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Iron Deficiency Anemia In Pregnancy: Pre And Post Iron Sucrose Therapy In A Tertiary Referral Centre

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Abstract:
Introduction*: Iron deficiency is commonly prevalent in women of reproductive age group.Early detection of iron stores before the development of anemia is beneficial. The maternal iron level is important for the growth of fetus and is always advantageous to have parameters which can detect iron deficiency at an early stage. The timely implementation of intervention to correct maternal iron status will improve the fetal outcome.*
Objectives*: To study levels of serum transferrin, iron and serum ferritin during pregnancy,pre and post intravenous Iron sucrose therapy in iron deficiency anemia.*
Materials and Methods*: Case control study was conducted on 60 pregnant women reporting to antenatal clinic between 18-34 weeks gestational age.Samples were collected and analysedfrom diagnosed cases of Iron deficiency anemia for Serum Iron, Ferritin and Transferrin before and after intravenous iron sucrose therapyand were compared with that of normal pregnant ladies.*
Result*:. The hemogobin levels were 11.97±1.09% in controls and 8.21±1.1% and 10.64±1.5% in cases on Day 1 and day 28. The Serum iron was 133.83±32.4µg/dl in controls and 20.66±10.01µg/dl and 79.97±40.32µg/dl in cases on day 1 and 28. Similarly serum ferritin was 35.6±7.85 µg/L, 13.25±10.7 µg/L and 40.2±62 µg/Lrespectively in normal pregenant women and iron deficient women pre and post iron sucrose therapy. The serum transferrin in contrlos was 271.31±35.13mg/dl and in cases were 471.05±70.6mg/dl on day 1 and 427.6±83.51mg/dl on day 28. All were statistically significant.*
Conclusion*: The finding of the present study suggests that serum iron, ferritin and transferrin levels measurement could be a better parameter for predicting iron deficiency in pregnancy and can be advised along with other routine hematological investigations.*

Key Words: *Anemia, Pregnancy, intravenous Iron sucrose, Serum Iron, Ferritin, Transferrin.*

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I. Introduction

Pregnancy is a physiological state, which is accompanied by a high-energy demand and an increased oxygen requirement exhibiting increased susceptibilityto oxidative stress, defined here as a disturbance in theprooxidant-antioxidant balance in favor of the former, leadingto potential damage. Pregnancy is characterized bydynamic changes in multiple body systems resulting in increasedbasal oxygen consumption and in changes in energysubstrate use by different organs including the fetoplacentalunit. The placenta is also rich in macrophages favoringthe local placental production of free radicals, including reactivechlorine species (RClS) in which free iron is also implicated.(1)(2).Under physiological conditions, there is a balance between iron absorption, iron transport and iron storage in the human body. However, Iron deficiency (ID) and irondeficiency anaemia (IDA) may result from the interplay of three distinct risk factors: increased iron requirements, limited external supply and increased blood loss(3,4). Iron-deficiency anemia is considered the most widespreadpregnancy-associated pathological condition.Severe anemia (hemoglobin (Hb) less than 8.0 g/l) inthe first half of pregnancy is proved to be associatedwith preterm delivery and small-for-gestational-agefetus.(2, 5) The serum levels of transferrin and ferritin and iron are not investigated as routine during pregnancy . As it has been already established that maternal iron deficiency is a risk factor for poor maternal outcome, a marker which can predict early changes in iron status and possible outcome of pregnancy is needed. The present study was conducted to study the changes in levels of serum transferrin and serum ferritin and iron during the second and third trimester.

II. Materials And Methods

The study was conducted at Bangalore Medical College and Research Institute, Department of Clinical Biochemistry, Victoria hospital, and the study groups were from Vani vilas hospital, Bangalore. The ethical committee clearance was taken from the Institution. The project was funded by National Rural Health Mission. (NRHM). The samples were collected from 30 normal pregnant females aged 20 to 40 years of age, between 18 to 34weeks gestational age, were considered as control group who didn't have any history of anemia, pregnancy induced hypertension, gestational diabetes, epilepsy, thyroid or psychiatric disorders who attended department of Clinical biochemistry OPD, Vanivilas hospital. The cases were also 30 in number between the age group 20 to 40 years females between 18 to 34weeks gestational age, who had complaints of generalized weakness, but the cases who had history of pregnancy induced hypertension, gestational diabetes, epilepsy, thyroid or psychiatric disorders were excluded from the study. Selection of the cases were made on basis of history given, clinical examination, hemoglobin and peripheral smear done.

