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A COMPARATIVE STUDY OF THE EFFICACY AND TOLERABILITY OF CARBONYL IRON FORMULATIONS WITH FERROUS SULPHATE IN PREGNANT WOMEN WITH IRON DEFICIENCY ANAEMIA

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CERTIFICATE

This is to certify that "**A COMPARATIVE STUDY OF THE EFFICACY AND TOLERABILITY OF CARBONYL IRON FORMULATIONS WITH FERROUS SULPHATE IN PREGNANT WOMEN WITH IRON DEFICIENCY ANAEMIA"** is the original work done by Dr.A.Sheela Fathima at the Institute of Pharmacology, Madras Medical College, Chennai – 600 003.

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CONTENTS

Anaemia increases the risk of maternal and foetal mortality and morbidity in pregnancy.[1] Anaemia is functionally defined as an insufficient Red Blood Cells (RBC) mass to adequately deliver oxygen to peripheral tissues. Haemoglobin (Hb) concentration of 14g/dl and 12g/dl were considered as the lower limits of normal, at sea level in adult men and women, respectively.[2]

According to the proposal by World Health Organisation (WHO) expert group "anaemia or iron deficiency should be considered to exist" when haemoglobin is below the following levels.[1] The cut off points for the diagnosis of anaemia is shown in Table 1.

TABLE - 1 : CUT – OFF POINTS FOR THE DIAGNOSIS OF ANAEMIA[1]

CATEGORY	g/dl	MCHC%
Adult Male	13	34
Adult Female – Non Pregnant	12	34
Adult Female – Pregnant	11	34
Children, 6 months to 6 years	11	34
Children 6 to 14 years	12	34

Anaemia in non-pregnant women is defined as haemoglobin concentration less than 12 g/dl and less than 10 g/dl during pregnancy or the puerperium. Haemoglobin concentration is lower in mid pregnancy. Early in pregnancy and again near term the haemoglobin level of most healthy women with iron stores is 11g/dl or higher. For these reasons the centre for disease

control (1990) defined anaemia as less than 11g/dl in the first and third trimester and less than 10.5 g/dl in the second trimester.[3]

Incidence

Globally 30% of the total world population is anaemic and half of these, some 600 million people have iron deficiency.[4] The WHO report gives an anaemia prevalence at the global level as 55.9% among the expectant mothers.[5]

In India 5-6% of general population suffer from the disease. It is prevalent among 3% of men and 10 – 14% of women. About 10% of attendance in General hospitals is accounted for by anaemia. In specific groups like slum dwellers, plantation labourers and pregnant women, the prevalence rate is 30-50% or even more.[6] Similarly the incidence at Institute of Obstetrices and Gynacology Madras Medical College, Egmore, Chennai was also 40% .

India has probably the highest prevalence of nutritional anaemia in women and children. About one half of non-pregnant women and young children are estimated to suffer from anaemia. 60-80% of pregnant women are anaemic. 20-40% of maternal death is attributed to anaemia. The most frequent cause of anaemia is iron deficiency and less frequently folate and Vit B_{12} deficiency.[1]

Incidence of anaemia in pregnancy ranges widely from 40 to 80 % in the tropics compared to 10 to 20 % in the developed countries.[7] Survey in

different parts of India indicates that about 50 to 60% of women belonging to low socioeconomic groups are anaemic in the last trimester of pregnancy. The major etiological factors are iron and folic acid deficiency. It is well known that anaemia per se is associated with a high incidence of premature birth, postpartum haemorrhage puerperal sepsis and thromboembolic phenomenon in the mother.(1)

Indian Council of Medical Research (ICMR) in 1989 carried out a countrywide evaluation of the anaemia in pregnant women at or beyond 20 weeks of gestational age. The prevalence of anaemia was found to be 87%, with 32 % of women having Hb less than 8g/dl.(8) Another study by ICMR in 1992 among pregnant women in second trimester reported a prevalence rate of 62 %. (9) The ICMR Multicentric Study under District Nutrition Project 2001, showed over all prevalence of anaemia among pregnant women as about 85%.(10) According to National Family Health Services (NFHS–2) data, the prevalence of anaemia among pregnant women was 49.7%.(11)

Classification of Anaemia

Major Classification of anaemia:

1. Marrow production defect (hypoproliferation)
2. Red cell maturation defect (ineffective erythropoiesis)
3. Decreased red cell survival (Blood loss / Haemolysis)

Kinetic Classification of Anaemia

Impaired Erythrocyte Production

1. **Hypoproliferative**

   Iron deficiency Anaemia

   - Iron deficiency
   - Anaemia of chronic disorders

2. **Erythropoietin deficiency**

   - Renal disease
   - Endocrine deficiencies

3. **Hypoplastic anaemia**

   - Aplastic anaemia
   - Pure red cell aplasia

4. **Infiltration**

   - Leukemia
   - Metastatic Carcinoma
   - Myelofibrosis

5. **Ineffective**

   Megaloblastic

   - Vitamin B12 deficiency
   - Folate deficiency
   - Other causes

   Microcyctic

   - Thalassemia
   - Certain sideroblastic anaemia[12]

Diagnosis

There are two steps in the diagnosis of anaemia.

1. To establish that the anaemia is due to iron deficiency
2. To determine the cause of the iron deficiency.

The diagnosis of iron deficiency anaemia is often recognised by the clinical features, and history. It can be established with certainity only by blood examination. Satisfactory response to iron therapy confirms the diagnosis.[13]

Initial Investigation of Anaemia

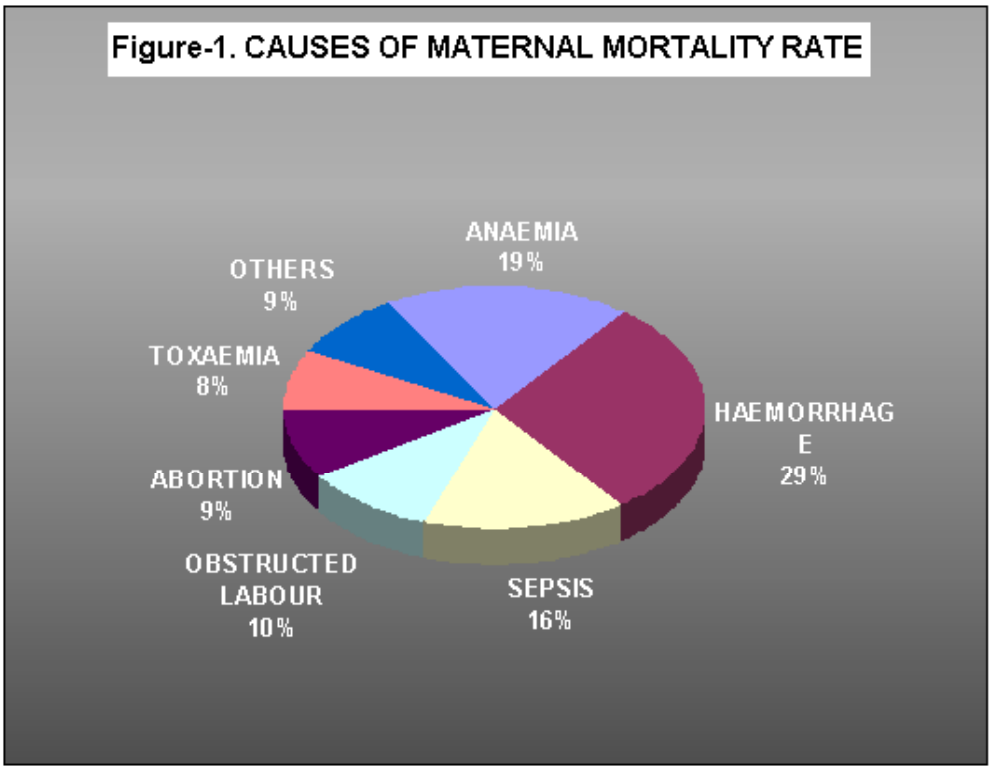
The initial investigations required for diagnosis of anaemia are

