these cases do not improve postpartum and most of those that do never fully recover; many succumb. In many instances identification of the offending agent is impossible (Mcfee, 1973).

Summary

Iron deficiency results from five groups of causes.

(1) Low dietary intake as seen in cases of poverty, anorexia, alcoholism and nutritional deficiency in childhood or old age.

(2) Increased requirements for iron occur with growth including pregnancy.

(3) Obstetric haemorrhage and blood loss from the gastrointestinal tract, for example due to hookworm infection, can lead to iron deficiency.

(4) Malabsorption can result from many conditions including dietary habits, idiopathic steatorrhoea, coeliac disease, tropical sprue, anatomical derangement of the gastrointestinal tract and alcoholism.

(5) Iron metabolism may be disturbed by infections and drugs - particularly in areas where administration of native herbs and medicine is common. Enzyme activity necessary for iron function is reduced in liver disease, alcoholism, protein deficiency, folic acid deficiency, pyrexia and infection.

The main cause of iron deficiency in pregnancy is a low dietary intake insufficient to meet high demand. Blood loss, malabsorption and metabolic disturbance can contribute coincidentally.

OBJECT OF THIS STUDY

The aim of the present study are as follows:

(a) To assess the prevalence of iron deficiency anaemia amongst our expectant women especially those with mild to moderate degree of anaemia (packed cell volume 20% - 30%).

(b) To determine the possible aetiological factors of iron deficiency among these patients.

(c) To examine if any change is necessary in our present antenatal routine for prophylaxis against anaemia, and

(d) to evaluate the place of parenteral iron

therapy in the management of some of these patients.

The results of such study would allow recommendations to be made with regards to the correct prophylactic treatment and it would give useful guidelines as to the proper management of patients with anaemia during pregnancy in Nigeria.

Sections

The first section deals with the historical review of relevant past reports on anaemia in pregnancy in Nigeria; the methods used to determine its prevalence and the aetiology of iron deficiency anaemia amongst Nigerian pregnant women. The second section refers to the place of parenteral iron therapy in the management of established iron deficiency in these patients.

SECTION ONE

A. Historical Review of Relevant Past Work on Anaemia in Pregnancy:

Pregnancy anaemia is very common in Nigeria (Ojo 1965, Lawson,1971). There is a seasonal incidence of severe anaemia in Nigeria this complication being more prevalent during the rainy season the months of May to September. (Apperdix 2). The factors responsible may be single or multiple. Some have ascribed it to increased malarial transmission during this period (Lawson,1967 & Ojo,1965) and others to lack of foods in these months, the period of planting crops (Fleming, 1968a). We do not yet have a significant food storage facilities. As a result, foods are abundant during one period of the year and very scarce at some other periods.

Interest in anaemia among Nigerians followed the report of Woodruff, (1951) that anaemia was very frequent and severe during pregnancy. He also stated that management and treatment of these cases were difficult, as their cause was not known with certainty. Malarial infection being endemic in our area is inevitably the commonest cause of

anaemia by producing haemolysis. Next to malaria there is dietary deficiency of folates (Fleming et al, 1969) and Haemoglobinopathies (Hendrickse et al, 1966). Occasional mention is made of Hookworm anaemia.

Malaria & Pregnancy

The influence of malaria on pregnancy is well doucmented by Lawson (1969). The effect that malaria exerts on a population is largely governed by its epidemiological pattern. Malaria in a community may be either stable or unstable. Stable malaria occurs in regions in which there is constantly repeated infection (holoendemic areas.). The population has a high degree of immunity and epidemics do not occur. Unstable malaria occurs in regions in which transmission is intermittent: communal immunity is poorly developed and dramatic epidemics can occur

The degree of immunity possessed by an individual is the sum of phylo-genetic or racial immunity, transmitted passive immunity, and acquired active immunity. Phylogenetic immunity to malaria results from natural selection over the ages, an example being the immunity to P. vivax infections possessed by Negroes. Passive immunity is transmitted across the placenta to the foetus. It is transient, and begins to wane after the first month of extra-uterine life.

Active immunity is slowly acquired in response to parasitaemia, and increases with age as a result. There is little cross-immunity to the predominant local strain. In holoendemic areas immunity is usually well-developed by the seventh year, though at the cost of many casualties in early childhood.

There are wide differences in the effect of malaria on the course of pregnancy between immune women native to endemic areas and highly-susceptible women with no acquired immunity. The latter may be immigrants from non-malarious regions or indigenous women whose immunity, as a result of long-continued protection from malaria, either has waned or has never developed.

Acquired immunity to malaria is precariously established, and is liable to break down under conditions of stress, particularly the stress of pregnancy. It seems likely that when protein requirements are unusually high, as in pregnancy, metabolic channels may be altered so that, if the dietary intake is insufficient, protein is withdrawn from the immunity system. This is supported by preliminary observations of a lower rate of gamma-globulin synthesis in pregnancy in unprotected African adults in a hyperendemic area.

Whatever the explanation, there is no doubt that immunity declines. The break down of malarial immunity is most marked in first pregnancies for reasons which are yet obscure. Clinical manifestations of malaria in communities where tolerance has been acquired therefore become more important in pregnancy.

Apart from an increase in the frequency and severity of attacks of malaria during pregnancy, the most important influence of the disease on maternal health is indirect by causing anaemia through the process of haemolysis. As a result of haemolysis there is an increased rate of haemopoiesis to keep abreast of red cell destruction. This increase the folic acid requirements, which may not be satisfied by a preexisting insufficiency and the demands of the developing foetus.

With the increasing use of antimalarials and improving sanitation there has been a significant fall in the incidence of patients with severe anaemia, seen at the University College Hospital, Ibadan.

Folic Acid Deficiency Anaemia

Lawson (1962), Fullerton and Turner (1962) and Fleming and Elliot (1964) had indicated that folic acid deficiency was important in relation to anaemia in patients of Western part of Nigeria.

The best evidence for this deficiency during pregnancy was provided by Fleming et al in 1968. Peripheral blood films were made and examined for neutrophil polymorphs. Marrow smears were made from specimens aspirated from the anterior iliac crest. They were fixed and stained with May-Grunimwald and Giemsa stain. The degree of megaloblastic change was assessed by the scoring system of Chanarin et al (1965b). The slides were examined from every specimen, each by a practised haematologist, the changes in the red cell series and white cell series were observed separately, scoring 0, ½, 1 or 2 according to the degree of megaloblastic change. The serum folic acid activity (S.F.A.) was also determined. Lactobacillus casei was the test organism used in an assay method following the technique of Chanarin and Berry (1964).

Seventy-five women were included in the trial. They were primigravida, less than 26 weeks pregnant with P.C.V. 27% or more who had not received any treatment so far as was known. Patients with abnormal haemoglobins were not included. The marrow specimens were examined and their serum folic acid activity determined. In addition slides were screened for malarial pigment.

From this study thirty percent of primiparous patients were deficient of folic acid (as evidenced by hypersegmentation of the polymorphs and low S.F.A.) at their first attendance to the clinic. Eighty five percent were deficient by the end of pregnancy, with 30% of them having frankly megaloblastic erythropoiesis.

In 1968, Fleming et al conducted another folic acid clinical trial on 54 ante-natal patients, with severe anaemia (packed cell volume 23% or less, attending the University College Hospital, Ibadan. The study was designed to determine an economic routine of haematinic supplements to our antenatal patients. Two main groups of patients were studied. One group received folic acid and antimalarials and the second group had ferrous sulphate and antimalarials. It was found that next to antimalarial prophylaxis, the most important antenatal requirement in preventing anaemia in Western Nigeria was the administration of folic acid.

The main cause of folic acid deficiency is dietary insufficiency together with the increased requirements of folic acid for haemopoiesis after malarial haemolysis.

Haemoglobinopaties:

These diseases, as they affect Nigerians, have been well described by Hendrickse et al (1966). There are three normal human haemoglobins. Haemoglobin F (foetal) is the major type present at birth, but in the first year of life it is replaced by the 'adult' haemoglobins A and A2, the latter being a minor component. Sickle cell haemoglobin has been appropriately called s but other variants have been named alphabetically (commencing with C) or by the hospital, town, or country of discovery.

It has been suggested that the S gene originated in the Middle East, being carried by migration to Africa, India, and Southern Europe (Lehmann, 1959). The highest incidence of this gene reported is in parts of Uganda where 45 per cent of the population carry the trait (Lehmann, 1949). The C gene has its highest incidence in Northern Ghana where frequency of the trait of 21.5 per cent has been reported (Edington 1955). In all the surrounding countries the frequency is lower (Hendrickse et al, 1966).

Abnormal haemoglobins are produced as a result of inheritance of abnormal genes and the structural loci responsible for haemoglobin formation. Clinical effects are seen mostly in those individuals who are

homozygous for the abnormal gene or are heterozygous for two abnormal genes at the same locus. Furthermore, relatively few of the abnormal haemoglobins have seriously deleterious effects even in the homozygous state. Thus, the influence of the haemoglobinopathies on reproduction has been recorded in large series of patients who are S homozygotes, heterozygotes for S & C and combinations of these with thalassaemia, and the hereditary persistence of high foetal haemoglobin.

Anaemia is a major problem and is related to the shortened red cell survival found in these diseases. There is a considerable variation in red cell survival in patients with sickle cell anaemia, with a half-life estimated by chromium^{51} - labelling technique ranging from 2 to 15 days (Sprague and Patterson, 1952; Weinstein et al, 1954; Oliver and Heller, 1959; and Hugh - Jones et al, 1964). Fullerton and Watson-Williams (1962) found that the half-life of cells labelled was between 7 and 21 days in haemoglobin SC disease. The haemolytic anaemia causes increased erythropoiesis, and Movitt, et al, (1963) have shown that the rate of haemoglobin synthesis was increased up to five times that of normal.

Sickle cell disease in Nigeria constitutes a special problem because 24 per cent of the Yoruba's

in Ibadan have haemoglobin S while 5 per cent have haemoglobin C (Lawson 1967). During pregnancy these patients are liable to develop severe anaemia, bone pain crises acute segregation crises, and bone marrow embolism. With good supervision the perinatal mortality in sickle cell disease may not be significantly raised.

Hookworm Infection and Anaemia

Hookworm infection is endemic in Nigeria. It is however difficult to be sure to what extent it is responsible for disease in the community, and what significance to attach to its presence in an individual. Giles (1975) has shown that hookworm anaemia could result if there is a breakdown of adaptation of the parasite. The epidemiology of hookworm infection in man has been well described in details by Gilles (1975).

Although man is the only important source of human hookworm infection, the epidemiology of the disease is dependentupon the interaction of three factors - the suitability of the environment for the eggs or larvae; the mode and extent of faecal pollution of the soil; and the mode and extent of contact between infected soil and skin.

The survival of hookworm larvae is favoured in a damp, sandy, or friable soil with decaying vegetation, and a temperature of 24^{o} - $32^{o}C$. (Gilles 1975). Insanitary disposal of faeces or the use of human faeces

as soil fertilizer are the chief sources of human infection in countries where individuals are barefooted. Thus, it is to be expected that hookworm infection will have a higher prevalence in agricultural than in town workers - and that in many tropical countries it is an occupational disease of the farming community. Experiments have shown that although Necator infection is acquired almost exclusively by the percutaneous route, Ancylostoma infection may be contracted either percutaneously or orally - the latter mode of entry gives special point to the reports of contamination of vegetables by these larvae.

The main feature of the established infection is the production of anaemia. The pathogenesis of the anaemia caused by hookworm is dependent upon three parameters; (1) the iron content of the human diet; (2) the state of the iron reserves; (3) the intensity and duration of infection. These factors will vary in different tropical countries but must always be taken into account for a proper evaluation of a particular situation. Thus in Nigeria, where the iron intake is high, 21 - 40 mg. daily, people whose only pathological source of bleeding is hookworm infection show no evidence of iron depletion, as evidenced by a low serum iron concentration or an

iron-deficiency anaemia, unless they harbour more than 800 worms Gilles et al (1964). Hookworm loads of this magnitude are usually seen in males, who work barefoot and defacecate in the fields. Yoruba women, of Western Nigeria, do not do agricultural work generally, and they do not have hookworm - anaemia.

Iron Deficiency

The first reference to Iron deficiency in pregnancy was made by Watson-William in 1959 in the Annual Report of the Department of Pathology, University College Hospital, Ibadan. Iron deficiency was then reported to be relatively rare in Western Nigeria. Subsequent workers Lawson (1962) Fullerton & Turner (1962) Fleming & Elliot (1964) and Ojo (1965) confirmed that the aetiology of anaemia amongst Nigerian pregnant women were mainly haemolysis related to malarial infection, and folate deficiency.

