ORIGINAL ARTICLE

# Effect of Calcium Supplementation on Iron Absorption in Iron Deficiency anemia in Pregnancy

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## Abstract

***Background:*** *Iron deficiency anemia is a common problem worldwide. It is more problematic in case of pregnancy. Usually irons along with minerals specifically calcium are advised during pregnancy to fulfil the deficient state. In the present study the effect of calcium supplementation on iron absorption in iron deficiency anemia in pregnancy was investigated.* ***Materials & Methods:*** *A total of 36 patients, aged 19-35 years with moderate degree of iron deficiency anemia in their second trimester participated in the study. The patients with haemoglobin concentration between 7.0 to 9.9 gm/dl were included in the study. Haemoglobin concentration, packed cell volume, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and red blood cell count (RBC), serum iron, total iron binding capacity (TIBC) and serum ferritin level were measured at baseline (day 0), day 30, day 60 and day 90.* ***Results:*** *Inhibitory influence of calcium on iron absorption was observed initially but on chronic administration this inhibitory influence lost. Statistically significant increased observed in all parameters except serum iron and TIBC in which there was no significant difference from baseline level seen.* ***Conclusion:*** *It is recommended that women should consume an iron supplement containing more than 30 mg elemental iron per day from meals during the second and third trimesters, to diminish the risk of developing iron-deficiency anemia.*

***Keywords****: Calcium supplementation, Iron deficiency anemia, Iron supplementation*

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## Introduction

Iron deficiency is believed to be the most prevalent nutrient deficiency in the world. Women have increased risk of iron deficiency due to their higher iron demands.[1] It is common problem in pregnancy. Haemoglobin below 10.5 g/dl is regarded as iron deficiency anemia. It is believed to be 20-80% prevalence worldwide.[2] It's prevalence is more common in developing world.[3]

Iron deficiency anemia during pregnancy has been related to several adverse health consequences, including increased risk of maternal mortality during the perinatal period, low birth weight and preterm births. Anemia during pregnancy may also compromise maternal immunologic status and in severely anaemic women, increased placental weight. [4]

This may be related to high iron requirements during gestation because iron is necessary to cover basal iron losses, the increase in maternal red cell mass and development of the fetus and placenta. The risk of iron deficiency is particularly high in women who begin gestation with depleted or low body iron stores.[5]

Furthermore, mothers given iron supplementation had decreased risk of preterm delivery compared with mothers without supplements. Thus the relationship between maternal iron deficiency and preterm birth and fetal growth restriction seems to be well established. [6]

For the past several decades the provision of oral iron supplements to pregnant women has been the primary method to decrease the prevalence of anemia. A commonly cited reason for the ineffectiveness of iron supplementation in developing countries is the reluctance of women to adhere to a regimen that is often associated with gastrointestinal side effects.[7]

Iron and calcium are essential nutrients and the requirements for both nutrients are especially high in the pregnant women. The recent findings thus imply that the calcium inhibition of iron absorption might be very important nutritionally. It would thus be essential to attempt to discover ways of counteracting these effects. [8]

High intakes of dietary or supplemental calcium are known to reduce the incidence of osteoporosis. Conversely, the potentially inhibitory effects of calcium on iron absorption may increase the problem of iron deficiency anemia. There is convincing evidence from human studies that at least some forms of supplemental calcium inhibit the absorption of inorganic iron when they are taken simultaneously.[9]An iron-calcium interaction may be especially significant in pregnant women, since most prenatal supplements contain large amounts of iron and calcium, and it is not unreasonable to suspect that iron bioavailability from such supplements is low indeed, in non-pregnant women, iron absorption from a variety of parental supplements containing ferrous fumarate plus calcium as (sulfate or carbonate) was significantly reduced compared to iron bioavailability from ferrous fumarate alone. [10]

In addition to replacing the normal external iron loss that averages 0.5 to 1.0 mg per day in a non-menstruating women an addition averages of 3.5 mg must be absorbed throughout pregnancy to allow for the expansion of maternal red blood cell mass and to compensate for maternal iron loss to the fetus, iron loss in placenta, cord and iron loss from bleeding at delivery. The average of an additional 3.5 mg of iron that must be absorbed daily throughout pregnancy must come from iron supplements.[10]Hence the present study was planned to investigate the effect of calcium supplementation on iron absorption in iron deficiency anemia in pregnancy.