- Full blood count
- Examination of blood film
- Serum Ferritin
- Serum B_{12}
- Red cell folate
- Haemolysis screening (if indicated), Reticulocyte count, Bilirubin, Lactate dehydrogenase, Haptoglobin

- **Examination of Peripheral Smear**
    - Anisocytosis
    - Hypochromic
    - Microcytic[14]

Complications of Anaemia

Severe anaemia in pregnancy is associated with increased maternal death. Reports indicate 19% of all maternal deaths are attributable to anaemia.(1)



General

1. High output heart failure
2. Infections are more common in iron deficiency anaemia (IDA) especially those of respiratory, gastro intestinal and urinary tract. Tuberculosis is common in them. Cell mediated immunity is reduced in these subjects.

3. Chronic anaemia reduces the efficiency in work.
4. Decreased oxygen consumption.
5. Decreased oxygen affinity due to increased amount of 2,3-bisphosphoglycerate and this phosphate compound has the capacity to combine with deoxygenated haemoglobin and decrease its affinity for oxygen.
6. Increased tissue perfusion
7. Increased cardiac output
8. Increased pulmonary function.
9. Uncorrected tissue hypoxia.

During pregnancy

1. Pre-eclampsia.
2. Intercurrent infection- not only does anaemia diminish resistance to infection but also pre – existing lesion, if present will flare-up. It should be noted that infection itself impairs erythropoiesis by bone marrow depression.
3. Heart failure at 30- 32weeks of pregnancy.
4. Pre term labour

During labour

1. Uterine inertia
2. Postpartum haemorrhage
3. Cardiac failure
4. Shock

Puerperium

1. Puerperal sepsis
2. Sub involution
3. Failure of lactation
4. Puerperal venous thrombosis
5. Pulmonary embolism

Effect on Baby

1. Low birth weight
2. Perinatal mortality
3. Intrauterine death – due to severe anoxaemia
4. Increased perinatal loss.[7]

To prevent these complications

The objectives of the treatment are correction of the deficit in haemoglobin mass and eventually restoration of iron stores. Both these objectives can be accomplished with orally administrated simple iron compounds- ferrous sulphate, fumarate or gluconate – that provide a daily dose of about 200mg of elemental iron. If the women cannot or will not take oral iron preparations, then parenteral iron is given. To replenish iron stores oral therapy should be continued for three months or so after the anaemia has been corrected.[3]

Considerable increase in haemoglobin by an oral agent will obviate the need for blood transfusion and parenteral iron and reduced the maternal mortality and morbidity associated with anaemia in pregnancy.

Ancient History

The empirical use of iron in the treatment of anaemia dates from ancient times. The calcined iron preparation of ancient Hindu medicine, known as Lawha Bhasma was prepared by casting sheets of iron and then macerating them to a fine white powder in oil, whey , vinegar, cow's milk. The Greek physicians employed iron for the cure of weakness, a prominent symptoms of anaemia, in the attempt to impart to the patient the strength of the iron. Indeed , it was believed that, Mars the god of war, had imbued the metal with strength and alchemists designated iron as Mars. Patients with marked pallor were given drinking water in which old swords, had been allowed to rust, and Celsus advised that enlarged spleens be treated by using water in blacksmith shops and in which white hot iron had been drenched. He claimed that animals drinking such water had abnormally small spleens.(15)

Recognizing Anaemia In Iron Deficiency Anaemia

Sydenham was probably the first physician to employ iron in a manner that would be approved today; in 1681, Sydenham prescribed, "steel in substance or iron or steel filings steeped in cold rhenish wine", the dose amounting to 0.5 to 1.0g of iron daily.(15)

The Clinical Picture

Chlorosis

Chlorosis (also the 'green sickness', morbus virgineus, mal d'amour and other names) was described in relatively modern times as 'a hypochromic

anaemia in adolescent girls usually associated with gastrointestinal and menstrual disorder.[16]

Hirsch quotes Sennart stating that ‘pallor or yellow tinge to the skin’ was a sign of chlorosis.[17] Hart cites the eminent US physician W.Crosby’s 1955 case of anaemia with green discoloration, which he explained as combined protein and iron deficiency.[18]

Most features of chlorosis fit well with severe IDA in adolescent girls and young women. Long before the microscopy of stained blood was commonplace, Gabriel Andril had commented on the very small red cells in chlorosis.[19] John Coakley Lettsom in 1795, a successful physician who founded the London Society of Medicine and the Royal Seabathing Hospital at Margate among other institutions, wrote reassuring tracts on a number of common medical problem, including one on chlorosis in girl’s boarding schools.

He described the features of chlorosis as paleness and sallowness of complexion, palpitations of the heart, difficulty breathing on exertion, bloated appearance, loss of appetite, reluctance to exercise and amenorrhoea. Amenorrhoea is difficult to explain except that delayed puberty can be a feature of severe anaemia, and amenorrhoea features in severe malnutrition.[20]

One hundred years later, Stockman concluded that excessive menstrual loss together with habitually low intake of iron from the diet have the direct causes of chlorosis. Treatment was iron.[21]

In 1832, Blaud introduced pills containing 1.39g of Ferrous sulphate and 0.1g of potassium carbonate, and these became widely recommended for chlorosis and other conditions.(22) The original pills contained 64mg of iron. Many physicians, even into the 1930s, Thomson, Findlay and Osler, thought iron was more effective.(23)

Understanding of IDA by the early 1930s can be summarised by the Americans, Wintrobe and Beebe . They stated that ‘there is only presumptive evidence that idiopatic hypochromic anaemia develops because an individual is unable to meet the demands for haemoglobin or replace the normal loss of blood on account of defective utilization of blood building materials in the diet. This was the era, when micronutrient deficiencies had been recognized. Further, haemorrhagic conditions were known to lead to hypochromic microcytic anaemia, so the relevance of balancing iron intakes with needs might have been made.(24)

Defining The Role of Iron in Iron Deficiency Anaemia

Helen Mackay And The Children Of East London

After working in Vienna post-World War 1, Helen Mackay, the first woman to receive the fellowship of the Royal College of Physicians of London, studied young children in East London in the 1920s to determine ‘normal’ haemoglobin values for different stages of infancy.(25)

In earlier studies, Mackay had found that infants attending her clinics gained weight when treated for infection and given supplementary milk. These interventions had not prevented the decline in haemoglobin levels.