In 1969 the iron status of anaemic pregnant Nigerians was studied by bone marrow examination (Fleming, 1969). A large series of 248 consecutive pregnant or recently delivered women admitted to the University College Hospital with packed cell volume 23% or less were studied. The majority of these anaemic patients had large deposits of intra-cellular stainable iron. From this elaborate study it was confirmed that iron deficiency was rarely the factor

limiting erythropoiesis in pregnant anaemic Nigerians. Only two patients out of the 248 consecutive admissions with anaemia in pregnancy or the puerperium had possible evidence of iron deficiency and both were amongst the 5 patients with heavy hookworm infection. The low incidence of iron deficiency was explained partly by a high intake of about 40 mg. per day of elemental iron in an absorbable form reported by Gilles et al (1964). From that time on the routine recommendation for expectant Nigerian women of pyrimethamine 25 mg. weekly and folic acid 5mg. daily was extended to patients referred to other Maternity Centres from the University College Hospital, Ibadan. (Appendix 1).

Summary:

Thus, past studies on anaemia in pregnancy in Nigeria showed that the two most important aetiological factors were red cell haemolysis from malarial infection and folic acid deficiency. Accordingly, the recommndation for prophylaxis against anaemia in Nigeria have been the administration of antimalarials and folic acid throughout pregnancy and the puerperium. However, a careful observation is that all these reports were based on studies performed on patients with severe anaemia. The more common milder anaemias were clearly not fully investigated for iron deficiency.

B. MATERIALS AND METHODS

Patients Studied

The study has been on anaemic pregnant patients seen at the Inalende Maternity Centre which is about 4 kilometres from the University College Hospital together with others referred to the University College Hospital, Ibadan (U.C.H.) from other centres seen at different periods between March 1975 to July 1978. They had a packed cell volume (P.C.V.) 30% or less during pregnancy. Ibadan is the Capital of Oyo State and it is situated about 120 kilometres from Lagos, which is the Capital of Nigeria (Appendix 3 . The main study was on patients with mild to moderate degree of anaemia (P.C.V. 19% o- 30%). All subjects were Nigerians. The patients were resident in the western part of Nigeria which is predominantly populated by the Yorubas. There are three main parts in Nigeria, the Northern, Eastern and Western set of states (Appendix 3). Food habits vary from one region to the other but the bulk of the food in all parts is carbohydrate. In the North it is in the form of millet and its products; in the East the main food item is yam while in the western part of Nigeria Cassava (Gari) is the crop most commonly eaten.

The vast majority of the people are illitrates and many people belong to the low income group. The

less educated the family the more children are produced. This factor further aggravates the inadequate economic status of the low socio-economic group.

The study was carried out at several stages as indicated in the various parts of the thesis. Only expectant women with no other complication than anaemia were studied. For example, patients with abnormal haemoglobins were excluded from the study.

Social Classification:

An attempt was made to determine the socio-economic class of each patient. There is no generally recognised method of social classification in Nigeria. Patients in this study were asked five questions and scored 0, 1, or 2 each, giving a maximum score of 10 points. This was the system used by Fleming (1969) in his thesis.

Question 1: Women's own education:

(0) None

(1) Primary 1 - 6

(2) Higher than primary 6

Question 2: Education of Women's Parents:

(0) Neither literate

(1) One parent literate

(2) Both parents literate

Question 3: Husband's Education:

(0) None

(1) Primary 1 - 6

(2) Higher than primary 6

Question 4: Husband's Occupation:

(0) Traditional Farmer - small farm

(1) A modern occupation clerk, teacher etc.

(2) Higher occupationl Lawyer, Engineer, Doctor etc.

Question 5: Residence cf Woman (including environment during childhood):

(o) Grew up in traditional compound or village (no modern amenities).

(1) Grew up in an area with minimum amenities.

(2) Grew up in an environment with modern amenities (urban area).

Patients were later classified as 'upper' socio-economic class - score 6 - 10 and low socio-economic class scoring 0 - 5.

Diet Histories: (with general comments)

Dietary histories were obtained from all the patients. A typical completed questionaire is

shown in Appendix 4. Because these answers were not suitable for careful analysis an additional study was designed to estimate the daily dietary iron intake of patients with iron deficiency anaemia. A research assistant went to the homes of 9 of the anaemic expectant women to carry out the following investigations. Foods consumed by each patient were recorded. The type of food was noted and the amount taken determined by weighing the foods before and after each meal. Samples of meals eaten were obtained and sent to the department of Nutrition, University of Ibadan for estimation of the iron content. This exercise was carried out for 4 consecutive days for each patient. To serve as a comparison, samples of food to 10 patients, over the same period, were collected from the hospital meals which represent an adequate and balanced meal. The average daily available iron were calculated from the foods of each group.

MAIN TYPES OF FOODS

Carbohydrate, Cassava, in the form of Gari, formed the staple carbohydrate. Yam and its products formed the second form of carbohydrate particularly during the dry season. The third staple food for all was maize. This was eaten boiled or roasted as a snack when freshly harvested, but was

used in dried or ground forms throughout the year. Rice used to be something of a luxury but is now fairly common because of the massive importation of this item. It is eaten once or twice a week by the majority of people but dwellers in urban areas eat rice more often 3 - 4 times a week. Plantain usually fried in palm oil (dodo) is another source of carbohydrate. This forms a seasonal additions to the diet. Carbohydrate formed the bulk of all foods of the patients studied.

Fat: The predominant fat source was palm oil, but three of the patients used the more expensive groundnut oil, which is usually used by people of a higher income group.

Proteins: The average money spent on meat by the patients was 30 kobo (20 pence) a day. This sum has been calculated from the patient's answers, which were usually given as the total sum spent for all the family eating from the same pot. Thirty kobo would purchase about 2 oz. (approximately 60 g.) of beef. As a more accurate method of assessment meat eaten once or twice daily were weighed and found to be between 50gram and 120 gram daily. Meat was sometimes supplemented by cows head & leg (which were little more than skin) and small animals (bush meat). Chicken & fowls were occasionally eaten

instead of meat usually on festive days. Dried fish and stock fish (imported)were eaten in small amounts by all patients as an alternative to meat or as a flavouring to soups. All the patients ate eggs, occasionally, two per week being the maximum. It was clear from the completed diet sheets that the protein intake was grossly inadequate.

Vegetables & Fruits: All patients ate various forms of green vegetables (efo) in large quantities added to soups. The soups (made of palm oil, meat or fish, green leaves, onions, tomatoes & peppers) were prepared about two to three times a week and reheated until finished. They were added to the bulky carbohydrates as a sauce rather than as a main item of a meal.

Except during the seasonal period when fruits are in abundance very little fruit was eaten by these patients. Fruits available are oranges (including tangerines) bananas, pawpaw and pineapples.

Antenatal care Before Admission to the Study

Questions were asked as to previous antenatal care. All the expectant mothers were attending the clinic for the first time.

Anti-Malarials Received in Pregnancy Before Attendance to the Clinic

Patients were questioned as to whether they were

taking anti-malarials before reporting for booking. A note was made of the length of time prophylactic anti-malarials had been taken.

Other drugs taken in Pregnancy

Patients were also questioned as to medicines they had been taking, including iron, folic acid, Vitamin tablets and native medicine. Many of the patients were not taking haematinics before reporting for antenatal care. It was, however, a common practice to take multi-vitamin and various blood tonics such as 'Ferbelan' tonic.

The obstetric history included the parity, number of children alive, and time of last pregnancy . A note was made of previous anaemia in pregnancy. The first day of the last menstrual period was recorded in patients who knew it.

Physical Examination

This included height and weight of the patient when first seen.

Period of gestation was judged from the height of fundus as many of the patients were not sure of the exact date of their last menstrual period.

Liver and splenic sizes were recorded in centimetres below the right and left costal borders respectively.

INVESTIGATIONS

The study was a continuous and developing one. Accordingly not all the investigations listed below were carried out on every patient at one time. Thus the first set of patients studied had serum iron TIBC determination; in the second set bone marrow biopsy and some other investigations were added, while patients who had parenteral iron therapy had liver function tests before the administration of iron. The specific tests performed at each stage of the study are reflected by the results stated for the particular group.

Haematology on Admission to the Study

Packed cell volume (P.C.V.) measurements were made using Hawksley Microhaematocrit (Dacie and Lewis 1963), and recorded in percentages. The microhaematocrit has completely replaced the haemoglobinometer as the instrument of routine and emergency investigation at the University College Hospital, Ibadan.

Samples of venous blood were obtained from the ante-cubital fossa (2 ml. in a sequestrine and 10-15 in an iron free universal container). The initial laboratory investigations included the P.C.V., a reticulocyte count, total white blood count and differentials and a blood film for malarial parasites.

Red Cell Appearance:

The usual criteria of size and degree of staining were used to determine microcytes, megaloblasts and hypochromatism. The appearance to the sickle cell form, was considered to be diagnostic of abnormal haemoglobinopathy although electrophoresis was still performed on all blood samples.

Haemoglobin Electrophoresis

Haemoglobins present were identified by paper electrophoresis using tris veronal discontinuous buffer system, p^H 8.6, modified from the method of Watson-Williams and Weatherall (1965) and by Starch gel electrophoresis (Fessas and Mastrokalos, 1959). Patients with any haemoglobinopathy were excluded from the study.

Malarial Parasites

Thick films were examined for the presence of malarial parasites. All films in which parasites were not seen were sent to the laboratory to be examined by a second observer.

Blood Group and Rhesus Factor

Were determined in all patients.

Venereal Diseases Research Laboratory Tests

Venereal Diseases Research Laboratory tests were performed routinely on all the patients.

Bone Marrow Biopsy Erythroid Series

Marrow specimens were collected from the sternum. Smears were made, fixed and stained for iron by prussian blue method using 20% aqueous solution of potassium ferocyamide added to N/5 hydrochloride acid. 1% neutral red was used as counter stain. The degree of iron staining were classified - as follows:

(1) No Iron: absence of stainable iron

(2) Scanty: almost complete absence of haemosiderin granules in sections of marrow stained for iron.

(3) Adequate Iron: Only patients in categories 1 & 2 were included in the drug trials.

Serum Iron and Total Iron Binding Capacity

The serum iron and T.I.B.C. were determined by the method of William & Conrad (1966).

Liver Function Tests (Mohun & Cook 1957)

Were carried out by standard methods on all patients before and 4 weeks after drug therapy.

Microscopy of Faeces for Hookworm Ova:

A suspension of stool was scanned for hookworm ova. In those patients in whom the hookworm load was heavy, counts of ova were made and expressed as ova per gram of faeces. The degree of hookworm infestation was graded as follows:

(1) None seen

(2) Scanty - less than 4 ova per high power field

(3) Heavy - more than 5 ova per high power field.

This test was carried out on 94 patients studied and there was no significant finding from the report of of Gilles (1964) that hookworm load are generally low in Nigerian women.

Urinalysis

A midstream specimen of urine was obtained from each patient by a trained nurse. This was collected in a sterile container and immediately sent to the laboratory for microscopy and culture for bacterial organisms.

Dietary Iron

Diet samples obtained from 9 randomly selected anaemic patients were analysed. To serve as a control diet samples were also collected from the University College Hospital, Ibadan wards as they were being served to 10 pregnant and non-pregnant women. As soon as the foods were collected, they were weighed and transported to the laboratory for preparation before the determination of Iron. Preparation involved blending whole diets in a quartz mortar with a pestle. After thorough mixing, the

samples were put in clean plastic plates and dried at 80°C. in an air oven to constant weight. The dried samples were then sub-sampled by weighing out in duplicate 2g into clean silica crucibles and then dried to constant weight in an air oven, this was immediately followed by dry ashing in a muffle furnace at 450°C. for 16 hours. The residual white ash was dissolved in 2 ml. of concentrated nitric acid and solution diluted with deionized water after being transferred to a 250 ml. standard flask. 2 ml of 5% Lanthanum solution was added and the solution made up to the 250 ml. mark with de-ionised water.

The iron content of diets were then determined in these solution with the Atomic Absorption Spectrophotometer (Perkin Elmer model 305B) and the appropriate hollow Cathode lamp using a wavelength of 248.3nm. Results read off from the calibration curve were multiplied by the appropriate dilution factor to arrive at the iron content of diets.

Treatment and Progress

As an additional test of iron deficiency, during the second study period, patient with absent iron in the marrow were given iron supplements and the response to therapy monitored. Thus, the eighty-four anaemic pregnant patients found to be iron deficient,

were randomly split into two groups for the purpose of treatment and follow-up studies. Sixty-one patients received parenteral iron in the form of intramuscular iron sorbitol-gluconic acid (Ferastral^{R}) in doses calculated from the manufacturers table (Appendix 5). Required dosage related the P.C.V. level to the body weight in kilogram. Twenty-three patients were treated with oral iron supplements (Ferrous sulphate 200 mg. thrice daily throughout pregnancy).

In a supplementary study carried out between November 1977 and April 1978 sixty-two patients with iron deficiency anaemia were treated with two different parenteral iron preparations. Thirty-two were treated with Ferastral, while thirty patients received imferon by total dose infusion. Irrespective of the form of iron therapy all patients received the routine prophylaxis of pyrimethamine (25 mg.) weekly and Folic acid 5 mg. daily.

The antenatal patients were seen at the clinic at weekly or two weekly intervals depending on the stage of gestation when first seen.