## Materials and Methods

A total of 36 patients, aged 19-35 years with moderate degree of iron deficiency anemia in their second trimester who agreed to participate in the clinical study were included. Patients were recruited from the antenatal clinic of Indira Gandhi Government Medical College and Mayo Hospital, Nagpur. Gestational age was 12-16 weeks of pregnancy at the beginning of the study. The patients with haemoglobin concentration between 7.0 to 9.9 gm/dl were included in the study. Blood parameters such as blood glucose, urine albumin and sugar were normal.

Patients having pre-eclampsia, urinary tract infection, malaria, bleeding tendencies renal, cardiac (including rheumatic or congenital heart disease) and hepatic disorders were excluded from the study. Patients having history of sickle cell disease, recent infection or of disorders known to impair iron absorption from the gastrointestinal tract, history of seizure disorders, mal-absorption and gastrointestinal disorders were also excluded from the study. Patients on iron and calcium supplements at the time of enrollment and patients with obstetric problems such as multiple pregnancy and diabetes mellitus were not part of the study.

Prior approval for the study was obtained from the Institutional Ethical Committee. A written informed consent was obtained at the time of enrollment from each patient who participated in the study.

Drug dosage chosen represent the therapeutically as well as prophylactically used dose. Patients received calcium as calcium carbonate 875 mg (elemental calcium 350 mg), ferrous fumarate 100 mg (elemental iron 32 mg) and folic acid 0.5 mg separately. Patients were instructed to take tablet ferrous fumarate, tablet calcium carbonate and tablet folic acid simultaneously one after another orally three times a day.

Clinical examination of the patient was done to detect anemia. Haemoglobin concentration was determined simultaneously by Acid Haematin method (Sahli's Haemoglobinometer) to correlate with the clinical findings.

Venous blood was drawn from each patient for baseline measurement of parameters on day 0. To determine complete blood count (CBC) such as haemoglobin concentration, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and red blood cell count (RBC) automated counter was used. Serum iron, total iron binding capacity (TIBC) and serum ferritin level were also measured.

The follow up of the study was at every 15 days for a period of 90 days. At each follow up visit patient compliance with the study medication and tolerability of the study medication was recorded. Blood sample were collected from each patient at 30, 60 and 90 days follow –up visit to monitor the haematological response. Six patients discontinued the study due to abortion, sickle cell anemia, failed to co-operate and discontinued treatment. Thus 30 patients completed the study. Mean values (at baseline, day 30, day 60 and day 90) were compared by One way ANOVA test using Graph Pad Prism software version 8 (Trial).

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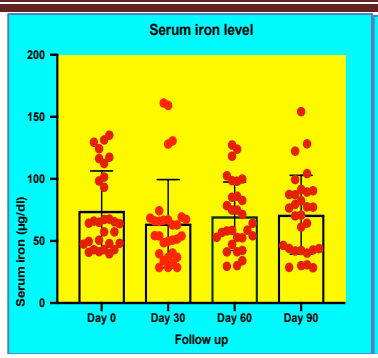
## Results

Mean age of patients was 22.3 ± 0.14 and the mean weight was 42.23 ± 0.45. Serum iron level was not increased during the 90 days of study period, infact serum iron level was relatively more at day zero in comparison to day 30, day 60 and day 90. It was observed that Total iron binding capacity (TIBC) was increased during the entire study period although it was statistically not significant. In the present study, serum ferritin levels were low initially but as pregnancy advanced; it was found that serum ferritin levels were increased significantly at 30 and 60 days follow ups. The reticulocyte was significantly more at day 60. It was found that the haemoglobin level progressively increased from day 0. Red blood cell count was increased at day 90. Mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) were significantly more at day 60. Mean corpuscular haemoglobin concentration (MCHC) and packed cell volume were also increased. Statistically significant increased observed in all parameters except serum iron and TIBC (Table-1 and Graph 1 to 10).