Supplementation with iron salts, however, produced dramatic changes. The late anaemia of infancy (that is after the physiological post-natal fall) was either prevented or, when iron was started after 6 months, diminished in iron-supplemented infants compared with those not receiving supplementary iron Mackay also remarked that iron-treated infants looked much healthier. Iron supplemented infants had only around 50% of the episodes of respiratory tract infection, diarrhoea and specific fevers experienced by the unsupplemented infants.[25]

Mackay showed high haemoglobin levels at birth, a gradual fall from birth to around 2 months and then (in Mackay's infants), a steady level until further fall from 6 months into the second year. Although the low haemoglobin of late infancy seemed more common and more severe in non-breast-fed than in breast-fed infants, both methods of feeding led to falling haemoglobin levels, hypochromia and microcytosis from 6 months onwards with the most marked falls in low-birthweight infants. As it was not known whether these findings reflected normal physiology or not, trials of likely therapeutic interventions seemed the logical way to resolve the question.[26]

Mackay's studies established the pattern of haemoglobin change in early infancy and demonstrated the nutritional vulnerability of premature infants. She drew very definite conclusions that the anaemia of late infancy resulted from insufficient iron in the diet and could be eliminated by iron therapy. Her recommendation, that iron should be given to non-breast-fed infants from the first months of life because this can support higher levels of haemoglobin later in infancy, stands good today.[25,26,)]

Iron Deficiency Anaemia In Pregnancy

Anaemia is the commonest medical disorder in pregnancy.[27] Anaemia is a common denominator in most of the maternal death.[28]

Physiological Change During Pregnancy

Plasma volume expands in pregnancy. There is a relatively greater expansion of plasma volume compared with the increase in haemoglobin mass and red cell volume.[4]

Iron Requirement In Pregnancy

The total iron requirement during pregnancy ranges between 580-1340 mg. Table - 2 shows the iron requirement during pregnancy.

TABLE - 2 : IRON REQUIREMENTS DURING PREGNANCY[29]

Sl.no	Parameters	Average	Range
1	External iron loss	170 mg	150 – 200 mg
2	Expansion of red cell mass	450 mg	200 – 600 mg
3	Foetal iron	270 mg	200 – 370 mg
4	Iron in placenta and cord	90 mg	30 – 170 mg
5	Blood loss at delivery	150 mg	90 – 310 mg
6	Total iron requirement	980 mg	580 – 1340 mg

Hence pregnant and lactating women need 5 -6 mg of iron daily in food.[29] The recommended dose may be as high as 240 mg / day in developing countries.[30]

In 1989, the World Health Organization (WHO) recommended universal supplementation of all pregnant women with 60 mg of Ferrous iron twice daily in populations where gestational anaemia is common and once daily in population where overall iron nutrition is better.[31] Since 1990, National nutritional anaemia control programme has been implemented in which the dose of iron supplement of women was increased from 60 mg to 100 mg with 0.5 mg of folate.[32]

Causes of IDA in pregnancy

Dietary habits : Vegetarians are at an additional disadvantage because certain food stuff that include phytates and phosphates reduce iron absorption by about 50%. When ionisable iron salts are given together with food, the amount of iron absorbed is reduced. Iron in vegetable is only about one – twentieth as available, egg iron one-eight, liver iron one half and haem iron one half to two third. Hence liver and haem iron are absorbed nearly as well as iron salt added to food, while the iron in vegetables and eggs is much less available.[33]

Worm Infestation : Iron deficiency anaemia may also arise from certain associated illness such as ankylostomiasis.[34]

Repeated Pregnancy : Singh *et al.,* reported anaemia to be higher in multigravida.[39]

Maternal Effects : Anaemia is associated with palpitation, tachycardia, breathlessness and increased cardiac out put which can lead to cardiac failure. Increased risk of preterm labour is associated with anaemia. Postpartum

problems may get aggravated by anaemia, especially failure of lactation, puerperal sepsis, subinvolution of the uterus and delayed wound healing.[4]

Foetal Effects : Mola *et al.,* showed maximum still birth rate in severe and moderate anaemic group. Increased perinatal mortality rate, preterm birth, intrauterine death, low birth weight, early neonatal complications were significantly higher in women with severe anaemia.[36]

Symptoms

Pregnant women with mild anaemia are usually diagnosed by performing haemoglobin estimation at the initial visit. Moderate anaemia may present with fatigue, dizziness. Breathlessness and palpitation are features of severe anaemia.[7]

Signs

Pallor of the tongue and conjunctiva are important signs of anaemia; Bilateral pedal edema is common feature of severe anaemia.[7]

Laboratory Findings

Iron deficiency develops in stages. The first stage is depletion of iron stores. At this point there is anaemia but no change in red blood cell size. A ferritin value less than 30 micro grams/dl is an indicator of iron deficiency. The serum total iron binding capacity rises.

After iron stores have been depleted red blood cell formation will continue with deficient supplies of iron. Serum iron values decline to less than 30 μg/dl and transferrin saturation to less than 15%.

In the early stages, mean corpuscular volume remains normal; subsequently mean corpuscular volume falls and the blood smear shows hypochromic microcytic cells. With further progression anisocytosis and poikilocytosis develop. Severe iron deficiency will produce a bizarre peripheral smear, with severly hypochromic cells, and occasionally small number of nucleated red blood cells.(37)

Treatment

Iron therapy is indicted only for the prevention or cure of iron deficiency. When oral therapy is used there is an enormous variety of official and proprietary iron preparations.(38)

When IDA is diagnosed, the usual treatment is an oral iron preparation; Several iron preparations are available for oral administration.(38)

Oral Iron Therapy

Sources of Iron

Diet

On average, 1000 calories worth of food provides about 6 mg of iron.(39) Meat is an important source of haem iron, which is the most bioavailable form of iron in the diet. The content of iron in food has been significantly reduced since the

stone age, when the diet contained about 28.5 mg of iron per 1000 K.calories, compared to presently 4.5 to 5.0 mg per 1000 K.calories.[40] Haem iron is highly available for absorption, about 20 – 30% is absorbable. Non-haem iron is absorbed less than 5%. Availability is determined by the balance between inhibitors – phytates, tannates, phosphates and enhancers – amino acids and ascorbic acid.[41] The bioavailability of iron in vegetarian diet is of special concern because vegetarians eliminate meat and their diet commonly contain more inhibitors of iron absorption such as phytic acid. The absorption of non-haem iron from a vegetarian diet is up to 70% lower than from non-vegetarian diet, which explains why vegetarians often have small iron stores.[42] Tea is a stronger inhibitor than coffee, while orange juice and other Vitamin C containing food stimulate the uptake of iron.[43]

Vegetable Foods Rich in Iron

Green vegetables, peas, beans, bananas, spinach are rich in iron.[39]

Animal Foods Rich in Iron

Meat, liver, heart, crab muscle, fish. Food cooked in iron and stainless steel pans can be significant source of iron.[39]

Iron Preparations

Ferrous Sulphate

Ferrous sulphate is the hydratred salt $FeSO_4.7H_2O$, contains 20% of iron; it consists of pale bluish green crystal or granules, soluble in 1 : 1.5 in water. It effervesces in dry air; in moist air, crystals of ferrous sulphate readily

oxidized and become coated with a brownish yellow, basic ferric sulphate and must then not be used for medicinal purposes. The drug is odourless and has a saline, astringent taste. It is usually dispensed as pills or tablets coated to protect them from moisture. The salt is mixed with glucose or lactose to protect it against oxidation. Official ferrous sulphate tablet usually contains 300 mg of the salt.[15]

Pharmacokinetics and Pharmacodynamics of Iron

Iron is quantitatively the most important biocatalytic element in human enzymology, with important roles in oxygen transport and storage, oxidative metabolism in cellular growth and proliferation. This is because of its ability to reversibly and readily cycle between the ferrous(Fe^{2+}) and ferric iron(Fe^{3+}) oxidation state.