Progress of response to treatment was assessed by estimation of the reticulocyte counts on patients admitted to the hospital for treatment but principally

by the estimation of the packed cell volume of the patients at each visit to the antenatal clinic.

Repeat Marrow Biopsies After Iron Therapy

During the study period December 1975 to April 1976 when Eighty four anaemic expectant mothers were examined for iron deficiency their response to iron therapy was noted. A repeat marrow examination was performed on samples, randomly selected, from 3 patients who received oral iron and 13 patients who had intramuscular iron. A further repeat marrow biopsies were performed on twenty one patients who had parenteral iron in another study (10 from Ferastral Group and 11 from Imferon Group) - November 1977 to April 1978.

After delivery a note was made of the foetal state by assessing the Apgar Score of the babies 1 minute after delivery. The birth weight of each child was also recorded.

C. DIAGNOSIS OF IRON DEFICIENCY ANAEMIA AMONG NIGERIAN PREGNANT WOMEN BY SERUM IRON/T.I.B.C. DETERMINATION (March 1970 to July 1975)

The diagnosis of iron deficiency is often made upon the characteristic finding of microcytic hypochromic erythrocytes by indices and or morphology (Stevens,1956). In Nigerian women, red cell morphology has been found to be unreliable because of the dimorphic appearance produced by folic acid deficiency and haemolysis from malarial infection (Fleming, 1969). Holly, 1953; Lawrence 1962; Bainton Finch, 1964; Committee on Maternal Nutrition 1970; and Hellmann and Pritichard, 1972 also reported that the peripheral blood smear is not often helpful in the diagnosis of iron deficiency during pregnancy except in long standing cases. Other tests used in establishing the diagnosis of iron deficiency anaemia have been the mean corpuscular haemoglobin concentration (M.C.H.C.), the mean corpuscular haemoglobin (Stevens, 1956) as well as serum iron determination (Holly, 1955, Lawrence, 1962) and/or bone marrow examination (Chanarin, Rothman & Berry, 1965). Although a sensitive diagnostic test when properly performed, a bone marrow examination is probably not widely utilized except in severe anaemia (Hamilton et al, 1972). Therefore to investigate our patients for iron deficiency, the first method used, which is

quite simple to perform, was the determination of saturation of serum transferin (Fe/T.I.B.C.).

Serum iron determination has been reported to be a satisfactory method of diagnosing iron deficiency anaemia. It has been shown that when the serum iron (Fe) was less than 16% of the total iron binding capacity (T.I.B.C.), a state of iron deficiency existed (Bainton & Finch, 1964; Carr 1971 & Fairbanks, 1971). In 1974, Carr studied 62 pregnant women with various Fe/T.I.B.C. Below 20% responded to iron with a significant mean increase in haemoglobin and restitution of mean Fe/T.I.B.C; above 20% showed no mean increament in their haemoglobin after comparable treatment. This finding supports the concept that Fe/T.I.B.C. ratio is as useful a test for evaluating iron deficiency in the pregnant as in the non-pregnant state.

The purpose of this study was to determine the magnitude of the problem of iron deficiency in mild degrees of anaemia in pregnancy and thereby suggest the need for further investigations of iron deficiency. This section will present data from a group of pregnant women. The relationship between a depressed Fe/T.I.B.C. (less than 18%) and haematological response to folic acid, principally the packed cell volume was examined.

Fifty-five pregnant patients with a haemoglobin of 10 grams% (P.C.V. 30%) or less attending the ante-natal clinic of the University College Hospital, Ibadan (U.C.H.) constituted the first set of anaemic expectant women studied. Only patients in the first and second trimesters of pregnancy were included in this study to permit an adequate follow-up of the haematological response to folic acid (5 mg. daily), the haematinic normally prescribed to pregnant women in this hospital.

After an initial dose of chloroquine sulphate (800 mg.) to eradicate malarial parasitaemia, chemo-prophylaxis with pyrimethamine 25 mg. was prescribed weekly.

The peripheral films were reported upon by the same haematologist to ensure consistency.

All the patients in this study were accepted for ante-natal care and delivery at the U.C.H. and the more anaemic patients were admitted to the wards after pre-liminary investigations. Patients who were admitted to the study were followed up at 2 weekly intervals for a period of at least 8 weeks.

Of the 55 patients who had full haematological tests, 41 patients were followed serially because 14 patients defaulted. There are therefore 2 sets of results viz:

(i) the results of the blood tests on all the 55 patients studied, and

(ii) the results of the response to the administration of anti-malarial and folic acid on 41 patients.

Clinical Features & Results

The parity distribution of the patients studied is shown on Table 2A and shows that most of the patients studied were multiparous. Table 2B shows the distribution of the Fe/T.I.B.C. ratio in relationship to the parity. In the iron deficient group at percentage saturation of 18 or less, 95% were parous women.

Table 3 shows the period of gestation at the first visit to the clinic. The majority of patients reported in the second trimester of pregnancy.

Splenic enlargement was present in 5 patients and in one of these the liver was also enlarged.

Laboratory results

Blood film: Fifty films showed a normocytic dimorphic picture suggestive of both iron and folic acid deficiency.

Malarial parasites: Only three of the 51 films showed the presence of malarial parasites.

Serum Iron/T.I.B.C. Ratio: The distribution of the groups under study in terms of the Fe/T.I.B.C. ratio

in table 4A.

Thirty patients (58%) had saturation values of less than 18%. When the Fe/T.I.B.C. ratios in these patients were compared with their blood film appearance, in only 5 patients who had low values did the blood film show evidence of iron deficiency.

Table 4B shows the distribution of the percentage saturation of Fe/T.I.B.C. with respect to the trimesters. It shows that iron deficiency anaemia as suggested by a low percentage saturation was more common in the first and second trimesters of pregnancy among our patients.

Response to Folic acid and Pyrimethamine

Table 5 shows the initial characteristics of the two groups with respect to their serum iron levels and saturation. It also shows the respone to treatment with folic acid using the packed cell volume level as an index monitored fortnightly over a period of eight weeks.

From the table it is evident that the two groups had the same mean P.C.V. levels initially. With treatment, in each group there is a significant rise in the mean level at the end of four weeks. Thereafter group A showed no further increase in the mean P.C.V. while group B continued to show a steady and significant rise as illustrated in Figure 1.

At both six and eight weeks, the mean levels of P.C.V. for group B were significantly higher than the corresponding ones for group A (0.02 P0.01 and 0.005 P0.001 respectively).

Discussion

Iron deficiency anaemia is recognized as widespread in the female, especially during pregnancy when the need for iron by the conceptus, the placenta and the mother's expanding blood volume is substantial (Gelfand, 1968). The anaemia of iron deficiency has for long been associated with microcytic hypochromic red blood cells. In the present group of patients, the examination of the blood film was not found to be useful. Only 5 films showed a hypochromic, microcytic appearance. The remaining patients possessed indices within normal limits, and were therefore in a stage in which the aetiology of the anaemia might not have been appreciated, if only the red cell indices were relied upon. In this regard, we agree with Carr 1971 and Fairbanks 1971, that the red cell morphology and M.C.V., M.C.H.C. are very unreliable in the diagnosis of iron deficiency anaemia.

Thirty patients had depressed Fe/T.I.B.C. (18% or less). Twenty of them had a serum iron levels of 60ug/ 100 ml. or less. These low values are accepted as diagnostic of iron deficiency anaemia (Holly, 1955 &

Fairbanks, 1971). Thus, by applying a critical Fe/ T.I.B.C. ratio of 18% or less, 58% of the patients studied were found to be iron deficient.

Iron deficiency was found to be more common in parous women, most probably from the prolonged blood loss through menstruation and during previous deliveries. Iron deficiency anaemia, amongst the patients studied, was also more prevalent in the second trimester - the period of most rapid foetal growth, during which the utilization of iron and folic acid is high. None of the patients was in the third trimester of pregnancy in order to permit adequate follow up following treatment with iron preparations. As a result, it was impossible to assess the prevalence of iron deficiency during the last trimester of pregnancy.

Apart from the foetal needs from the second trimester of pregnancy some decrease in haemoglobin concentration is inevitable as the plasma volume always increasesto a greater extent than the total red cell volume (Caton et al, 1951; Berlin et al, 1953 and Paintin, 1962). The demands for iron has been shown to be significantly increased during the later half of pregnancy (Pritchard and Scott, 1970), although Fenton et al reported that the decrease in iron stores begins early in pregnancy (1977).

Some workers, Fisher and Briggs (1955); Kerr and Davidson (1958), have shwon that as pregnancy proceeds most women show haemotological changes suggesting iron deficiency. Sturgeon (1959), Morgan (1961), and Painton et al (1966) have even demonstrated a moderate fall in the plasma-iron and a rise in the T.I.B.C. from the second trimester of pregnancy. Even with the awareness of these physiological changes the Fe/T.I.B.C. ratios observed in the patients studied were so abnormal as to make the results significant. Besides, all the patients had a P.C.V. below 30% (Haemoglobin value 10g. per 100 ml.). It has been shown that at this level of haemoglobin there is often a deficiency of iron (Paintin et al, 1966).

The response to the administration of folic acid in the group with normal Fe/T.I.B.C. ratio was statistically significant if compared with those with a low Fe/T.I.B.C. ratio. The poor response of patients with low Fe/ T.I.B.C. ratios to oral folic acid (Table IV) gives additional support that these patients required more than just folic acid and anti-malarials for the correction of anaemia. They probably required iron supplements as well.

Patients with severe anaemia (P.C.V. less than 18%) had normal to high Fe/T.I.B.C. ratios confirming the reports of Fleming, Hendrickse & Watson-Williams (1969)

and Harrison (1975), that in severe anaemia in pregnancy iron deficiency is rare in Nigerians. However, quantitation of serum iron/T.I.B.C. ratio has shown a significant incidence of iron deficiency amongst our expectant mothers with mild to moderate degree of anaemia.

Summary

Fifty-five patients have been investigated for anaemia in pregnancy. Using the serum iron/T.I.B.C. ratio as a diagnostic index, there was a strong suggestion that iron deficiency existed in approximately 60% of our expectant women with mild anaemia. This type of anaemia was more common in multiparous women and more prevalent in the second trimester of pregnancy.

Further studies to determine the actual incidence and aetiology of iron deficiency anaemia during pregnancy was thus indicated.

D. IRON DEFICIENCY ANAEMIA IN NIGERIAN PREGNANT WOMEN (USING BONE MARROW AS THE DIAGNOSTIC INDEX) - INCLUDING AETIOLOGY (DECEMBER 1975 - April 1976)

From the last section it became evident that iron deficiency anaemia is not as uncommon as previously suggested by earlier studies. It was therefore necessary and important to investigate further the prevalence and aetiology of iron deficiency during pregnancy among our expectant women. This section deals with re-evaluation of the iron status of anaemic Nigerian women by bone marrow biopsy.

Between December 1975 and April 1976, patients attending the Antenatal clinic, Inalende Maternity Centre at Ibadan, with haemoglobin estimation of 10g% (packed cell volume 30%) or less were selected for further investigations. Patients with clinical evidence of any infection were excluded from the study. Also excluded were those with abnormal haemoglobin genotype (SS or SC) and those who had had any form of bleeding during the current pregnancy.

The investigations carried out on each patient included estimation of the packed cell volume (P.C.V.) using the micro-haematocrit technique, peripheral blood smear stained with leishman stain, serum iron, total iron binding capacity T.I.B.C.) and bone marrow aspiration. The bone marrow specimen was obtained

from the sternal bone puncture.

Eighty-four anaemic pregnant patients found to be iron deficient, were randomly split into two groups for the purpose of treatment and follow-up studies. Sixty-one patients received parenteral iron in the form of intramuscular iron sorbitol gluconic acid (Ferastral) in doses calculated from the manufacturers table, which related the P.C.V. level to the body weight in kilogram; while 23 patients were treated with oral iron supplements (Ferous sulphate 200 mg. thrice daily throughout pregnancy). All patients were given chloroquine sulphate 800 mg. at first attendance to the clinic. Malarial prophylaxis was maintained throughout pregnancy with pyrimethamine 25 mg. weekly. Folic acid 5 mg. daily was also prescribed for all the patients.

The parity distribution of the patients studied is shown in table 6 and table 7 shows the stage of gestation at first attendance at the clinic.

Results:

Eighty-four of the (94) patients studied (i.e., 90%) were found to be iron deficient by absence or very scanty iron stores in the bone marrow. The relationship of the percentage saturation of iron to the bone marrow appearance in the patients studied

has been reported by Olubcyede (1977). In Nigerians, percentage saturation of 25% or less correlated well with absence of iron in the bone marrow. The outstanding feature of these patients was that 70 of the 94 patients studied were of low socio-economic group. Fifteen other patients scored a little over 5 points of the socio-economic classification, used for our patients. Only 9 patients were regarded as clearly in the upper social class.

Asymptomatic bacteriuria was present in 10% of the specimen obtained from 84 patients. Three of these patients had urinary tract infection due to Escherichia coli, Staphylococcus aureus and Klebsiella organisms. They were treated with the appropriate antibiotic accordingly to the sensitivity results.