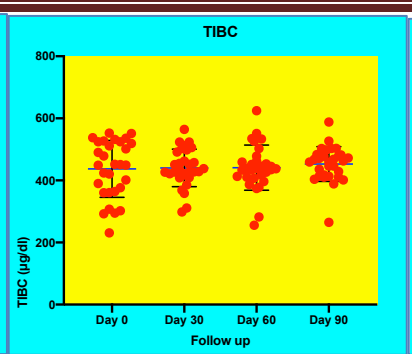
**Table- 1: Mean values of Serum iron, TIBC, Serum ferretin, Reticulocyte count, Haemoglobin, RBC, MCV, MCH, MCHC and PCV**

| | **Day 0** | **Day 30** | **Day 60** | **Day 90** | |
|---|---|---|---|---|---|
| | **Mean±SD** | **Mean±SD** | **Mean±SD** | **Mean±SD** | **p value** |
| Serum iron (µg/dl) | 74.32±32.16 | 63.97±35.52 | 70.02±27.60 | 70.88±31.64 | 0.6472ns |
| TIBC (µg/dl) | 433.77±93.03 | 440.26±60.36 | 447.71±80.83 | 452.81±56.02 | 0.8413ns |
| Serum Ferritin (ng/dl) | 5.93±1.79 | 13.10±3.52 | 10.71±3.81 | 6.90±2.22 | P<0.001* |
| Reticulocyte count (%) | 0.57±0.17 | 1.45±0.44 | 1.97±0.45 | 1.67±0.59 | P<0.0001* |
| Haemoglobin (gm/dl) | 7.87±0.91 | 8.54±0.89 | 9.29±0.76 | 10.00±0.73 | P<0.0001* |
| RBC (million/cu.mm) | 3.81±0.40 | 3.48±0.39 | 3.61±0.34 | 4.13±0.41 | P<0.0001* |
| MCV (fl) | 70.88±7.58 | 86.04±10.90 | 84.64±8.35 | 77.04±8.10 | P<0.0001* |
| MCH (pg) | 20.84±2.83 | 24.81±3.48 | 25.87±2.89 | 24.44±2.70 | P<0.0001* |
| MCHC (gm/dl) | 29.35±1.90 | 28.82±1.45 | 30.59±1.90 | 31.76±1.86 | P<0.0001* |
| PCV (%) | 26.83±2.81 | 29.62±2.45 | 30.41±2.05 | 31.49±1.52 | P<0.0001* |

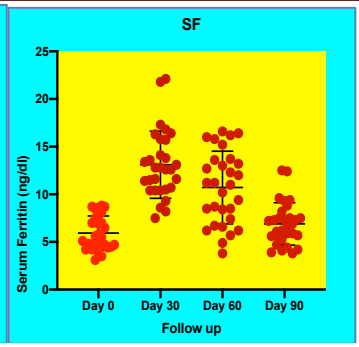
ns=non significant, *= significant p value, TIBC- Total Iron Binding Capacity, MCV – Mean Corpuscular Volume, MCH – Mean Corpuscular Haemoglobin, MCHC – Mean, Corpuscular Haemoglobin Concentration, PCV- Packed Cell Volume



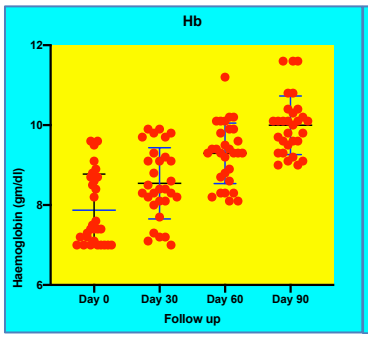

**Graph-1**



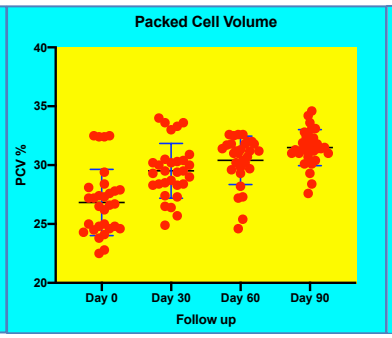

**Graph-2**




**Graph-3**




**Graph-4**

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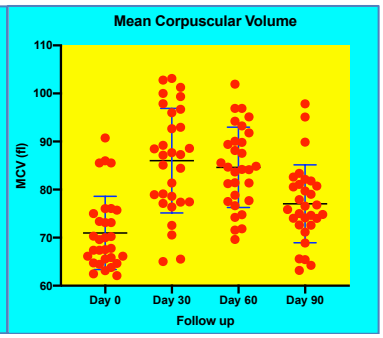