Iron is present in the body in three compartments

1. Functional iron
2. Transport iron
3. Storage iron.[41]

Functional Iron Proteins

Haem contains a porphyrin molecule namely protoporphyrin IX, with iron at its center. Haemoglobin is a conjugated protein, containing globin – the apoprotein part – and the heme – the non-protein part.[44] Four of them in turn bind loosely to form the whole haemoglobin molecule.[45]

The functional iron compartment includes iron 30mg/kg as haemoglobin iron contained within the circulating red cells and an additional 6-7mg/kg that is present in tissues throughout the body in myoglobin and in a variety of haem enzymes and non haem enzymes.[41]

Transport Iron and Storage Iron

Apotransferrin is a single chain glycoprotein. Composed of two lobes. Each lobe bind a single ferric ion so that the molecule exist as transferrin. The total amount of apotransferrin in human is about 240mg/kg, equally divided between the plasma and extravascular fluids. Apotransferrin is produced by hepatocytes.[41]

Transferrin Receptor

Transferrin receptor is transmembrane glycoprotein. The transferrin receptor can bind two molecules of transferrin. They are expressed virtually on all nucleated cells. They are expressed virtually on large numbers in erythroid precursors, placenta and liver. The number of transferrin receptor on the cell surface is a prime determinant of cellular iron supply. The half life for disappearance of transferrin receptors from the cell has been reported to range from < 24 hours to 2 – 3days.[41]

Storage Iron

Apoferritin is a spherical protein; has two subunits; provide route for movement of iron in and out of the interior of sphere. [41]

Ferritin is major storage protein. Composed of 24 subunits. Each ferritin molecule can reversibly store as many 4500 iron atom with in the cell. Catabolism of cellular ferritin may result in digestion of protein shell with reutilization of the iron core. Normally, the amount of plasma ferritin synthesized and secreted seems to be proportional to the amount of cellular ferritin produced in the internal iron storage pathway so that the plasma ferritin concentration is related to the magnitude of body iron stores.(41)

Iron Regulatory Proteins (IRP)

IRP–1 and IRP–2. These are proteins involved with regulation of cellular iron metabolism called iron regulatory proteins. The two IRPs bind with equally high affinity to (IRE) Iron responsive element.(41)

Nramp–2 (National resistance associated macrophage protein) is a mammalian iron transporter involved in the transport of iron from the intestinal lumen into the enterocytes; controls transport of iron across the endosomal membrane for cellular utilization.(41)

Iron Metabolism At Cellular Level

Iron Absorption

Iron is absorbed at the brush border of epithelial cells of the intestinal villi particularly in the duodenum and upper jejunum.

Gastric juice stabilizes dietary ferric iron; preventing its precipitation as insoluble ferric hydroxide. At pH less than 3, ferric iron is stable and binds

loosely to mucin. Within the brush border of the epithelial cell a transmembrane ferric reductase converts Ferric to Ferrous ion.[46] Nramp-2 transports iron from the intestinal lumen into the enterocyte.[41]

Enhanced level of absorption is found in the iron deficient state, increased erythropoietic activity and hypoxia. Second transporter governs the movement of mucosal cell iron across the basolateral membrane to bind to plasma protein.[29]

Mucosal Regulation of Iron Absorption

It is regulated by

1. Mucosal uptake of iron across the brush border membrane.
2. Retention of iron in storage form within the mucosal cell.
3. Transfer of iron from the mucosal cell to the plasma.

It is taken up by apotransferrin in the interstitium. It circulates in the plasma as transferrin bound iron. Two molecules of transferrin bind to the transferrin receptor. This complex is internalized to form a clathrin coated pit. In acidic environment iron is released from transferrin and is made available for cellular use or storage. When the iron is incorporated into protoporphyrin in the mitochondria, haem is synthesized. Any excess iron is stored in the cytoplasm as ferritin. Each transferrin molecule undergoes 100–200 cycles of iron binding and release during its life time in the circulation.[41]

Role of Iron Regulatory Proteins

Iron regulatory proteins IRR-I and IRP-2 function as both sensors and controller of intracellular iron supply.[41]

A decrease in intracellular available iron results in an increase in the proportion of high affinity IRPS. Increased IRP binding to IRE increases transferin receptor protein production but decrease ferritin protein production.

An increase in intracellular iron results in fewer IRP binding with IRES, decreasing transferin receptor protein production while increasing ferritin protein production.[41]

In the red cells, most iron is utilized for haemoglobin synthesis. Synthesis of haem is linked to iron availability by regulation of δ amino levulinic acid synthetase, which is the first enzyme in the biosynthesis of protoporphyrin. The final step in haem synthesis is the formation of heme from protoporphyrin IX and ferrous iron catalysed by the mitochondrial enzyme ferrochelatase.[41]

Transport of Iron between compartments

The catabolism of senescent erythrocyte release iron, which requires return to plasma transferrin, for delivery to the erythroid marrow. The outpouring of iron to plasma apotransferrin from macrophages in the bone marrow, liver and spleen constitute the largest single flux of iron from cells in the body. With iron deficiency, all the iron derived from the hemoglobin catabolism is promptly returned to the plasma and none is diverted to macrophage store. Maximal rate of release from this source in the adult is

limited to 40 – 60 mg of iron per day. All the haemoglobin is catabolised, with the globin proteolytically processed to aminoacids, releasing heme. The heme is transported to the endoplasmic reticulum of the macrophage to be degraded by heme oxgenase. Heme oxygenase is a microsomal enzyme that catalyse oxidative catabolism of haem to yield biliverdin and iron.(41)

Iron Excretion

Physiologically, iron is excreted by the following mechanism.

1. Exfoliated epithelial cells of Gastro intestinal tract
2. Exfoliated cells of skin
3. Bile
4. Urine
5. Sweat
6. Menstrual blood loss.(46)

Side Effect of Oral Iron preparations of Iron

Conventional doses of iron salts used in anaemia may cause gastrointestinal reactions such as heart burn, nausea, upper gastric discomfort, constipation and diarrhoea. Intolerance to oral iron preparations of iron is primarily a function of the amount of soluble iron in the upper gastrointestinal tract. Nausea and upper abdominal pain are common. If liquid is given, transient staining of teeth also occurs.(29)

Toxicity of Oral Preparation of Iron

Long continued administration of iron results in haemochromatosis. (29)

Overdose of Iron

Accidental iron poisoning occur in children due to ingestion of iron preparation intended for adult use. Fatal dose is 2–10 grams. All iron preparations should therefore be kept in child proof bottles.

The earliest manifestations are vomiting, often associated with hematemesis, pallor, cyanosis, lassitude, drowsiness, hyperventilation due to acidosis and cardiovascular collapse. Death occurs within 12-24 hours.

Depending upon the concentration of iron in the plasma, treatment is offered. If it is less than 3.5 mg/litre, the child is not in immediate danger. If it is more than 3.5mg/litre DEFEROXAMINE should be administered.