Stool results obtained for hookworm ova count are shown in Table 8. Significant hookwom infestation was present in only 4% of the patients.

Malarial parasites were seen in 4 of the 84 films examined.

Haematolcgical response

Response to iron therapy is shown on Table 9. There was improvement in the two groups although the group that received the intramuscular iron preparation had a better response (Figure 2).

Discussion

Iron deficiency anaemia amongst Nigerian pregnant women is not as uncommon as previously suggested. The earlier impression of the rarity of this condition was based mainly on findings from the study of only severe cases of anaemia - a condition which accounts for less than 10% of anaemic patients seen in most ante-natal clinics in Western Nigeria, Ojo (1965). In this study, only 6% of the patients studied were severely anaemic - (Table 10).

The concept of adequate iron in the diet in Nigeria is based on the report of Gilles (1964) that the average Nigerian has an adequate nutrition from a high iron content in their foods. High iron content of some soils may provide excessive iron in foods, but this does not necessarily mean that iron deficiency could not occur. For example, in the Gambia, a high iron content of the soil exists and yet iron deficiency anaemia is prevalent (Topley, 1968). Here in Nigeria, malnutrition is very common particularly in [illegible] patients of low socio-economic group. Therefore, although our foods have been found to be rich in iron (Gilles, 1964, Gilles, 1975), it does not follow that the average person would be able to make available to himself, the required amount to keep him in a positive iron balance.

Iron deficiency anaemia is present in 90% of our expectant mothers with mild to moderate anaemia (P.C.V.) 20 - 30%). The cause, following the suggestion of Lawson (1971) is most probably dietary deficiency anaemia from general undernutrition. Furthermore blood loss from hookworm infestation was uncommon in the group of patients studied and abnormal haemoglobin genotype had been excluded. An additional confirmation of the presence of iron deficiency anaemia in these patients was the clinical improvement and the therapeutic response as indicated by increase in the packed cell volume level after treatment with iron preparations.

Although like others (Baintin & Finch, 1964, Carr, 1971; and McFee, 1973) we had found the serum iron/T.I.B.C. determination useful in the diagnosis of iron deficiency anaemia(Ogunbode et al, 1976) it was clear from the present study that the lack of stainable iron in the bone marrow is the best method of diagnosis. Marrow examination improved the detection of iron deficiency from 60% (Ogunbode et al, 1976) to 90%. However, in agreement with the opinion of McFee (1973) this procedure should not be used routinely on initial evaluation and it should be done during pregnancy only when an anaemia is severe and when diagnosis is not apparent by other simpler methods. The procedure

was used on these patients in order to have an accurate assessment of iron deficiency anaemia among our expectant mothers.

Clinical microcytosis and hypochromia was present in only 4 of the 84 films examined. Most of the films (80) showed a dimorphic picture of microcytosis and megaloblastosis. This finding supports the reports of Bainton & Finch (1964), Lawrence (1962), Deleeuw et al (1961) and McFee (1973) that the peripheral blood smear is not often helpful in the diagnosis of iron deficiency anaemia. This is more so in areas of multiple deficiencies.

Significant asymptomatic bacteriuria was present in 10% of the patients. This is similar to the report of Ojo & Akinkugbe (1976) on urine specimen obtained from 2,588 pregnant patients. Patients who had overt infection were treated with the appropriate antibiotics. The response of these patients to iron therapy was, as would be expected, poor while the infection was being treated.

From the present study, it is clear that the majority of our expectant women with mild to moderate degree of anaemia have iron deficiency.

Summary

Ninety-four Nigerian pregnant women, many of who had mild to moderate anaemia, were investigated for the

presence of iron deficiency. Using the bone marrow as the diagnostic index, 90% of these patients were found to be iron deficient. Iron deficiency is thus common among our expectant women and the cause is most probably nutritional. There is therefore, a need to look into the nutritional status, with special reference to the dietary iron, of patients who are iron deficient during pregnancy.

To reduce this high incidence of mild to moderate anaemia in our pregnant patients they should be advised to have a better nutrition and they should have iron supplement in addition to the present routine of folic acid and anti-malarials, throughout pregnancy and the puerperium.

DIETARY IRON INTAKE OF ANAEMIC NIGERIAN EXPECTANT WOMEN (Nov. 1977 - April 1978)

Investigations into the aetiology of the iron deficiency strongly suggested undernutrition because it was not found to be associated with any particular complication of pregnancy including endemic parasitic infections like malaria and hookworm. The main characteristic of these anaemic patients was that they belonged to the low socio-economic group. The present study was therefore designed to estimate the average iron intake of patients who present with anaemia during pregnancy. To serve as a control the dietary iron from Nigerian foods served in the University College Hospital Ibadan to expectant women was also determined.

Materials and Methods: as previously described.

Results

The dietary history from completed questionaire was much different between the two groups of patients studied. The nine patients with anaemia lived mainly on gari - carbohydrate and usually had two meals a day. The protein consumption was very low. Animal protein in the form of meat when included in the meal constituted less than ten per cent of each meal. A typical diet is shown on Appendix 4. On the other hand, the hospital patients were served meals which contained a variety of carbohydrate and the foods were rich in animal proteins. Three main meals were

served to the patients in hospital.

Dietary iron intake

Patients in the hospital took about 3.5 kg. of foods daily. The mean daily dietary iron in the hospital foods was 36.72 mg. with a range of 25.09 to 46.47 mg. Except for 2 patients in the anaemic group with daily iron intake of 21.62 mg. and 23.72 mg. respectively the other patients had a daily iron intake below 14 mg. The mean daily iron intake in the anaemic group was 13.23 mg. with a range of 8.37 to 23.72 mg. Table 11 shows the comparative daily iron intake in the 2 groups of patients. The iron contents of our foods taken in the right proportion is much higher than that reported for the United Kingdom by the National Food Survey Committee (1961), who found that families containing an expectant mother had an average of 17.9 mg. iron per head per day.

The iron content of the common foods consumed by the inhabitants of the Western part of Nigeria is shown on Table 12. It can be seen that gari had the least iron content with yam flour and ground beans with condiments having a relatively high iron content.

Discussion

Lawson (1971) thought that anaemia was commoner in pregnancy in the tropics because of dietary deficiency of iron and folic acid. He, however, did not give the

daily consumption of these blood forming substances. Iron deficiency had, all along, been considered to be unimportant in Nigeria because of the richness of iron in our foods. It is true (table 12) that the main food items of the people of the Western Nigeria are rich in Iron, in support of Gilles reports (1964 and 1975). What is not true is that the average Nigerian can at the moment afford an adequate and balanced diet. Patients with an average intake of 13.23mg. are by no means the poorest in the community. They probably represent the upper low class. Even in this group 40% of them had a daily intake of less than 10 mg. of iron in their diet.

Food intake of any individual is understandably determined by economic sufficiency. The restricted intake of food can be further aggravated by tribal taboos, by pregnancy, anorexia and by ignorance of the need to take an adequate, balanced and nutritious diet during pregnancy. All these factors combine to favour the development and exacerbation of the anaemic state.

The two patients with tolerable dietary iron intake 21 - 22 mg. daily, and yet who were anaemic probably have a combination of causes for their anaema, including folic acid deficiency, malarial infection, malabsorption and

general undernutrition.

Iron supplements during pregnancy is thus clearly a necessity in our environment because the vast majority of the people cannot afford the hospital type of meals which have been found to be of high iron content.

SECTION ONE - CONCLUSION

The Western world shows an almost uniform pattern of marginally sufficient intake of absorbable iron, with deficiency arising whenever there are high physiological demands (for example during pregnancy, in infants and in post-pubertal girls) or from chronic blood loss (Widholm et al 1967, Scott & Pritchard, 1967, and Rogers et al, 1968). In contrast, iron status in the tropics shows wide variation between communities and between individuals because of large differences of iron intake from food, absorption and blood loss.

In Nigeria, the iron status of patients with mild to moderate degree of anaemia which constitutes the commonest form of anaemia now seen in our ante-natal clinics have been determined as described in the foregoing section. Clinical trials have shown that iron deficiency anaemia is very common in expectant women in Western Nigeria. Similar prevalence was reported at the first international conference of the Society of Obstetrics & Gynaecology held in Ibadan, Nigeria, in October 1977, from other parts of the country, Eastern Nigeria (Chukudebelu), Lagos (Akinsanya) and Kwara State (Oloruntoba).

The most significant feature of these patients is that they belong to the low-socio-economic group.

Their foods are very poor in animal protein which is a good source of organic iron (World Health Organisation 1972). The foods in Southern Nigeria had been reported by (Gilles 1964, Ball, 1966 & Gilles, 1975) to contain sufficient iron-30-40 mg. per day and this has been confirmed by the present study. All the same, the iron content of the individual's diet may itself be wholly inadequate. The daily iron intake from cooked foods by a sample of anaemic expectant Nigerian women was 13.23 mg. daily. Therefore, in agreement with Topley (1968), even with high iron content in soils and foods iron deficiency could still be very common, as in the Gambia.

There are some additional factors that may account for the present high incidence of iron deficiency anaemia in our population. The first is the change in dietary habits. The use of iron pots for cooking and for brewing beer is a recognised inorganic source greatly raising the dietary iron among the Bantus of South Africa (de Bruin et al 1968, Bezwoda et al 1975). In Nigeria, the traditional clay and iron pots have been replaced by aluminium pots. This is a possible cause of reduced iron component of a diet that may be already inadequate in iron content.

Another factor that has come into play is that food habits are changing rapidly in the cities and

becoming more like those of the Western Countries. Eggs were once for the rich, but are now readily available and when consumed in excess may contribute to a low iron absorption, because iron is chelated into non-absorbable complexes by ligands from eggs. Polished rice has flooded the country (in 1977 rice import to Nigeria was estimated at 400,000 tonnes) and with its high phytic content could result in some degree of malabsorption of iron.

Thus, the poor diet of the low socio-economic group together with the change in dietary habits, brought about by 'civilization', would explain why iron deficiency associated with pregnancy and other types of high physiological demand is becoming more common as predicted by Ball (1966), twelve years ago.

Problems Associated with Anaemia in Pregnancy

This is well documented by Harrison (1975) writing on severe anaemia.

(1) Work capacity is severely limited by anaemia (World Health Organisation 1975).

(2) All complications of pregnancy are aggravated by anaemia.

(3) Even if the mother is treated successfully, foetal loss is still above 30%, if maternal haemoglobin is below 7.09% (Fleming 1974).

(4) Post-partum haemorrhage and puerperal complications are more common in anaemic patients.

Prevention & Treatment

It is clear that generalisation cannot be made and that every community has to be studied as to diet, social habits, parasitology and haematology before conclusions are reached concerning the aetiology, prevention and treatment of anaemias. Prevention is the final aim. As for iron deficiency, the most important single requirement is that the average Nigerian should be able to have an adequate and balanced diet. To achieve this end, efforts must be made to improve the socio-economic status of the population. In this regard, the Federal Nigeria Government has embarked on three programmes which hopefully would being about the desired changes. The first is the Universal Primary Education Scheme. By this, every child must attend school from the age of 6 years. This programme would make it possible for people to become aware of their needs when they acquire a better understanding of information being disseminated. This would allow them make the best use of the limited available amenities at the moment. The second programme is the gigantic farming scheme aimed at increasing food production. Included in this scheme is storage of foods which would

make food available all the year round. By increasing production, prices are bound to come down to bring an adequate and a more balanced diet within the purchasing power of the population. The third programme is family planning which is being extended to the rural areas. Previously the Family Planning Units were situated in the urban areas. With the expansion of this programme; the diminishing traditional and religious resistance to family planning as a result of improved medical services; and economic realities, it should be possible to arrest the rapidly rising population.

The present study has contributed new knowledge to obstetric practice in Nigeria, by giving evidence of the prevalence of iron deficiency during pregnancy. The need for iron supplementation has also been clearly demonstrated.

Clinicians in the tropics will for some time continue to see patients with more severe forms of iron deficiency anaemia. Treatment has to be given to them. The next section examines different methods that can be used in treating iron deficiency anaemia among our patients, who are usually first seen late in pregnancy.

SECTION TWO

A. PARENTERAL IRON THERAPY FOR PATIENTS WITH IRON DEFICIENCY ANAEMIA (Dec. 1975 - April 1976)

Introduction

It is accepted that there is a place for parenteral iron therapy in obstetric practice (Basu, 1963 & Varde, 1964). The degree of use would depend on the environmental circumstances and personal experience of the practitioner.

In Nigeria, iron deficiency anaemia has now been found to be common in patients with mild to moderate degree of anaemia. Many of these patients (at least 80%) first report in the second and third trimesters of pregnancy. Many of them cannot be relied upon to take oral drugs--this is not peculiar to Nigerians. Groden and Will (1968) and Sadeghi (1976) have demonstrated that people have difficulty in keeping appointments and following instructions in using their medications once outside medical supervision. Moreover, blood is very scarce here because of inadequate blood donation and increased demands by health care expansion. The blood position is made worse by further demands caused by increasing industrial and automobile injuries. Therefore, because of the prevailing circumstances, it is important to assess the efficacy including safety of parenteral iron in the management of patients with established iron deficiency anaemia.