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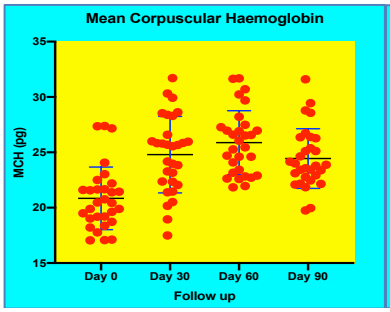
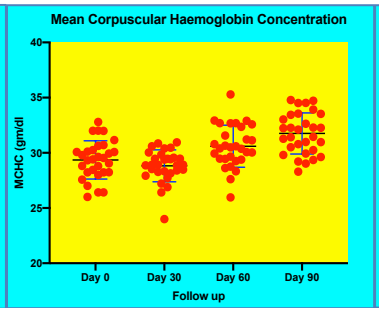



**Graph-7**

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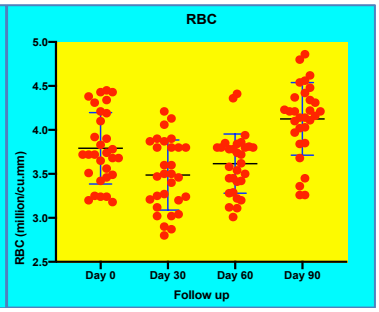
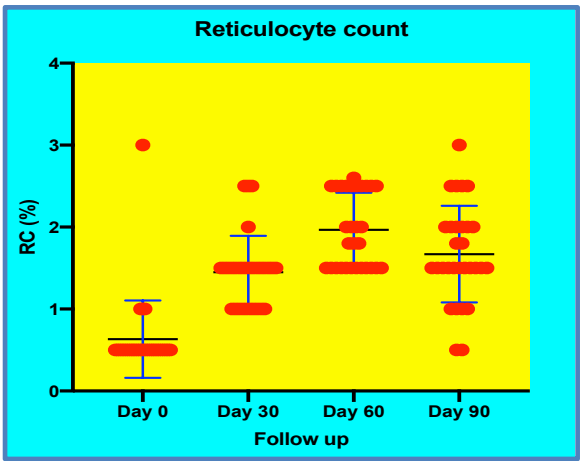



**Graph-9**




**Graph-10**

## Discussion

The major cause of anemia in pregnancy is iron deficiency and has severe consequences for the mother, foetus and neonate.[11] Because of the high frequency of iron deficiency in pregnancy and it's potential interference with health for both mother and child, routine iron supplementation during pregnancy should be given.

It is a common in clinical practice to give iron supplementation along with variety of other minerals such as calcium. Ferrous iron is absorbed much well than ferric iron hence ferrous fumarate was used in the present study. Calcium carbonate was chosen for study

because it is less expensive and widely used supplement.

The iron balance situation in pregnancy is determined by the amount of storage iron available and the amount of iron absorbed. Serum iron concentrations reflect the balance between the flow of iron into and out of the plasma pool and thus when iron stores are depleted the serum concentration will generally be reduced. Conversely, when iron stores are filled, the serum iron will also increase. [12] In the present study there was no increase in serum iron found.

In pregnancy serum ferritins is lower and mean values are close to the iron-deficient range. Serum ferritin is considered as more sensitive and specific test of iron deficiency than serum iron and total iron binding capacity (TIBC) as measured by the response to iron supplements. [13] Ferritin is a protein-iron complex, which exists as individual molecules. Iron supplementation given to anaemic patients increases the ferritin production and is also used for haemoglobin synthesis. [14]

Ferritin was measured because plasma concentrations are directly proportional to iron stores in the body and the ferritin is one of the most sensitive plasma measures of iron-depletion. [15]

In the present study, serum ferritin levels were low initially indicating a below average iron store and may explain a large proportion of pregnant women who develop exhausted iron stores. As pregnancy advances and iron absorption increases, the iron stores are partly replenished as is serum – ferritin, depending on the consumption of supplemental iron.[13] In the present study increased serum ferritin levels were observed at 30 and 60 days follow ups. One possible explanation for increased ferritin levels might be due to the absence of some menstrual periods and the accompanying decrease in iron requirements during early gestation as well as supplemental iron status and raise serum ferritin concentration.