The initial treatment is prompt evacuation of stomach either by inducing emesis or gastric lavage. Gastric lavage should be done with sodium bicarbonate solution and at the end of lavage, 5 – 10 mg of Deferoxamine solution in approximately 60ml of sodium bicarbonate should be left in the stomach. Increased serum level require intramuscular administration of deferoxamine in doses 0.5 to 1.0 gm. The children who survive initial 3-4 days usually recover without much sequalae. Gastric stricture, fibrosis and intestinal stenosis are rare late effects.[29]

Other Iron Preparations

Therapy with oral Iron

Therapy with parenteral iron

Therapy with Oral Iron

Iron is absorbed in the ferrous form. Ferrous salts are absorbed about three times as well as ferric salts. Various iron preparations are available. Ferrous sulphate, Ferrous fumarate, ferrous gluconate, polysaccharide iron complex are some of the iron preparations.

Other iron compounds have utility in fortification of food. Reduced iron (metallic iron, elemental iron) is as effective as ferrous fumarate, provided that the material employed has a small particle size.[15]

Ferrous Fumarate

This salt occurs as an anhydrous, reddish brown granular powder. It contains 33% of iron and is moderately soluble in water, stable and almost tasteless. Unlike ferrous sulphate it does not require mixing or coating with glucose to protect it against oxidation. Official ferrous fumarate tablets usually contain 200 mg of the salt. The average adult dose is 3 – 4 tablets daily.[15]

Ferrous gluconate

Gluconate contains 12% of metallic iron. [15]

Ferrous lactate

Ferrous lactate contains 9% of metallic iron.[15]

The average dose for the treatment of iron deficiency anaemia is about 200 mg of iron per day (2–3 mg/kg), given in three equal dose of 65 mg. When the object is the prevention of iron deficiency in pregnant women a dose of 15–30 mg of iron per day is adequate to meet the 3–6 mg daily requirement of

the last two trimesters. When the purpose is to treat iron deficiency anaemia, a total dose of about 100 mg may be used[15].

Therapy with parentenal iron

When oral therapy fails, parenteral iron administration may be an effective alternative. Indications are severe oral iron intolerance and in patients, with renal disease who are receiving erythopoietin. Parenteral iron therapy should be used only when clearly indicated, since acute hypersensitivity, including anaphylactic and anaphylactoid reactions can occur in from 0.2% to 3% of patients.

Iron dextran injection is the parenteral preparation. It contains 50mg/ml of elemental iron. It can be administered Intramuscularly or Intravenously.

Sodium ferric gluconate complex in sucrose : Another parenteral iron preparation used in patients undergoing chronic haemodialysis who are receiving supplemental erythropoietin therapy.

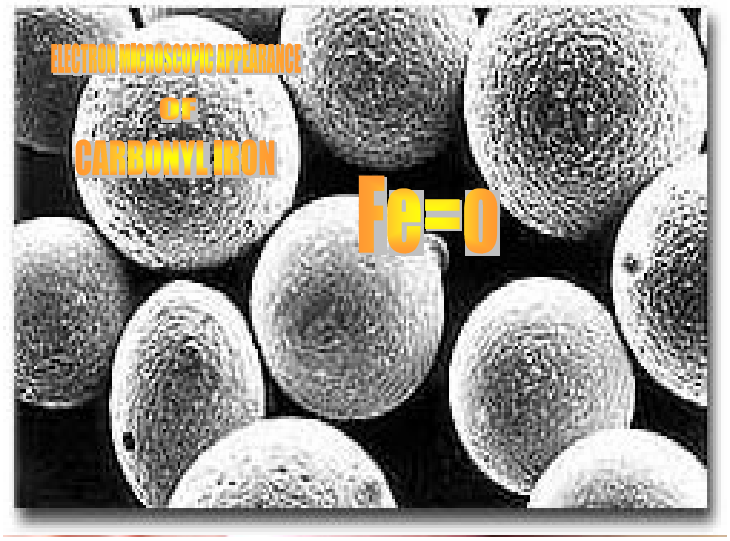
Reactions to parenteral therapy include arthralgia, fever and rare anaphylactic reaction, which may be fatal inspite of treatment. Thus, there must be specific indications for the parenteral administrations of iron[29].

CARBONYL IRON

Chemistry

Carbonyl iron powder is an elemental iron preparation.[47] As per Sacks PV and Houchin DN, carbonyl iron powder does not refer to the composition of the iron particles but refer to the manufacturing process in which controlled heating of vapourised iron pentacarbonyl leads the deposition of uncharged elemental iron as submicroscopic crystals, that form microscopic spheres of less than 5µm in diameter.[48] As per HL Sharma and KK Sharma, the time required for disintegration is saved in powders. This is the rate limiting step in the process of absorption and bioavailability.[49]

FIGURE - 4 : CARBONYL IRON



Bioavailability

Size and Shape

The Carbonyl iron powder is microscopic spheres of less than 5µm in diameter.[48] A drug usually dissolves more rapidly when its surface area is increased by decreasing its particle size. This facilitates their absorption and hence enhances the bioavailability.[49]

Elemental Iron Content

The preparation is 98% pure.[48] Absorption also depends upon the iron content. Amount of iron rather than in the mass of the total salt in iron tablet is important.[29]

In a randomized double blind study for bioavailability of carbonyl iron by Devasthali *et al*, after 16 weeks of therapy, the mean increase in hemoglobin iron was similar in both groups. Estimate of net changes in total body iron suggested that the overall bioavailability of carbonyl iron was high about 70% that of ferrous sulphate.[50]

Pharmacokinetics

Absorption

The conversion of particulate carbonyl iron to soluble ionized iron by stomach acid was a prerequisite for absorption and was limited by the rate of gastric acid production. With carbonyl iron, only that fraction solubilized by

gastric acid is available for absorption; in addition, the rate of solubilisation is restricted by the rate of gastric acid production.[51]

In a randomized double blind trial by Victor R.Gordeuk *et al*., in high dose carbonyl iron for iron deficiency anaemia, comparing high dose of carbonyl iron (1800mg/day) and a standard ferrous sulphate therapy (180mg/day) for the short term (3 week) treatment of mild iron deficiency anaemia. There was no significant difference in overall incidence of gastrointestinal side effects observed with the two forms of iron although the dose of iron as carbonyl iron was 10 times that of ferrous sulphate. In these studies, the conversion of particulate carbonyl iron to soluble iron by stomach acid was prerequisite for absorption and was limited by rate of gastric acid production.[51]

Sustained Absorption

With carbonyl iron, serum iron increase was less abrupt but more sustained, with maximal increase occurring at the end of six hour period of observation.[52]

Side Effects

Gastrointestinal side effects such as diarrhoea and unpleasant taste was noted only with 3000 mg carbonyl iron as single dose.[52]

Toxicity

Crosby suggested that carbonyl iron may be an ideal therapeutic agent, effective, yet lacking in toxicity.[53]

Human volunteers have taken oral dose of 10,000mg of carbonyl iron. About 140 mg Fe/kg without deleterious effect.[53] Toxicity studies of carbonyl iron in rats and guinea pigs found that the LD_0 was 10,000 to 15,000 mg iron/kg and the lethal dose LD_{100} was 50,000 to 60,000 mg of iron/kg.[47]