Three parenteral iron preparations are well known; iron-dextran (Imferon^{R}) has been widely used in the treatment of iron-deficiency anaemia in pregnancy (Basu 1963, Varde, 1964, Dawson et al, 1965, Davies et al, 1971) and in the treatment of anaemia resulting from blood loss (Ferastratopaulos et al, 1973, Ogunbode & Ayeni, 1973).

However, iron-dextran has been reported to have undesirable reactions (Lane & Scott, 1965; Machasin & Wallenstein, 1964; Clay et al, 1965, Manson, 1965, Callender, 1974). Iron-sorbitol (Jectofer^{R}) has also been used for a few years with good haematological results in the treatment of iron deficiency anaemia. It is a complex of low molecular weight, and it is rapidly absorbed from the injection site via the capillaries as well as by the lymphatics. The recommended daily dose is limited to 1.5mg. of iron per kg. body-weight. It has, therefore, to be administered over a long period in order to achieve satisfactory haematological response. The third preparation at present available is dextriferron (Astrafer^{r}), an iron-carbohydrate complex, for intravenous injection only. This has not been widely used in clinical practice. Its special quality is that it is neutral in reaction and thus does not irritate the vascular intima when given intravenously.

This report represents experience with a new parenteral

iron preparation, iron-poly (sorbitol-gluconic acid) complex (Ferastral^{R}) Domeij et al 1977, which can be administered intramuscularly in high doses without discomfort to the patient, in pregnant women with established iron deficiency anaemia.

MATERIALS AND METHODS

Eighty-four anaemic expectant mothers with packed cell volume (P.C.V.) less than 30% attending the ante-natal clinic at the Inalende Maternity Centre and the University College Hospital, Ibadan, between December 1975 and April, 1976 were admitted into the trial.

The existence of iron deficiency was established by bone marrow aspiration. Only patients with absent stainable iron or scanty iron in marrow aspiration were included. Bone marrow smears were obtained by sternal aspiration and prepared in the manner described in (Section One B.).

Table 7 shows distribution by gestational age at the time of entry into the trial. A high proportion of the women (about 39% for the oral iron group and 36% of the Ferastral group) were in the last trimester. The two groups were closely comparable with regard to parity.

The amount of Ferastral given to each patient was calculated from the manufacturer's table according to initial P.C.V. and patient's weight, plus a further 1000 mg. By this calculation, the total dose given ranged from 25 ml.

to 40 ml. Ferastral 500 mg. (10 ml.) was given intramuscularly (5 ml. in each buttock) on alternate days. The more severely anaemic patients were admitted to the wards for treatment; most were treated as outpatients.

Sixty-one patients were treated with Ferastral and 23 patients received 200 mg. ferrous sulphate orally thrice daily. In all patients, response to treatment was assessed by weekly or twice weekly determinations of haematocrit, depending on the stage of gestation. Reticulocyte counts were also determined 6-7 days after commencement of treatment.

All patients were observed carefully during the period of treatment for reactions to treatment. The effect on the foetus was assessed by Apgar score, taken one minute after birth, and recording of birth-weights. The placentae were also examined histopathologically for possible effects of treatment with Ferastral.

Results

The 61 patients who initially received Ferastral have been divided for analysis into two groups consisting of 51 and 10 patients, respectively, The latter group consists of those defaluted after the initial selection but who were subsequently traced and restarted on treatment.

Haematological

The response to the drugs as measured by the mean P.C.V. for the group of 51 patients on Ferastral and for

the 2[illegible] patients on oral iron are shown in Table 13 and Figure 5. Response among the "defaulters" (Table 14) showed a pattern similar to the others, but the mean values were slightly higher at each stage of observation. Incorporation of the results in this groups with the main group of 51 on Ferastral did not affect the pattern of results illustrated in Figure 2.

Initially, the oral iron group had a higher mean P.C.V. ($P < 0.001$) than the Ferastral treated group. Two weeks later, the Ferastral group had achieved similar levels to the oral iron group. At four weeks, those receiving Ferastral had a significantly higher ($P < 0.005$) mean P.C.V. than the group on oral iron. The superiority continued to the eight week.

Table 15 and Figure 3 show the response of the Ferastral group classified by severity of anaemia at entry into the trial. The increases in P.C.V. among those with severe anaemia were much more rapid than for the less severe anaemia.

Other observations

None of the patients had local or systemic reactions. The liver function tests were normal before and four weeks after treatment with Ferastral. The serum creatinine concentrations were within the normal range and generally the value increased with advancing gestation. Significant

asymptomatic bacteruria was present in 10% of the patients. This is similar to the report of Ojo & Akinkugbe (1976) on urine specimen obtained from 2,588 expectant mothers. The examination of faeces showed hookworm infection, sufficiently great to cause anaemia from blood loss in only 4% of the patients examined (Table 8).

Malarial parasites were seen in four blood films. Marrow-iron absent before therapy was restored in 12 of thhe the 13 patients treated with Ferastral (Table 16) whereas there was no restoration of iron in the marrow of the three retested patients who received oral iron.

All the babies born were of good weight, above 2.5kg. with a mean of 3.4 kg. Except for one baby with Apgar score of 6, the state of each baby at birth was excellent. placental examination, both macroscopic and microscopic sh placental abnormalities and there was no stainable iron observed in sections (Abioye 1976).

Discussion

Although in Nigeria there are other important causes of anaemia in pregnancy, it has been found that most cases with mild to moderate degrees of anaemia are due to iron deficiency. This is in agreement with recent reports from many parts of the world (Woodruff, 1972, McFee, 1973, & Nnonolli, 1974). A simple method of treatment is oral administration

of iron, but when a rapid replenishment of iron is desired, as in our patients, many of whom report late in pregnancy, and who may not often be seen in the ante-natal period, parenteral therapy is preferred.

In this study, using iron-poly (sorbitol-gluconic acid) complex as described above, the overall clinical response was good, and correction of anaemia resulted in all but two of the patients so treated. The response was statistically significantly better than the oral iron group which was comparable to the Ferastral group in terms of gestation of parity. The initial response to iron-poly (sorbitol-gluconic acid) complex was excellent as indicated by reticulocytosis and resulted in elevated haematocrit values with a higher rate of rise in the more anaemic patients (Figure 3).

Complete correction of anaemia was achieved in most patients between the 4th and 6th week of treatment. This means that this preparation can be used as late in pregnancy as the 36th week to correct iron deficiency anaemia, a clear advantage in an environment where more than a third of the patients are first seen in the third trimester of pregnancy.

This preparation not only corrects the anaemia but restores marrow iron. This is a great advantage in an area where parasitic infestationsare endemic. Treatment of iron

deficiency anaemia with parenteral iron will therefore protect against early recurrence of anaemia when subsequent re-infestation occurs.

Babies born after treatment with Ferastral were of good birth-weights, greater than the average for Nigerian babies (Effiong et al 1976), and were in good condition as judged by Apgar scores. The reason for this is most probably in part, a result of the correction of the anaemia before birth and is in agreement with the report by Harrison (1974). Histopathological examination showed no abnormalities of the placenta (Abioye 1976).

Conclusion

In view of the good clinical improvement observed, the satisfactory haematological response, the restoration of iron to the bone marrow, and the relative absence of complications in patients treated with Ferastral, it is concluded that parenteral iron in the form of iron poly (sorbitol-gluconic acid) complex is a practical and effective form of treatment for iron deficiency anaemia in pregnancy, particularly in our environment.

It also has economic advantages as the period of hospitilization can often be shortened and the frequency of blood transfusion reduced.

Summary

The treatment of iron deficiency anaemia in pregnancy with a new parenteral iron preparation, iron poly (sorbitol-gluconic acid) complex (Ferastral^{R}), has been assessed and compared with oral iron therapy. Sixty-one of the eighty-four patients studied, many of whom had mild to moderate degree of anaemia were treated with Ferastral. The results were satisfactory, the mean increase of haematocrit at the sixth post treatment week was 28.7% for the whole series. The mean haematocrit of the group treated with oral iron was initially significantly higher than for the group treated with Ferastral. At the first follow-up, two weeks after beginning treatment, the mean values for both groups were similar; at four weeks, those receiving Ferastral had a significantly higher mean P.C.V. than those on oral iron, and remained so through the period of observation. No side-effects were detected using 10 ml. of Ferastral intramuscularly on alternate days. The mean hospitalization time of patients with severe to moderate anaemia was reduced when given parenteral therapy, and the frequency of blood transfusion in these patients was also decreased.

B. IRON DEFICIENCY ANAEMIA DURING PREGNANCY A COMPARATIVE TRIAL OF TREATMENT BY IRON-POLY (SORBITOL-GLUCONIC ACID) COMPLEX, FERASTRAL(RR) GIVEN INTRAMUSCULARLY AND IRON DEXTRAN (IMFERON)(R) BY TOTAL DOSE INFUSION (NOV. 1977 - APRIL 1978)

Since the introduction of Ferrivenin (iron saccarate) into clinical use (Nissim, 1947) a succession of parenteral iron preparations has been made available for the treatment of iron deficiency. There is no question that parenteral iron could be given to patients with iron deficiency anaemia when there is an indication for such therapy. Discussions nowadays centre on the particular type of injection most suitable for routine use. The introduction of iron dextran (Imferon) given by total dose infusion (TDI) in 1963 by Basu made it possible to give a high single dose of iron in a short period of time in contrast to previous parenteral iron preparations which were limited to 100 mg. of iron in a single dose. A more recent parenteral iron preparation is iron-poly (sorbitol-gluconic acid) complex (Ferastral) which may be given in daily single doses of 500 mg. of iron intramuscularly (Domeij et al, 1977). The favourable experience reported in the last section and other investigators (Evers, 1977; Ezem et al, 1977; Fleming et al, 1977; and Simonsson et al, 1977) with Ferastral in controlled clinical trials has encouraged comparison of

the therapeutic effect and side effects with that of Imferon given by TDI in patients with established iron deficiency anaemia. Imferon was selected as the preparation for comparison because it has a similar high stability to Ferastral and it is a parenteral iron preparation in wide spread use.

Allocation of Patients into treatment groups

Patients with established iron deficiency anaemia by bone marrow examination were allocated into Ferastral or Imferon treatment group by restricted random allocation (Bradford Hill, 1965).

Thirty-two patients were treated with Ferastral, while thirty patients received Imferon by TDI. The volume of parenteral iron preparation used was calculated from tables prepared by the manufacturers (Astra Lakemedel for Ferastral, and Fisons Laboratory for Imferon). For both preparations, the dose given relates the haemoglobin deficit to the body weight of the patient and an additional amount of 1,000 mg. of iron administered during pregnancy.

Treatment

Ferastral was given 500 mg. (5 ml. into each buttock) intramuscularly on alternative days till completion of the required dose.

Imferon: The calculated dose was aseptically added to 540 ml. normal saline. 50 mg. of promethazine hydrochloride (Phernagan) was given intramuscularly before the infusion. The infusion was set up under medical supervision and the patient carefully observed during the early part of the infusion; thereafter throughout the period of infusion observation was carried out by a nurse. The drip was made to run slowly for the first 30 minutes then at 60 drops/ minute till completion of the infusion. Except for 10 patients who were kept in hospital for assessment of early response, those who received Imferon were discharged home same day.

Characteristics of the patients studied

Parity - The parity of the patients in the two treatment groups is shown on Table 17.

Period of gestation on admission to study - Table 18 shows the trimester of pregnancy when these patients first reported to the ante-natal clinic. Eighty per (80%) reported after the first trimester.

Severity of anaemia - The distribution of patients in each group is shown on Table 19.

The distribution of the parameters showed no significant differences between the two treatment groups. In each situation the difference between the two groups was not statistically significant ($p > 0.3$).

Results

Sixty-three patients were treated but 62 were analysed because one patient in the Imferon group who reacted to the infusion was withdrawn from follow up.

Reactions

One patient who received total dose infusion had a severe reaction 5 minutes after commencement of the infusion. She was covered with generalised urticarial rash and complained of severe chest and back pains. The drip was clipped off and patient kept in hospital for 24 hours for observation.

One patient who was treated with Ferastral was admitted 3 months later with viral hepatitis which responded to the usual treatment of bed rest, dietary regime and gut sterilisation with neomycin 2 gram 6 hourly for 2 weeks. Pregnancy progressed normally and she had a normal delivery of a live healthy female child weighing 2.9 kg. 3 weeks after admission to the hospital.

Pregnancy

The patients all felt well within 2 weeks of treatment, Two patients were later found to have multiple pregnancy (twins). Except for 2 patients who had a lower segment caesarian section and one patient who had a mid-cavity forceps delivery for complications in labour, all the patients had a normal delivery.