7ml of venous blood was collected from both cases and controls into plain and edta vacutainers under aseptic precautions after obtaining informed consent. The investigations done in the collected sample included Hemoglobin, reticulocyte count, peripheral smear in the whole blood and iron, ferritin, transferrin in the serum. Iron, Ferritin and transferrin were considered as indicators of iron deficiency anemia. The hemoglobin levels less than10gm%, and PBS with microcytic and hypochromic blood picture were diagnosedas anemic. These patients were administered with intravenous infusion of 200mg iron sucrose diluted in 100ml normal saline over a period of 30minutes; was repeated up to three times a week.{The required dose of injection was calculated according to the formula [2.4xpre-pregnancy weight in kg x Hb%deficit(11-actual Hb% of patient) in mg]}. All participants were given protein powder as part of therapy. The repeat analysis of the samples for the same parameters was also done on day 28 of the start of the therapy. Biochemical analysis of the samples was done in fully automated random access chemistry analyzer Cobas Integra 400 plus, Roche make.

III. Results

Data was analysed with Microsoft excel and Statistical software using Unpaired 'T' test

Table 1 showing Mean,S.D,SEM, t value, p value of Controls and cases on Day 1 (Pre Iron sucrose therapy)

Variable	Groups	Mean±S.D	SEM	't_1' value	'p_1' value	Significance
Hemoglobin (%)	Controls Cases-Day 1	11.97±1.09 8.21±1.13	0.23 0.20	14.41	p_1<0.0001	Very highly significant
Serum Iron (µg/dl)	Controls Cases-Day 1	133.83±32.4 20.66±10.01	6.13 1.84	14.86	p_1<0.0001	Highly significant
Serum Ferritin (µg/L)	Controls Cases-Day 1	35.6±7.85 13.25±10.7	2.16 6.33	0.81	p_1- 0.4206	Not Significant
Serum Transferrin (mg/dl)	Controls Cases-Day 1	271.31±35.13 471.67±70.58	6.93 20.01	9.50	p_1<0.0001	Very highly significant Significant

S.D – Standard deviation
SEM – Standard error of mean
t_1 – t value between Controls and Day 1
t_2 – t value between Day 1 and day 28
p_1 – p value between Controls and Day 1
p_2 - p value between Controls and Day 1

Data was analysed with Microsoft excel and Statistical software using Paired 'T' test

Table 2 showing Mean,S.D,SEM, t value, p value of cases (Day 1 and Day 28) Pre and post iron sucrose therapy.

Variable	Groups	Mean±S.D	SEM	t_2 value	p_2 value	Significance
Hemoglobin (%)	Cases-Day 1 Cases-Day 28	8.21±1.13 10.64±1.41	0.20 0.27	9.33	P_2<0.0001	Extremely statistically significant
Serum Iron (µg/dl)	Cases-Day 1 Cases-Day 28	20.66±10.01 79±40.32	1.84 7.35	7.81	P_2<0.0001	Extremely statistically significant
Serum Ferritin (µg/L)	Cases-Day 1 Cases-Day 28	13.25±10.7 40.2±60.5	1.96 11.35	2.28	P_2<0.0302	Statistically significant

Serum Transferrin (mg/dl)	Cases-Day 1 Cases-Day 28	471.67±70.58 429.9±83.51	12.89 15.25	2.20	$P_2 < 0.0315$	Statistically significant

S.D – Standard deviation

SEM – Standard error of mean

t_2 – (Test of significance) t value between Day 1 and Day 28 (Pre and post iron sucrose therapy)

p_2 - p value between Day 1and Day 28. (Pre and post iron sucrose therapy)

IV. Discussion

The pregnancy itself contributes to an oxidative stress condition. It has been demonstrated that hypoxia and the resultant decrease in the oxygenation of RBChemoglobin destabilizes hemoglobin increasing the rate of hemoglobin autoxidation . Thisrelationship between hypoxia and red cell oxidative stress explains how anemia generates redcell oxidative stress. With fewer RBCs and less hemoglobin available the consumption ofoxygen by the tissues lowers the partial pressure of oxygen and a greater fraction ofthe RBC oxygen is transferred to the tissues. The increase in partially oxygenated hemoglobinincreases autoxidation generating metHb and superoxide. Most of the metHb formed duringautoxidation is reduced back to functional Fe(II) hemoglobin by cytochrome b5 reductase.However, the excessive autoxidation of hemoglobin that results from anemia is not fullyreduced and an increase in methemoglobin is observed.(6) Iron-deficiency anemia is considered the most widespread pregnancy-associated pathological condition.(5) The release of oxygen from maternal hemoglobin (Hb) is favored by the lower partial pressure of oxygen in the placental cellular structure and fetal circulation (rich in fetal hemoglobin), which has a greater affinity for oxygen, and by the release of fetal and placental metabolites (the placenta produces abundant lactic acid), which lower blood pH causing a displacement of the Hb dissociation curve favoring oxygen delivery . Initially the placenta, has a hypoxic environment. As it matures and its vascularization develops, it changes to an oxygen-rich environment and its abundant mitochondrial mass favors the production of reactive oxygen species (ROS), which increases free iron liberated from iron-sulfur clusters (1).