Since the lethal dose is high, there is no risk of poisoning in children in case of accidental poisoning. In a multicenter retrospective evaluation of carbonyl iron ingestion by Spiller *et al*, retrospective chart review of all patients were collected. Thirty three patients with carbonyl iron ingestion were reported. Twenty seven patients were managed without referral to a health care facility. The mean and median age of these patients was 3 years and 20 months respectively. The mean dose ingested was 11.2 mg/kg (range of 2.2 to 34.5mg/kg) with no effects noted. Six patients evaluated in the emergency ingested a mean of 34 mg/kg (range of 12 to 72 mg/kg). The mean peak serum iron concentration in 4 out of 6 were 82µg/dl (range of 36 to 177 µ/dl). One child with a history of flu like symptoms reported diarrhoea, fever and lethargy and had a serum iron concentration of 36 µg/dl; in this study, serious toxicity did not occur.[54]

In another study of acute toxicity of carbonyl iron and sodium iron EDTA compared with ferrous sulphate in young rats by Whittakar.P, Ali.SF, Iman SZ, Dunkal VC, both sodium iron EDTA and carbonyl iron were compared with Ferrous sulphate, to obtain information relevant to the acute toxicological profile in young rats. With $FeSO_4$ and sodium iron Ethylene

diamine tetra-acetate (NaFeEDTA), total liver non haem iron increased with increasing dose, but the response was approximately 50% lower with NaFeEDTA compared with ferrous sulphate. Serum iron peaked at approximately 0.5 to 1 hour for both ferrous sulphate and carbonyl iron, while NaFeEDTA was elevated upto 4 hours. Ferrous sulphate has an LD_{50} of 1.1 g Fe/kg and was approximately 45 times more toxic than carbonyl iron, which had an LD_{50} greater than 50 g Fe/kg. NaFeEDTA had an LD_{50} of 1.3 g Fe/kg and when compared with ferrous sulphate had approximately the same level of toxicity.[55]

AIM OF STUDY

Study objectives

Primary objective

To compare the efficacy of carbonyl iron formulations with ferrous sulphate in pregnant women with iron deficiency anaemia.

Secondary objective

To assess the tolerability of carbonyl iron.

To record the adverse effects of carbonyl iron.

METHODOLOGY

STUDY CENTER	:	ANTENATAL OUTPATIENTS DEPARTMENT OF INSTITUTE OF OBSTETRICS AND GYNAECOLOGY, MADRAS MEDICAL COLLEGE
STUDY PERIOD	:	DECEMBER 2.12.2004 TO 22.12.2005
STUDY DESIGN	:	OPEN LABELLED SYSTEMATIC RANDOM SAMPLING PARALLEL GROUP COMPARATIVE, PROSPECTIVE STUDY
STUDY DURATION	:	12 WEEKS
INCLUSION CRITERIA	:	AGE- 20-40 YEARS Hb LEVEL7-9gm % PREGNANCY > 16 TO <20 WEEKS OF GESTATION
EXCLUSION CRITERIA	:	Hb LEVEL : LESS THAN 7gm% PREGNANCY WITH LESS THAN 16 WEEKS OF GESTATION OTHER : HYPER EMESIS PREGNANCY INDUCED HYPERTENSION ANAEMIA WITH CARDIAC FAILURE OTHER SYSTEMIC DISEASES

STUDY PROCEDURE

The study was conducted after obtaining clearance from Institutional Ethical Committee. Pregnant women attending the antenatal out patients department of Institute of Obstetrics and Gynaecology, Madras Medical College were explained about the purpose and procedure of the study.

The demographic data was recorded and screened for anaemia by history, clinical examination and haemoglobin estimation. Among them 60 pregnant women, who fulfilled the inclusion criteria were enrolled for the study. Written informed consent was obtained from those, who were willing to participate in the study. The demographic baseline laboratory investigations - RBC count, packed cell volume, haemoglobin estimation, blood urea, serum creatinine, SGOT, SGPT, Bilirubin, urine routine analysis, motion for ova, cyst and occult blood were estimated. The 60 pregnant women were enrolled by systematic random sampling into one of the three treatment groups. Every 1st patient enter Group I and the second patient in Group II and 3rd patient to Group III. The same was followed till each group had 20 patients.

Treatment Group

Group I - Received - 10 ml of syrup corbonyl containing 50 mg of carbonyl iron **twice** daily (elemental iron 98 mg) for 12 weeks.

Group II - Received - 1 capsule of carbonyl iron 100 mg, (elemental iron 98 mg) once daily for 12 weeks.

Group III - Received - 1 tablet of Ferrous sulphate 200 mg (elemental iron 40 mg) once daily for 12 weeks.

Follow up was given at the end of every 4 weeks apart from the regular antenatal checkup. They were asked to return the empty packs/bottles and were

issued respective drugs for the subsequent 4 weeks. They were also asked to report regarding the adverse effects and the same was recorded.

The laboratory investigations

- Haemoglobin estimation
- RBC count
- Packed cell volume

were estimated at the baseline, at the end of 4th, 8th and 12th week of the study.

Blood Chemistry

Blood urea, sugar, serum creatinine, (SGOT) serum glutamic oxaloacetic transaminase, (SGPT) serum glutamic pyruvic transminase and bilirubin level were estimated at baseline and at the end of 12th week.

Urine analysis was done at the baseline and at the end of 4th, 8th and 12th week.

Motion examination for ova, cyst and occult blood was done at the baseline.

Followup

The patients were followed up till delivery even after completion of the study. Those who could not tolerate the drugs were allowed to withdraw from the study. At the end of the study, the data were compiled and analysed statistically by ANOVA-F test and ANOVA-T test.

Primary End Point

To achieve a haemoglobin level of 12g/dl or more than 11 g/dl

Secondary End Point

To study the tolerability and drug related adverse effects.

Statistical Analysis

Demographic profiles were given in frequencies with their percentages for each group.

Age, Height, Weight difference between groups were analysed by using one way analyses of variance (ANOVA) F-test.

Blood chemistry and haemogram between groups were analysed by using ANOVA t-test.

RESULTS

Among the 114 pregnant women screened, 60 pregnant women who fulfilled the inclusion criteria were enrolled for the study. 57 completed study. There were 3 drops outs. The 3 drops were from ferrous sulphate group.

Total Pregnant women Screened for the study : 114

Pregnant women enrolled	: 60
Pregnant women completed the study	: 57
Drop outs (from Tablet. Ferrous sulphate group)	: 03

Reason

1. Lost for follow up	: 01
2. Withdrawl from the study	: 02

(Heart burn 1, diarrhoea - 1)

DEMOGRAPHIC CHARACTERISTICS

TABLE – 4 : MEAN AGE

Sl.No.	Group	Mean
1.	Syrup-Carbonyl	25.05
2.	Capsule -Carbonyl	24.15
3.	Tab. Ferrous sulphate	24.12

(p value = 0.68)

Table – 4 shows the mean age of the three study groups

Mean age in syrup carbonyl iron group : 25.05 (years)

Mean age in capsule carbonyl iron group: 24.15 (years)

Mean age in Tablet ferrous sulphate : 24.12 (years)

TABLE – 5 : MEAN HEIGHT

Sl.No.	Group	Mean
1.	Syrup-Carbonyl	148.00
2.	Capsule -Carbonyl	151.85
3.	Tab. Ferrous sulphate	148.12

(p value = 0.29)

The table- 5 describes the mean height of pregnant women in the three study groups.

Mean height in syrup carbonyl iron group : 148 cms

Mean height in capsule carbonyl iron group : 151.85 cms

Mean height in tablet ferrous sulphate group : 148.12 cms.