Repeat bone marrow

Results are shown on Table 20, Stainable iron remained absent in 2 of the 10 patients treated with Ferastral and 3 of 11 patients treated with Imferon, re-examined 6 weeks after treatment.

Haematological response

(a) Results are shown graphically on Figure 4 for reticulocytosis. Reticulocytosis was observed 4 - 6 days after treatment in the group which received Ferastral. There was no significant rise in the reticulocyte group.

(b) Packed cell volume response is shown on table 21 and figure 5.

Discussion

Iron deficiency anaemia in pregnancy is a very common problem all over the world both in developed and developing countries. Although malaria has in the past been the principal cause of severe anaemia in pregnancy, and still is, evidence that iron deficiency of nutritional origin is increasing in incidence in urban Nigeria in recent years (Ogunbode and Oluboyede, 1976, Oluboyede & Ogunbode, 1976). Its treatment requires long therapy and continuous use of iron when administered orally (Will and Groden, 1968, and Sadeghi et al, 1976). It normally responds to oral iron given in adequate doses and if tablets are taken regularly. It should be noted however that absorption of therapeutic iron

depends very much on the nature of the diet, absorption from vegetable diets being very poor. In addition, similar to what obtains in some parts of the world, Iran, Glasgow, the experience we have in Nigeria is that many patients have difficulty keeping appointments and fail to take oral medication once outside medical supervision. Treatment with parenteral iron in these circumstances is often indicated, especially in the anaemia of pregnancy where a response is needed with certainty before delivery.

Imferon by TDI has gained widespread use (Varde, 1964; Dawson et al, 1965; Duke et al, 1974 and Kernoff et al, 1975), since first introduced by Basu in 1963. The general concesus of previous investigations, is that Imferon by TDI is an effective therapy. However, a number of serious side effects have been reported even with prior injection of antihistaminics. In view of these adverse reports it is necessary to assess the efficacy and safety of new iron preparations, such as Ferastral which has been used in this study. We therefore compared Imferon by TDI with Ferastral, which may be given intramuscularly in high dosage.

The present results show that in the treatment of patients with iron deficiency anaemia Ferastral and Imferon TDI were both effective. Ferastral was, however, found to give a significantly better response particularly within the first few weeks of therapy. The evidence for the superiority

were early reticulocytosis and a significantly higher rate of P.C.V. rise observed in the group treated with Ferastral.

The reticulocyte count, which was not significantly raised during the first 10 days of treatment in the group treated with Imferon, is in agreement with previous reports (Pe - Benito and Guerrero, 1973) which state that the peak reticulocytosis occurs during the third week after Imferon administration. However, (Will & Groden reported a significant reticulocyte count after TDI within the first 10 days after Imferon infusion in the majority of treated patients.

A significant difference was found in the rise of mean packed cell volume in patients treated with Ferastral compared with the group given Imferon by TDI (Table 5.). The results as measured by PCV differs from the only other known clinical trial of Ferastral and Imferon, (Evers, 1977) which showed that haematological response to both forms of parenteral iron was the same over a period of 8 weeks. The difference in response obtained between the two groups studied is explainable by the report of Henderson and Hillman (1969) that up to 30% of the iron stores laid down by intravenous iron dextran treatment is not readily available for haemoglobin synthesis. This finding was confirmed by Olsson and Weinfeld (1972). The earlier more marked response to Ferastral suggests that iron given in this form is more readily available. It would therefore appear that in situations where rapid correction of iron

deficiency anaemia is required, Ferastral is the drug of choice.

In spite of the prophylactic administration of an anti-histaminic before infusion one paeitnt had a reaction serious enough to lead to discontinuation of iron dextran infusion. This is in agreement with many reports of reactions ranging from simple skin rash (Will & Groden, 1968; Pe Benito and Guerreno, 1973; and Sadeghi et al, 1976) to more severe reactions and even death after intravenous iron. (Baritt and Swain,1953). The possibility of a reaction stresses the important requirement that intravenous iron treatment must be given in a well equipped hospital with enough personnel to carry out strict observation during infusion.

No serious reactions were observed during treatment with Ferastral in agreement with previous investigations (Ogunbode et al, 1977; Fleming et al, 1977, Anderson and Grafford, 1977, Sundin, 1977; and Knight, 1977).

The absence of stainable iron in the bone marrow in 5 patients (2 Ferastral group, 3 from Imferon group) calls for comments. The probable explanation is the possibility that dosage may have been inadequate, since the method of calculating the dose makes it likely that this will sometimes occur. The formula used is based on average blood volume. One of the patients with absent iron following treatment with Ferastral was later discovered to have twin pregnancy. This

illustrates variability of factors considered in calculating required dose. Similarly, in individual patients, the blood volume, for example, deviates considerably from average, and in pregnancy even larger differences occur (Painton et al, 1966).

Summary

A new intramuscular iron preparation, iron poly (sorbitol-gluconic acid complex) Ferastral(R) has been compared with intravenous iron dextran, (imferon(R) in the treatment of sixty-three expectant Nigerian women with iron deficiency anaemia. Thirty-two patients were treated with Ferastral(R) while thirty-one patients received intravenous imferon (R) by total dose infusion.

Patients in the two treatment groups were comparable with respect to age, parity, severity of anaemia and the period of gestation when treatment was commenced. In each situation, the differences between the two groups were not satistically significant (P 0.3).

Both forms of iron therapy were found to be effective. Patients treated with Ferastral(R), however, had a significantly better response as measured by early reticulocytosis and a more rapid rise in the packed cell volume, particularly within the first few weeks of therapy.

SECTION TWO - CONCLUSION

The choice of iron preparation to use largely depends on prevailing circumstances. In places with sufficient doctors and nurses where full supervision can be given total dose infusion may be preferred because of the fact that the amount of iron required can be administered as a single dose. On the other hand, in areas where medical staff is inadequate, and this is the position in Nigeria and perhaps in other developing parts of the world, intramuscular iron with a preparation which may be given in high dosage, is the treatment of choice. When all factors are considered, Ferastral would appear to be a better alternative to Imferon because of its early effectiveness, ease of administration and relative absence of side effects. Other intramuscular iron preparations may also be used over a longer period of time, in the absence of Ferastral.

FURTHER POSSIBLE RESEARCH INTO IRON DEFICIENCY ANAEMIA IN PREGNANCY IN NIGERIA

Below are some of the areas needing urgent consideration.

1. The assay of iron content of foods eaten in Nigerian communities is an important work in Nutrition that must be performed. This study has been started in collaboration with the Department of Nutrition, University of Ibadan. The plan is to carry out a large study of dietary iron intake among Nigerian living in the rural and urban areas. Such study would indicate the precise influence of cooking habits on the iron available from our diets.

2. Because of the nature of our diet which is rich in vegetables cooked over again for several days and with the increasing ingestion of eggs by the urban population, it is important to assess the possible role of malabsorption in the aetiology of iron deficiency anaemia in Nigeria. Again, jointly with the Department of Nutrition, University of Ibadan, an iron absorption study has been started. Expectant mothers would be admitted to hospital and their dietary iron intake determined. Iron lost chiefly through the stool would be estimated. In this way it would be possible to know the influence of our type of diet on iron absorption. To assess the possible role of pregnancy on the absorption rate of food substances a similar study has been planned for the non pregnant patients.

3. Iron absorption tests using radio-active labelled iron could be carried out on non-pregnant females

4. Sometime in the future, we can hope for Universally improved nutrition through education and improved standard of living. Meanwhile, iron deficiency anaemia of moderate degree can be treated by parenteral iron particularly when patients are seen late in pregnancy. It can be prevented and its incidence should decline as oral iron is added to the present antenatal practice of malarial suppression and folic acid supplementation.

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14. P.C.V. Response: Mean value for Ferastral main group plus defaulters.

15. P.C.V. Response in patients treated with Ferastral analysed according to severity of Anaemia.

16. Bone marrow iron status before and after Ferastral treatment.

IRON DEFICIENCY ANAEMIA DURING PREGNANCY A COMPARATIVE TRIAL OF TREATMENT BY IRON - POLY (SORBITOL-GLUCONIC ACID) COMPLES FERASTRAL (R) GIVEN INTRAMUSCULARLY AND IRON DEXTRAN (IMFERON)(R) BY TOTAL DOSE INFUSION. (TABLES 17 - 21)

17. Parity distribution of patients.

18. Trimester of pregnancy.

19. Severity of Anaemia.

20. Repeat bone marrow biopsy - 6 weeks after beginning treatment.

21. Mean packed cell volume at indicated weeks after entry into trial for groups treated with Imferon and Ferastral.

TABLE 1

IRON REQUIREMENTS OF PREGNANCY (mg.)

6666

	Hunter (1960)	deLeeuw et al(1966)	Hellman & Pritchard(1971)
Maternal RBC Increase	500	570	500
Fetus	400	300	300
Placenta	400	300	300
Delivery	100	-	-
Normal Daily Loss	200	280	-
Total Iron Requirement	1200	1150	800

TABLE 2A

PARITY DISTRIBTUION OF ANAEMIC PREGNANT WOMEN

Parity	No. of Patients	%
0	8	14
1 - 4	41	74
5^{+}	6	12
-	35	-

TABLE 2B

Fe/T.I.B.C. Ratio in Relation to Parity

Fe/T.I.B.C. ratio	Parity			Total	%
	0	1-4	5+		
10	-	8	4	12	21.8
10-18	2	13	4	19	34.5
18+	11	7	6	24	43.7
Totals	13	26	14	55	-

TABLE 3

PERIOD OF GESTATION AT FIRST ATTENDANCE TO THE CLINIC

	No.	%
Before 16 weeks	17	31
16 to 28 weeks	38	69
Total	55	-

TABLE 4

SERUM IRON/TOTAL IRON BINDING CAPACITY RATIO
(55 PATIENTS)

Fe/T.I.B.C.	No. of Patients	Percentage
Less than 10%	13	24
10 - 18%	19	34
Over 18%	23	42

TABLE 4B

Fe/T I.B.C. RATIO DISTRIBUTION AT VARIOUS TRIMESTER

				Trimester			
T.I.B.C.	Total	1st	%	2nd	%	3rd	%
10	12	5	4.17	6	50	1	8.3
10-18	19	6	31. 6	12	63.2	1	5.2
18+	24	9	37.6	11	48.9	3	12.5

TABLE 5

INITIAL CHARACTERISTICS AND RESPONSE TO FOLIC ACID IN THE TWO STUDY GROUPS

$\bar{X}$ = Mean value; S.D. = Standard deviation;

S.E. = Standard error; N. = No. of observations.

Group		Saturation (%)	Serum iron	Packed cell volume				
				Initial	2/52	4/52	6/52	8/52
A								
	$\bar{X}$	12.18	57.20	28.48	28.89	30.00	29.94	30.00
	S.D.	4.98	24.74	1.60	1.59	1.36	1.75	1.73
Saturation less than 18%	S.E.	0.84	4.18	0.35	0.37	0.36	0.42	0.56
B								
	$\bar{X}$	36.94	141.75	28.45	29.89	30.16	32.00	33.07
	S.D.	15.98	72.75	1.57	2.89	3.20	2.81	2.46
Saturation greater than 18%	S.E.	3.57	16.27	0.35	0.68	0.75	0.66	0.66
	N.	20	20	20	18	19	18	14

TABLE 6

IRON DEFICIENCY ANAEMIA BY BONE MARROW EXAMINATION PARITY OF PATIENTS STUDIED

Parity	Number	Percentage
0	26	31
1 - 4	45	53.5
5+	13	15.5
Total	84	100%

TABLE 7

IRON DEFICIENCY ANAEMIA BY BONE MARROW EXAMINATION
DISTRIBUTION OF STUDY PATIENTS BY GESTATIONAL AGE

Gestational age (weeks)	Oral iron group No.	%	Ferastral group No.	%
⩽ 14	4	17.4	7	11.5
15 - 27	10	43.4	22	52.5
28 - 40	9	39.2	22	36.0
Total	23	100.0	61	100.0

TABLE 8

IRON DEFICIENCY ANAEMIA BY BONE MARROW EXAMINATION

HOOKWORM INFESTATION

4 or more ova in every field is found in heavy hookworm infestation.

Hookworm ova count (high power field)	No. of Patients	Percentage
0	48	69
1 - 2	9	13
3 - 4	10	14
- 4	3	4

TABLE 9

IRON DEFICIENCY ANAEMIA BY BONE MARROW EXAMINATION

Packed cell volume response in groups treated with parenteral iron and that treated with oral iron.

$\bar{X}$ = means P.C.V. S.D. = Standard deviation.

S.E. = Standard error n = number of observations.