In the present study there was a significant decrease in Hb in the anemic group as compared to the control group. But after the iron sucrose therapy there was an increase in the Hemoglobin level of the anemic patients on day 28.An elevated hemoglobin concentration is usually the result of 2 mechanisms: increased red blood cell production as a compensatory mechanism when blood oxygen carrying capacity is compromised to meet the demand of tissue (with a net increase in red cell mass), or contracted plasma volume resulting in an appearance of greater red cell volume (without a net increase in red cell mass)(7).

Authoritative international groups, such as the International Nutritional Anemia Consultative Group and the World Health Organization, have recommended universal supplementation of iron from the second trimester onwards (8,9). Oral iron therapy has been effective in correcting IDA in most cases (10). Its efficacy however is limited in many women especially in pregnancy because of dose-dependent side effects, poor compliance and insufficient absorption.(11,12) Considering inadequate effects of oral iron therapy, particularly in later months of pregnancy, it was pertinent to try an alternative treatment for IDA to achieve optimum health of mothers without risk various parenteral Iron preparations like sodium ferric gluconate are considered safer than iron dextran but study [13] reported 74 adverse events attributed to ferric gluconate complex and was reported to WHO. Therefore, considering significant adverse reaction to iron dextran and other similar molecules iron sucrose has been considered as an effective alternative in the management of IDA.(14,15) Since early 1990s, many obstetric clinics have been using only IV iron sucrose for management of IDA during pregnancy and puerperium.[16] Iron sucrose molecule is a type II iron complex of intermediate stability and strength. It is rapidly metabolized and readily available for erythropoiesis in the bone marrow. Complex stability and unique iron distribution profile makes iron sucrose clinically safe. Moreover, as complexes contain no biological polymers, anaphylactic reactions are unlikely and makes these preparations safe to use in pregnancy[17,18,19). In fact, hemoglobin response to iron supplementation is by far the most reliable method for diagnosing iron deficiency anemia in an individual or a population (20).

The serum iron levels and ferritin levels were also increased as compared to the normals in day 1 as well as day 28 after administration of iron sucrose. Parenteral iron sucrose complex has severaladvantages because it has a low allergenic propertieswith an extrmely low incidence of severeside effects such as anaphylactic reactions (21,22,23,24).Modern intravenous ironformulations have emerged as safe and effective alternatives foranaemia management, as they present several advantages overoral supplementation. The administration of intravenous ironenables a fivefold erythropoietic response to significant bloodlossanaemia in normal individuals,19 Hb starts to rise after a few days.Each iron product is taken up into the RES, where the shell isdegraded for iron to become bioavailable.(23)

The serum transferrin level in controls was 271.31±35.13, in day 1 was 464.05±67.72 and decreased on day 28 (429.9±83.83). Transferrin is the glycoprotein responsiblefor the transport of iron and is upregulated in serum during iron deficiency to maximize the efficiency of iron transport from the intestine to tissues [24, 25].

The serum transferrin raise in cases is in accordance with the studies made by Shailesh et al and chaudhari et al(25, 26, 27) except for that their studies were based on I,II and III trimesters.Serum transferrin carries iron from the maternal circulation to transferrin receptors located on the apical surface of the placental syncytiotrophoblast, holotransferrin is endocytosed, iron is released, and apotransferrin is returned to the maternal circulation. The free iron then binds to ferritin in placental cells where it is transferred to apotransferrin, which enters from the fetal side of the placenta and exits as holotransferrin into the fetal circulation. This placental iron transfer system regulates iron transport tothe fetus. When maternal iron status is poor, the number of placentaltransferrin receptors increases so that more iron is taken up by the placenta. Excessive iron transport to the fetus may be prevented by the placental synthesis of ferritin(28).

There are various investigations available nowadays which can diagnose and describe anemia accurately. Although, there could not be a single parameter for solving this problem. The finding of the present study suggests that serum transferrin level measurements could be a better parameter which can be advised along with other routine hematological investigations. At tertiary level health institution there is still more possibilities available for research to be done in this field. The drop out of subjects during follow up antenatal visits and at the time of delivery limits the number of subjects included in the study. Considering the cost for serum ferritin and transferrin estimation during entire duration of pregnancy effort should be undertaken to reduce cost of tests so that benefits of medical advancement can be afforded.

V. Conclusion

Iron deficiency Anemia is the most widespread pregnancy associated pathologcal condition. It is associated with preterm delivery and small for gestational age fetus. Pregnancy itself is known to induce oxidative stress. Anemia is known to promote oxidative stress due to inadequate tissue oxygen supply. This paper explores potential biological mechanisms that might explain how iron deficiency anemia related parameters can assess the outcome of storage parameers of iron in relation to intravenous iron sucrose therapy.

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