TABLE – 6 : MEAN WEIGHT (kgs)

Sl.No.	Group	Mean
1.	Syrup-Carbonyl	45.00
2.	Capsule -Carbonyl	44.75
3.	Tab. Ferrous sulphate	45.00

(p value = 0.99)

Table – 6 shows the mean weight in the three study groups.

Both syrup carbonyl iron and Tablet ferrous sulphate shows the mean weight of 45.0 kg. whereas capsule carbonyl iron had 44.75 kg. as mean weight.

TABLE – 7 : MEAN BLOOD PRESSURE (mm of HG)

Sl.No.	Group	Mean
	Systolic blood pressure	
1.	Syrup-Carbonyl	111.90
2.	Capsule -Carbonyl	109.00
3.	Tab. Ferrous sulphate	120.00

(p value =0.35)

	Diastolic blood pressure	
1.	Syrup-Carbonyl	80.40
2.	Capsule -Carbonyl	79.00
3.	Tab. Ferrous sulphate	81.53

(p value 0.28)

Table 7 shows the mean systolic and diastolic blood pressure in the three groups.

The mean systolic BP was 111.90 in syrup carbonyl iron group

The mean systolic BP was 109.00 in capsule-carbonyl iron group

The mean systolic BP was 120.00 in Tab. ferrous sulphate iron group

The mean diastolic BP was 80.40 in syrup carbonyl iron group

The mean diastolic BP was 79.00 in capsule-carbonyl iron group

The mean diastolic BP was 81.53 in Tab. ferrous sulphate iron group

Systolic blood pressure (p value = 0.35)

Diastolic blood pressure (p value = 0.28)

TABLE - 8 : MEAN HAEMOGLOBIN LEVEL

Weeks	Group		
	Syrup-carbonyl	Capsule-Carbonyl	Tab-Ferrous Sulphate
0	8.40	8.57	8.35
4	10.57	11.05	9.45
8	11.43	11.73	9.97
12	11.96	12.09	10.41

(p value - 0.001)

The above table 8, shows the mean Hb gm % of all the 3 group at baseline (0), at the end of 4th, 8th and 12th week respectively.

The mean Hb% for syrup-carbonyl iron at the baseline 8.40 gm %
The mean Hb% for syrup-carbonyl iron at the end of 12th week 11.96 gm %

The mean Hb% for capsule-carbonyl iron at the baseline 8.57 gm %
The mean Hb% for capsule-carbonyl iron at the end of 12th week 12.09 gm %

The mean Hb% for tab-ferrous sulphate iron at the end of baseline 8.35gm %
The mean Hb% for tab-ferrous sulphate iron at the end of 12th week 10.41gm %

TABLE - 9 : MEAN RED BLOOD CELL COUNT

Weeks	Group		
	Syrup-carbonyl	Capsule-Carbonyl	Tab-Ferrous Sulphate
0	3.27	3.41	3.17
4	3.58	3.77	3.31
8	3.76	3.92	3.42
12	3.89	4.04	3.51

(p value - 0.001)

Table-9 furnishes the mean RBC count among the three groups at baseline, at the end of 4th , 8th and 12th week of the study.

The mean RBC count for syrup-carbonyl iron at the baseline 3.27

The mean RBC count for syrup-carbonyl iron at the end of 12th week 3.89

The mean RBC count for capsule-carbonyl iron at the baseline 3.41

The mean RBC count for capsule-carbonyl iron at the end of 12th week 4.04

The mean RBC count for tab-ferrous sulphate iron at the end of baseline 3.17

The mean RBC count for tab-ferrous sulphate iron at the end of 12th week 3.51

TABLE-10 : MEAN PACKED CELL VOLUME

Weeks	Group		
	Syrup-carbonyl	Capsule-Carbonyl	Tab-Ferrous Sulphate
0	27.90	28.80	26.88
4	32.90	33.75	28.78
8	34.20	35.70	29.71
12	35.25	37.15	30.53

(p value =0.001)

Table-10 shows the mean packed cell volume for syrup carbonyl iron, Capsule Carbonyl iron and Tablet Ferrous sulphate at the baseline, at the end of 4th, 8th and 12th week of the study.

The mean packed cell volume for syrup-carbonyl iron at the baseline 27.90

The mean packed cell volume for syrup-carbonyl iron at the end of 12th week 35.25

The mean packed cell volume for capsule-carbonyl iron at the baseline 28.80

The mean packed cell volume for capsule-carbonyl iron at the end of 12th week 37.15

The mean packed cell volume for tab-ferrous sulphate iron at the end of baseline 26.88

The mean packed cell volume for tab-ferrous sulphate iron at the end of 12th week 30.53

TABLE -11 : SIDE EFFECT PROFILE

SIDE EFFECT	GROUP		
	Syrup Carbonyl iron	**Capsule Carbonyl iron**	**Tablet Ferrous sulphate**
CONSTIPATION	NIL	NIL	5 (29.4%)
DIARRHOEA	NIL	NIL	12 (70.6%)
HEART BURN	NIL	NIL	12 (70.6%)
EPIGASTRIC PAIN	NIL	NIL	15 (91.4%)
VOMITING	(3) 15%	NIL	NIL

Table-11, which describes side effect shows that there was no constipation, diarrhoea, heartburn and epigastric pain in syrup and capsule carbonyl iron groups. Vomiting was present in (3) 15% of syrup carbonyl iron group. In tablet ferrous sulphate group except for vomiting all other side effects were reported.

DISCUSSION

Nutritional anaemia is a world wide problem with the highest prevalence in developing countries. It is estimated to affect nearly two third of pregnant women and one half of non-pregnant women in developing countries.[1]

Detrimental Effect

Agarwal reported that maternal anaemia resulted in 12 to 28% of foetal loss, 30% of perinatal death and 7-10% of neonatal death. Low birth weight is the most important factor in determining the chance of survival of the new born.[56] Klenanoff *et al.,* stated that anaemia during the second trimester was associated with preterm birth. Preterm delivery increased five fold in iron deficiency anaemia.[57] Anaemia in pregnancy is also associated with increased maternal mortality. Maternal death to the extent of 15-20% are directly or indirectly due to anaemia.[58]

Anaemia which is a common denominator of maternal and foetal morbidity and mortality, can be treated effectively by oral iron therapy. Hence this study was chosen having carbonyl iron as the oral iron and compared with, Ferrous sulphate to assess the efficacy and tolerability in IDA during pregnancy.

This prospective, comparative, systematic random sampled open labelled study was carried out in the pregnant women attending the out patient department at Institute of Obstetrics and Gynaecology, Madras Medical College.

114 of them were screened and 60 of them who fulfilled the inclusion criteria were enrolled for the study. By systematic random sampling technique, they were assigned to receive either syrup carbonyl iron 50mg twice daily, capsule carbonyl iron 100mg once daily, or tablet ferrous sulphate 200mg once daily for 12 weeks. Among the 60, 57 of them had successfully completed the study. Three of them belonging to ferrous sulphate group were the drop outs. One did not come for follow up; two others with drew because one complained of diarrhoea and the other had heart burn.

The three groups were comparable in terms of age, height and weight at the base line and was not found to be statistically significant indicating that the study was conducted among the groups having similar baseline characters.

p value for age	=	0.68
p value for height	=	0.29
p value for weight	=	0.99

Erythropoietic Efficacy

This study has succeeded in demonstrating the efficacy, which was realised as increase in Haemoglobin level, RBC count and Packed cell volume with minimal gastrointestinal side effects. Effect of therapy on haematological parameters is depicted in Table - 8, 9, 10.