		Time in weeks after entry into trial			
	Initial	2	4	6	8
Ferastral					
$\bar{X}$	27.35	31.73	33.63	35.21	36.40
S.D.	2.59	3.56	2.00	2.25	1.95
S.E.	0.36	0.50	0.43	0.46	0.87
n	61	51	46	24	5
Oral iron					
$\bar{X}$	29.42	30.68	31.48	32.71	32.59
S.D.	1.59	2.44	2.11	1.95	0.78
S.E.	0.33	0.52	0.44	0.45	0.26
n	23	22	23	21	9

TABLE 10

IRON DEFICIENCY ANAEMIA BY BONE MARROW EXAMINATION
DEGREE OF ANAEMIA IN PREGNANCY

Degree of Anaemia	No.	%
Severe (P.C.V. 23% or less)	6	6.3
Moderate (P.C.V. 23% - 26%)	19	20.3
Mild (P.C.V. 27 - 30%)	69	73.4

TABLE 11

DIETARY IRON INTAKE

(a) ANAEMIC PATIENTS ON HOME DIET

Name	Daily Iron Intake in mg. (range)	Mean (mg)
A.O.	7.8 - 12.12	9.63
K.O.	8.5 - 15.00	11.37
S.I.	6.5 - 12.00	9.70
M.A.	18.5 - 29.60	21.62
K.A.	6.5 - 10.40	9.50
B.A.	10.4 - 11.50	13.35
A.M.	16.5 - 26.40	23.72
T.O.	7.2 - 7.50	8.37
A.A.	10.5 - 18.50	11.85

Total: Mean = 13.23 mg. Range: = 8.37 - 23.72 mg.

DIETARY IRON INTAKE OF PATIENTS ON HOSPITAL DIET

Name	Daily Iron Intake in mg. (range)	Mean (mg.)
A.M.		
A.M.	34.50 - 45.11	34.24
S.M.	30.79 - 51.52	33.88
O.O.	33.07 - 47.41	36.90
O.T.	29.51 - 29.72	25.09
O.V.	40.06 - 43.90	39.74
K.M.	32.20 - 34.30	34.26
A.E.	37.70 - 53.84	46.47
A.A.	51.83 - 53.85	43.89
A.E.	27.76 - 48.69	37.20
A.A.	25.23 - 42.99	35.50

Total: Mean = 36.72 mg. Range: 25.09 - 46.47

TABLE 12

IRON CONTENT OF THE MAIN ITEMS OF FOOD OF THE PEOPLE OF WESTERN PART OF NIGERIA

Amala + Ewedu, Okro, egusi soup + meat	7mg/100g
Eba + + Ewedu, Okro, egusi soup + meat	5mg/100g
Pap + moin-moin	10mg/100g
Rice + Stew + meat or fish	2mg/100g
Bread + eggs	2 mg/100g
Dodo + Stew + meat or fish	3mg/100g
Agidi + vegetables + meat or fish	3mg/100g
Pando yam + Ewedu with stew + meat or fish	3mg/100g
Yam + meat stew	2 mg/100g
Beans + Yam	5 mg/100g.

The above values are for freshly prepared foods. (The data were obtained from foods served to patients at the University College Hospital Ibadan).

TABLE 13

P.C.V. Response in Groups Treated with Ferastral and with Oral Iron Respectively

	Times in weeks after entry into trial				
	0	2	4	6	8
$\bar{X}$	27.35	31.73++	33.62++	35.21++	36.40++
S.D.	2.59	3.56	2.00	2.25	1.95
n	51	51	46	24	5
Oral Iron					
$\bar{X}$	29.42	30.42	31.48+	32.71+	32.89++
S.D.	1.59	2.44	2.11	1.95	0.78
n	23	22	23	21	9

$\bar{X}$ = mean P.C.V., S.D. = standard deviation, n = number of observations

Significance of difference from initial value:

+ $\angle$ p 0.001 ++ p $\angle$ 0.0001

TABLE 14

P.C.V. Response : Mean value for Ferastral Main Group Plus Defaulters

	Time in weeks since entry into trial				
	0	2	4	6	8
Mean PCV	27.49	31.97	34.03	35.00	36.40
Number	61	61	55	27	5

TABLE 15

P.C.V. Response in Patients Treated with Ferastral Analysed According to Severity of Anaemia

	Time in weeks since entry into trial			
	0	2	4	6
Severe				
$\bar{X}$	22.17	28.67	31.50	35.50
S.D.	1.83	6.25	4.68	1.00
n	6	6	6	4
Moderate				
$\bar{X}$	25.60	30.60	32.67	33.75
S.D.	0.52	3.41	2.87	2.63
	10	10	9	4
Mild				
$\bar{X}$	28.74	32.78	34.34	35.53
S.D.	1.29	2.56	2.58	2.42
n	35	32	31	16

$\bar{X}$ = Mean P.C.V.

S.D. = Standard Deviation

n = Number of observations

TABLE 16

BONE MARROW IRON STATUS BEFORE AND AFTER FERASTRAL TREATMENT

Iron Status	No. before treatment	No. after treatment
No iron	12	1
Scanty	1	5
Normal	-	7

TABLE 17

IRON DEFICIENCY ANAEMIA DURING PREGNANCY
PARENTERAL IRON THERAPY
PARITY DISTRIBUTION OF PATIENTS

Parity	Ferastral	Imferon
Primigravida	13	11
Multigravida	19	19
Total	32	30

TABLE 18

IRON DEFICIENCY ANAEMIA DURING PREGNANCY

PARENTERAL IRON THERAPY

TRIMESTER OF PREGNANCY OF STUDIED PATIENTS

Treatment Group	1st	2nd	3rd	Total No. of patients
Ferastral	1	14	17	32
Imferon	1	16	13	30

TABLE 19

IRON DEFICIENCY ANAEMIA DURING PREGNANCY

PARENTERAL IRON THERAPY

SEVERITY OF ANAEMIA

Degree of Anaemia	Ferastral		Imferon	
	No.	%	No.	%
Moderate P.C.V. 19 - 26%	12	37.5	13	30
Mild 27 - 30%	20	62.5	17	70
Total	32	100	30	100

TABLE 20

IRON DEFICIENCY ANAEMIA DURING PREGNANCY

PARENTERAL IRON THERAPY

REPEAT BONE MARROW BIOPSY 6 WEEKS AFTER BEGINNING TREATMENT

Treatment Group	Iron in the Bone Marrow			
	Before Treatment	After Treatment		
	Nil	Nil	Scanty	++
Ferastral	10	2	3	5
Imferon	11	3	3	5

++ = Adequate stainable iron.

TABLE 21

IRON DEFICIENCY ANAEMIA DURING PREGNANCY

PARENTERAL IRON THERAPY

MEAN PACKED CELL VOLUME AT INDICATED WEEKS AFTER ENTRY INTO TRIAL FOR GROUPS TREATED WITH IMFERON AND FERASTRAL

	Time in weeks since entry into trial				
	0	2	4	6	8
Imferon group					
Mean P.C.V.	26.93	28.46	30.21	31.40	32.95
S.D.	2.85	3.13	3.19	2.08	2.13
No.	30	28	28	25	22
Ferastral group					
Mean P.C.V.	26.94	30.32	22.39	33.31	34.43
S.D.	2.55	2.01	2.16	1.91	2.31
	32	31	31	29	21
Imferon vs. Ferastral					
t - value	0.01	2.74++	3.10++	3.52+++	2.19+

\+ $p < 0.05$

++ $p < 0.01$

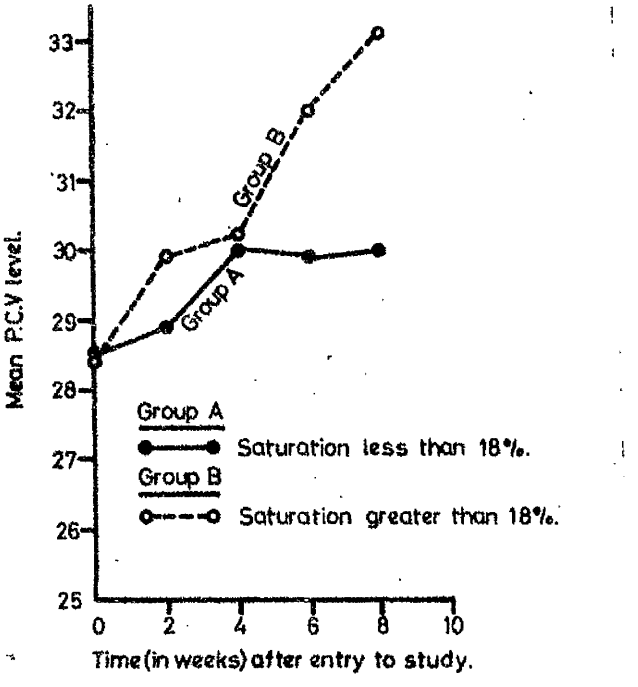
+++ $p < 0.001$

S.D. = standard deviation

No. = number

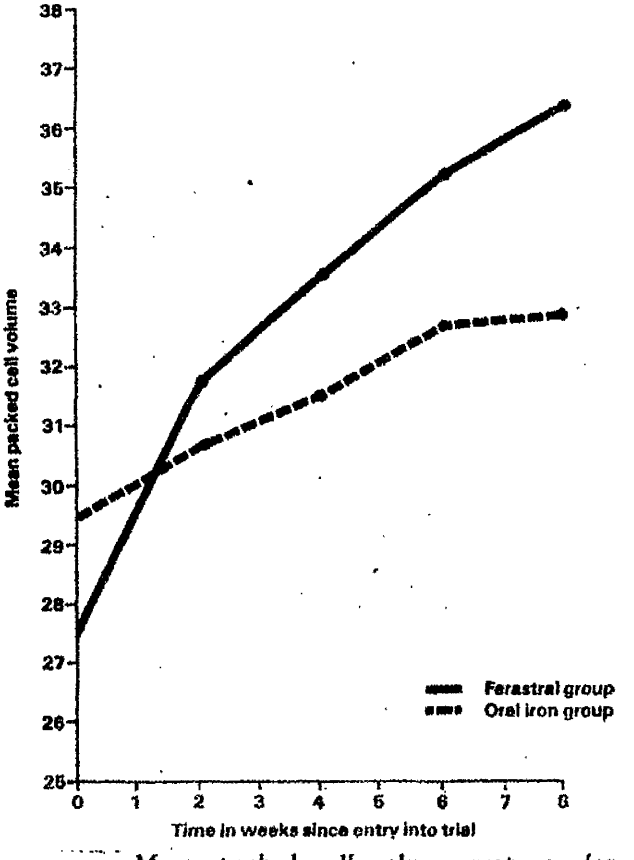
FIGURES

FIGURE 1.



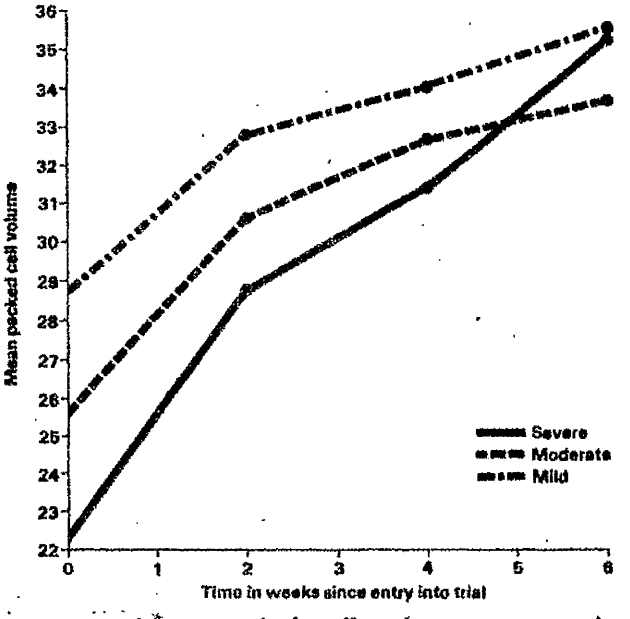
Trend of mean P.C.V. levels for each group.

FIGURE 2.



Mean packed cell volume response for Ferastral and oral iron groups.

FIGURE. 3.



Mean packed cell volume response in the Ferastral group by severity of anaemia.

FIGURE 4.

IRON DEFICIENCY ANAEMIA DURING PREGNANCY – PARENTERAL IRON THERAPY.

DAILY MEAN RETICULOCYTE COUNT ON 10 PATIENTS FROM EACH GROUP AFTER TREATMENT.