However, at day 90 serum ferritin decreased near initial level implying that as pregnancy advanced, the need for iron increased and the iron from iron-supplementation and iron-stores in the body was utilized for haemoglobin synthesis and failed to increase serum levels. The present study indicated a shift of iron from the stores into the red cell mass. The fall in serum ferritin levels could in part be secondary to the increase in plasma volume during pregnancy.[16]

Serum iron concentrations reflect the balance between the flow of iron into and out of the plasma pool and thus when iron stores are depleted the serum concentration will generally be reduced. Conversely, when iron stores are filled, the serum iron concentrations will also increase.[12] In the present study the serum iron levels showed no significant differences.

Calcium inhibits the absorption of iron and this hypothesis has been proved in several studies in human and rats. Studies in rats indicate that calcium inhibits mucosal uptake of iron and the subsequent delivery of iron into the circulation.[17] Though the serum iron levels showed no significant differences, the haematological parameters like reticulocyte count, haemoglobin and red blood cell indicated the inhibitory influence of calcium on iron absorption.

In this study, levels of TIBC was seen increased continuously throughout the study period, suggesting that iron-stores required more time to get filled up supporting the fact that calcium affects the absorption of iron. However, the changes in TIBC were not statistically significant.

Haemoglobin levels display great variations in pregnancy according to degree of haemodilution and haemoglobin is therefore a poor marker of iron status. However, haemoglobin levels less than 10.5 gm/dl can be attributed to iron deficiency only if iron stores are deleted. [18] Despite this, haemoglobin measurements are fast, simple and suitable for screening iron status and also important clinically.

Reticulocyte count was significantly more at day 60. This shows that, iron –stores required more time to get filled-up and start erythropoiesis, pointing towards the inhibition of absorption of iron by calcium.

Erythropoietic activity occurred during the study as evidenced by reticulocytes and PCV. In pregnancy, as a result of stimulated erythropoiesis there is a relative increase in circulating larger young erythrocytes and MCV is no longer thought to be an accurate index of iron deficiency.[19] This has been reflected in the present study, in which MCV was significantly

more at day 60. This macrocytic response is not related to folate deficiency.[16] The results of present study support the view that though calcium inhibits iron absorption adaptive response occur on chronic administration which results in a more efficient use of supplemental iron. [15]

Mean corpuscular haemoglobin concentration (MCHC) was maintained within very narrow limits and mean corpuscular haemoglobin (MCH) was only a reflection of mean corpuscular volume (MCV). Taylor DJ and Lind T [16] also found such correlation between these indices and have stated that mean cell haemoglobin concentration is a late sign of anemia.

Barton JC et.al [17] observed that calcium chloride solutions of between 1 and 100 mmlo/L (40-400 microgram/ ml dose) decreased iron absorption in a dose –related manner from the duodenum and jejunum. No significant changes in iron solubility, macromolecular structure or formation or ferrous-ferric shift were evident. The authors suggested that the negative effect is not a luminal one but rather that calcium decreases absorption by reducing receptor uptake of iron or by affecting the metabolism of iron within the enterocytes and its subsequent delivery into the circulation.

## Conclusion

Study indicated that there was inhibitory influence of calcium on iron absorption initially. But on chronic administration this inhibitory influence lost because of some adaptive changes probably at mucosal level. It is recommended that women should consume an iron supplement containing more than 30 mg elemental iron per day from meals during the second and third trimesters, to diminish the risk of developing iron-deficiency anemia.

The world-wide problem is, however, that a high proportion of women lack or have only small amounts of storage iron. Therefore, iron supplementation must be considered necessary in most populations. The present study demonstrates the importance of evaluating multivitamin-mineral supplements in terms the bioavailability and the therapeutic responses of their individual components.

***Conflict of Interest:*** *None declared*
***Source of Support:*** *Nil*
***Ethical Permission:*** *Obtained*

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