Haemoglobin level : All the three groups shared an increase in haemoglobin level at the end of 4th week and it was greater in carbonyl iron groups than ferrous sulphates. At the end of 12 weeks all the three groups had a further increase in haemoglobin level and the recommended 12 gm/dl was achieved in carbonyl group but was not achieved with ferrous sulphates.

Statistical analysis by repeated measure analysis of variance shows significant difference in capsule carboynl iron ($p=0.001$). Statistical analysis between weeks in all the groups showed a significance difference ($p=0.001$).

Other studies corroborate this finding. Gordeuk VR, Brittenham GM, Mc Laren.CE, Hughers MA, Keating LJ demonstrated in their study that anaemic volunteers who were treated with carbonyl iron daily showed a mean daily increase in haemoglobin of 0.01 ± 0.01 gm/dl.[52]

In another randomised double–blind study, regarding bioavailability of carbonyl iron, Devasthali SD, Gorduek VR, Brittenham GM, Bravo JR, Hughes MA, Keating LJ demonstrated that 49 female blood donors with iron deficiency anaemia were treated with equal doses iron either as carbonyl iron or ferrous sulphate in a randomised double-blind fashion. Mean value for

haemoglobin concentration, mean corpuscular volume, reticulocyte count did not differ significantly between the two groups, through out the study. After 16 weeks of the therapy , the mean increase in haemoglobin iron was similar with both groups. Estimates of net changes in total body iron suggested that overall bioavailability of carbonyl iron was high, about 70% that of ferrous sulphate.(50)

In accordance with the study by Swain JH, Hunt J.R 2002 in their study stated that carbonyl iron is a more effective haemoglobin repletion agent with more bioavailability than the reduced iron powder forms. (59)

In our study also both syrup and capsule carbonyl iron had statistically significant increase in haemoglobin level. Among the three groups the increase was significantly higher in the capsule carbonyl iron group as compared with syrup carbonyl iron and ferrous sulphate group.

In the study by Gordeuk *et al*, 25 healthy volunteers were given orally a solution containing 498mg of ferrous sulphate (100mg of elemental iron) and 100mg of ascarbic acid. Five volunteers received carbonyl iron in single incremental doses of 100mg, 1000mg and 5000mg at approximately 1 week interval. With 100mg of carbonyl iron the rise in serum iron was less abrupt, but more sustained with maximal increase occurring at the end of 6 hour period of observation. These studies revealed that there is an increase in haemoglobin level, mean corpuscular volume and serum iron level with carbonyl iron.(52)

In our study, the red blood cell count (RBC) also showed a statistically significant increase of in syrup carbonyl iron, capsule carbonyl iron and tablet

ferrous sulphate groups respectively. The statistically significant increase was greater in the capsule carbonyl iron group compared to that seen in syrup carbonyl and ferrous sulphate group.

In our study capsule carbonyl had a better response (p value =0.001).

The haemotocrit values also showed a statistically significant increase in capsule carbonyl iron, syrup carbonyl iron and tablet ferrous sulphate. The increase in haemotocrit value was significantly greater in carbonyl iron both within the groups and in between the groups.

Statistical analysis by repeated measure analysis of variance shows significant difference between groups (p=0.001) and weeks wise significance difference (p=0.001).

Analysis of our study results showed that capsule carbonyl iron group had registered a statistically significant increase in haematological response over syrup carbonyl iron and tablet ferrous sulphate group.

Blood chemistry

SGOT, SGPT bilurubin blood urea and serum creatinine remained within the normal range in all the three groups at the basement and at the end of the study. Statistical analysis shows no significant change.

Tolerability

Gastrointestinal side effects like constipation, diarrhoea, heart burn, and epigastric pain were noticed with tablet ferrous sulphate group. The

gastrointestinal side effects were absent with carbonyl iron groups although 3 patients registered vomiting in syrup carbonyl iron group.

Our study results coincides well with study on higher dose carbonyl iron for iron deficiency anaemia by Gorduek etal. A randomised double-blind trial comparing high doses of carbonyl iron(1800mg/day) and standard ferrous sulphate therapy(180mg/day) for short term (3week) treatment of mild iron deficiency anaemia. High dose carbonyl iron was well tolerated. These results suggest that the principal advantage to the use of carbonyl iron derive from its safety.[51]

According to the study conducted by Reddiah VP *et al*., to determine the optimum dose of supplemental iron for prophylaxis against pregnancy anaemia. 110 pregnant women randomly allocated to the three groups. Group A receiving equivalent of 60mg, Group B 120mg, Group C 240mg of elemental iron as Ferrous sulphate daily. The content of folic acid was constant in all the three groups. These women had atleast consumed 90 tablets in 100 +/– 10 days. Blood was drawn at the beginning and at the end of the study. Fifty percent were anaemic (less than 11gm/100ml). The haemoglobin levels rose similarly in all groups and the difference were statistically not significant. 56% had depleted iron stores, at the beginning of the study. The side effects increased with increasing doses of iron; 32.4%, 40.3% and 72% in groups A,B,C respectively. Based on these findings the authors advocate the optimum dose iron should be 120mg instead of 60mg as is currently being used in the National anaemia programme.[60] Hence the dose of carbonyl iron was chosen to be 100 mg once daily.

SUMMARY AND CONCLUSION

Sixty antenatal anaemic mothers were grouped into three.

Group I - Received - 10 ml of syrup carbonyl iron containing 50 mg of carbonyl iron twice daily (elemental iron 98 mg) for 12 weeks.

Group II - Received - 1 capsule of carbonyl iron 100 mg, (elemental iron 98 mg) once daily for 12 weeks.

Group III - Received - 1 tablet of Ferrous sulphate 200 mg (elemental iron 40 mg) once daily for 12 weeks.

Basal laboratory investigation were done before and after the treatment. Primary end point for the study was to achieve haemoglobin level more than 11 gm/dl. Secondary end point was to study the compliance, tolerability and adverse drug effects.

We concluded that there was no significant change in basal laboratory and clinical parameters after the study.

There is significant increase in haemoglobin level, RBC count, haemotocrit values in both Group I and II. As far as the side effects constipation, heart burn and epigastric pain are nil with Group I and II. Vomiting was reported in 15% of syrup carbonyl iron. Gastro intestinal side effects were more in tablet ferrous sulphate than the other two groups.

It is concluded that capsule carbonyl iron is the best preferred therapy in efficacy and tolerability than syrup carbonyl iron and tablet ferrous sulphate.

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$FeSo_4$	-	Ferrous Sulphate
g/dl	-	Grams per decilitre
Hb	-	Haemoglobin
ICMR	-	Indian Council of Medical Research
IDA	-	Iron deficiency anaemia
IRE	-	Iron Responsive Element
IRP	-	Iron Regulatory Proteins
MCHC	-	Mean corpuscular haemoglobin concentration
NaFeEDTA	-	Sodium iron Ethylene diamine Tetra-acetate
NFHS-2	-	National Family Health Services
Nramp-2	-	National resistance associated macrophate proteins
PCV	-	Packed cell volume
RBC	-	Red Blood Cells
SGOT	-	Serum glutamic oxaloacetic transaminase
SGPT	-	Serum glutamic pyruvic transaminase
WHO	-	World Health Organisation