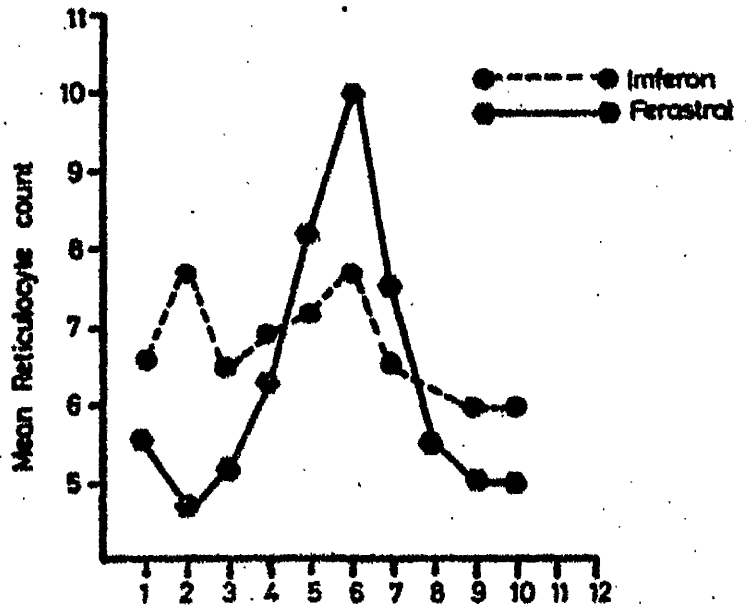
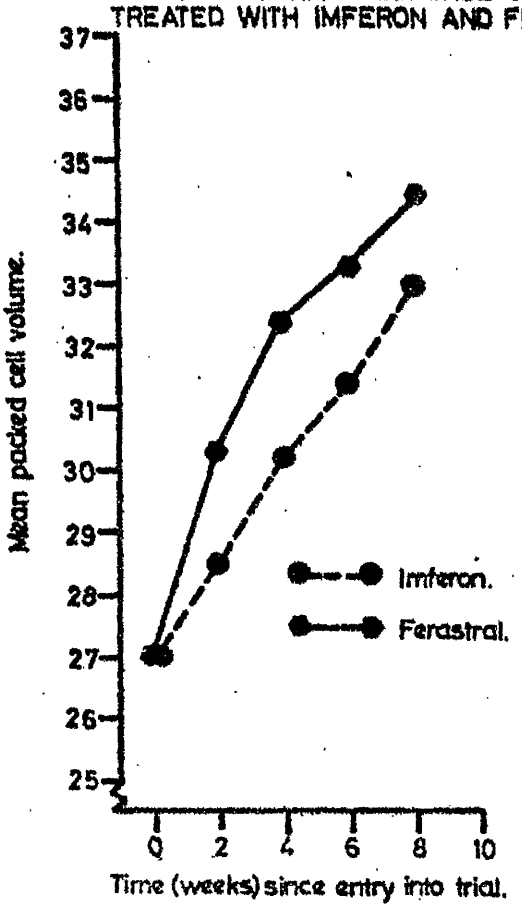


FIGURE 5.

IRON DEFICIENCY ANAEMIA DURING PREGNANCY-PARENTERAL IRON THERAP

MEAN P C V-TIME RESPONSE OF PATIENTS. TREATED WITH IMFERON AND FERASTRAL.



APPENDICES

1. University College Hospital, reference letter.

2. Seasonal variation in occurence of Anaemia from "Anaemia in Pregnancy", Ojo 1965).

3. Map of Nigeria showing the position of Ibadan.

4a. Questionnaire including diet histories (completed form).

4b. Measured consumption of Nigerian food items of one of the anaemic patients.

5. Ferastral(R) dosage guide (mg. of iron).

6. Degree of my participation in the studies on iron deficiency anaemia during pregnancy with reference to parenteral iron therapy.

APPENDIX 1

FORM S. 4941 A

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY
UNIVERSITY COLLEGE HOSPITAL, IBADAN

Date.....

Name.....U.C.H. Ref. No.....

Owing to heavy demands on the obstetric accommodation, it is impossible to accept all those who request antenatal care and delivery at University College Hospital and priority has to be given to those with compelling medical grounds for acceptance.

The above-named patient has therefore been regretfully advised to make alternative arrangements elsewhere. However, if any abnormality is suspected later in pregnancy, she should be referred back to the U.C.H. Obstetric Consultative Clinic for review, quoting the above reference number.

Clinical Details Date of Examination.....

Previous Pregnancies: Total:.....

Relevant previous history

Physical Findings:

Height .....
Weight .....
B.P. .....
Urine .....
P.C.V. .....
Genotype .....
Blood group .....
Kahn

Approximate E.D.D.....

Specific Treatment advised:
Rx. Pyrimethamine (Daraprim) 25 mg. weekly.
Folic acid 5 mg. daily.

Other comments and suggestions:

Signed.....
pp.

.....
Consultant Obstetrician

APPENDIX 2

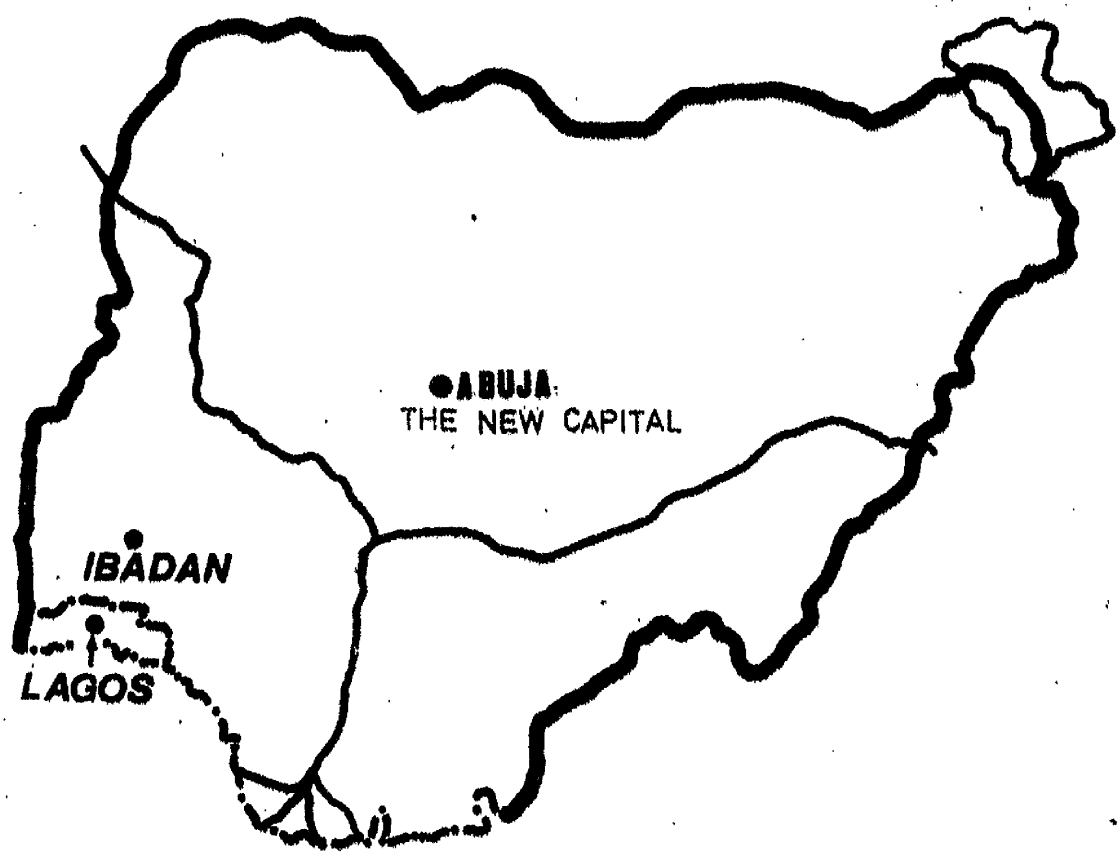
SEASONAL VARIATION IN OCCURRENCE OF ANAEMIA

IBADAN 1961

TOTAL 241 CASES

Month of Year	No. of cases
January	17
February	17
March	15
April	13
May	34
June	45
July	29
August	27
September	17
October	15
November	4
December	8

MAP OF NIGERIA SHOWING THE POSITION OF IBADAN.



APPENDIX 4a

GENERAL QUESTIONNAIRE INCLUDING HAEMATOLOGY

Mrs. O.A. Age 25

Para 2^{+0}, One living child

Date seen: weight: 59.8kg.

Height: 5' 2".

Fundal height 30 weeks

P.C.V. 25%; marrow, stainable intracellular iron = Nil.

Social details

Lives in Ibadan.

Occupation: housewife (Muslim)

Husband's Occupation Native priest.

Money supplied for food by husband

Fixed or variable? variable

How often? weekly

How much? ₦5 (five Naira)

How often do you cook soup? 2ce weekly

How many people are fed? Three (husband, wife and one child - aged 3 years).

Dietary sheet of patient.

APPENDIX 4b

Anaemia in Pregnancy

Dietary History

(MEASURED CONSUMPTION OF NIGERIAN FOOD ITEMS OF ONE OF THE PATIENTS)

Name of Patients: Bolanle Abiodun 30.6.78

Address. NW5/183A Kajola Street, Inalende, Ibadan.

Type of Meal	Type of Food served	Quantity left over	Quantity	Quantity taken
Morning Breakfast	Rice	200	35	165
	Beans	95	10	85
	No meat			
Mid-Morning Snack	Nil			
Lunch	Eko	525	25	500
	Moinmoin	300	75	225
	No meat			
Mid-Day Snack				
Dinner	Iyan (Pando yam)	400	50	350
	* fish	25	-	25
	Stew	-	-	-
Supper	Ewedu	27	-	27
Supper				

* Proteins when taken represent less than 10% of total food intake

APPENDIX 5

FERASTRAL

DOSAGE GUIDE

(mg. of iron)

Recommended single dose: 500 mg. (2 ampoules), 5ml in each buttock

Hb (g/100ml)	Body weight (kg) 30	40	50	60	70	80
2.0	1000	1350	1650	2000	2300	2650
3.0	900	1200	1500	1800	2100	2400
4.0	850	1100	1400	1650	1950	2200
5.0	750	1000	1250	1500	1750	2000
6.0	650	900	1100	1350	1550	1750
7.0	600	800	950	1150	1350	1550
8.0	500	650	850	1000	1150	1350
9.0	400	550	700	850	950	1100
10.0	350	450	550	650	800	900
11.0	250	350	400	500	600	650

An addition of 250 - 1000 mg. is required to replenish the iron stores.

This dosage guide is based on the following formula allowing for 15% urinary excretion of iron:

$$\frac{\text{Normal Hb (14 g/100 ml) - observed Hb}}{100} \times 3.4 \times 7\% \text{ of bodyweight} \times 1.15$$

APPENDIX 6

DEGREE OF PARTICIPATION IN THE STUDIES etc.

The clinical work for this thesis was performed at the Inalende Maternity Centre and the obstetric unit of the University College Hospital, Ibadan. All the clinical work was performed by myself. Every patient was seen by me during pregnancy, labour and in the puerperium.

The laboratory work was performed prinicipally in the Department of Haematology. Other departments included were Bacteriology, Nutrition and Chemical Pathology.

a. I was actively involved with the haematocrit estimation, blood grouping, haemoglobin electrophoresis full blood count and serum iron, total iron binding capacity which were performed in the department of Haematology.

b. Bone marrow smears were prepared and examined by Dr. O. Oluboyede and thick films for malaria parasites by myself and a Senior Laboratory technician.

c. Faeces were examined for hookworm ova in the Department of Parasitology by Dr. Alawusa.

d. The liver function tests, were performed in the department of Chemical Pathology.

Patient who needed total dose inferon infusion were closely supervised by me. Intramuscular injection of parenteral iron was administered by the Nursing staff of the Department of Obstetrics and Gynaecology, University College Hospital, Ibadan.

This work was prepared while holding the following appointments.

a. Lecturer, University of Ibadan, 1975 - October, 1976.

b. Senior Lectuer, University of Ibadan, October, 1976 - Now.

ACKNOWLEDGEMENTS

Any form of research implies team work and co-operation. All the patients presented in this thesis were very understanding. Without their co-operation and that of my medical colleague - Dr. Oluboyede, it would not have been possible to carry out this research. I am grateful to my patients for their co-operation and to my clinical colleagues including those in the Department of Obstetrics and Gynaecology under whose care some of these patients were admitted.

The nursing staff of Inalende Maternity Centre gave enthusiastic support in the selection of anaemic pregnant women. Once in the University College Hospital, Ibadan, the entire Nursing staff of the Obstetric Unit were most helpful in making the patients comfortable and administering the drug prescribed. I must thank them all.

I would like to place on record my profound gratitude for the late Professor J.P. de V. Hendrickse for his encouragement and Professor V.E. Aimakhu for his helpful criticism throughout the study period and writing of the script.

Dr. O.A. Oluboyede, a Consultant Haematologist, helped immensely by performing the bone marrow examination on my patients. Dr. I.O. Akinyele and Dr. M.A. Hussain of the

Department of Human Nutrition were involved with the determination of dietary iron intake of patients with established iron deficiency anaemia. Dr. Ayeni of the Medical Statistics was very helpful with the design and statistical analysis of results obtained following drug treatment.

Professor B. Topley who has been interested in iron deficiency anaemia for many years gave me encouragement during the early stages of the study. To those five very helpful colleagues, I am immensely grateful.

Dr. Jack Fielding of St. Mary's Hospital, London, Dr. David Taylor of Newcastle General Hospital and Dr. J.B. Lawson of Newcastle, formerly Head of the Department of Obstetrics & Gynaecology, University College Hospital, Ibadan, assisted with useful comments on the scripts. I thank them very much.

I am grateful to the members of staff of the Medical Illustration Unit for preparing the illustrations.

I am profoundly grateful to my Secretary, Mrs. Sumbo Adelaja for typing the thesis.

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