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Serum Ferritin in Gestational Diabetes

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Abstract
Introduction: *Gestational Diabetes Mellitus (GDM) is carbohydrate intolerance of varied severity with onset or first recognition during pregnancy.GDM is detrimental to maternal and foetal health. Both mother and child are at higher risk to develop type 2 diabetes in later life. Many studies have shown a relation between elevated serum ferritin; the major iron storage protein and risk of GDM. This becomes more significant in the light of universal iron supplementation in pregnancy.*
Materials and Methods: *A case control study was conducted with 85 pregnant ladies with GDM as cases & 85 pregnant ladies without GDM as controls. The study population was in 24 to 28 weeks of gestation. Venous blood samples were collected for estimation of serum ferritin.*
Results: *Mean serum ferritin is higher in cases (55.06 ng/ml) than in controls (31.26 ng/ml). This difference in serum ferritin in cases and controls was found to be statistically significant. (p value <0.001) by Chi-Square analysis.*
Conclusion: *The present study found a statistically significant correlation between serum ferritin level in pregnancy and risk of GDM. Iron being a pro oxidant, universal iron supplementation irrespective of iron status becomes controversial. Hence the need for extensive studies to rationalize the estimation of serum Ferritin in pregnant mothers to diagnose iron deficiency anemia prior to starting iron therapy.*
Keywords: *ferritin, GDM.*

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of varied severity with onset or first recognition during pregnancy[1]. There is a general consenses that the prevalence of GDM is increasing globally and may be as high as 14%.[1]. A study by Dr K..Paulose showed the prevalence of GDM in south kerala to be 11.2% [1]. GDM usually develops between the 24th and 28th week of pregnancy and ends after delivery.

As significant brain growth and development takes place during second trimester abnormal fuel metabolism can result in low IQ, altered behavioural, intellectual and psychological pattern. In addition, exposure to abnormal fuel metabolism in third trimester can lead to unexplained IUD and macrosomia. If GDM is not treated properly, it can cause problems for the neonate that include hypoglycemia (due to hyperinsulinism), hypocalcemia, hyperbiliru-binemia, hypermagnesemia and respiratory distress syndrome. Babies born with excess insulin run a higher risk of obesity in adulthood, thereby putting them at higher risk of Type 2 diabetes later in life.

GDM makes the mother more prone to infections and Pregnancy Induced Hypertension (PIH). The big baby of a diabetic mother increases the risk of instrumental delivery and Lower Segment Caesarean Section (LSCS). Thus there is increased birth trauma and perinatal mortality. More over GDM increases the chance of developing Type-2 diabetes later in life. Once a woman develops GDM in pregnancy, the chances are 2 in 3 that she will develop GDM in future pregnancy.

Oxidative stress is thought to be a causative factor for GDM. Pregnancy is a condition that favours oxidative stress because of a mitochondria rich placenta. Iron an essential mineral that helps our body to transport and release oxygen to all cells is a catalyst of free radical stress[2]. The frequency of diabetes in women with haemochromatosis, an inherited iron overload syndrome, provided the initial suggestion that systemic iron overload could contribute to abnormal glucose metabolism.

When a woman becomes pregnant, her iron needs increase to support her pregnancy and the growth of her baby.

Iron deficiency anaemia was shown to be associated with greater risk of neonatal morbidity such as preterm birth. On the other hand, it was argued that a higher maternal haemoglobin level from iron supplementation would decrease placental perfusion due to increase in blood viscosity and cause adverse pregnancy outcomes such as low birth weight, preterm birth, pre-eclampsia and still births. This is further complicated by increasing concerns about the association between body iron stores and Type 2 diabetes mellitus[3]. Thus the need for prophylactic iron supplementation during pregnancy becomes controversial.

Ferritin is a major iron storage protein, which provides an indirect estimate of body iron stores. There was increasing evidence to show an association between elevated serum ferritin and development of Type 2 diabetes mellitus[3]

In this context it becomes important to establish the safety of iron supplementation in pregnancy particularly when there are suggestions that increased iron load would further increase insulin resistance.

The present study was an attempt to determine the relationship between ferritin level and development of GDM. A case control study was done with women with GDM as cases (85) and normal pregnant women as controls (85). Their ferritin levels were compared at 24 to 28 weeks of gestation to elucidate the causal relationship between iron stores and gestational diabetes. In the context of universal iron supplementation this would provide some evidence for the safety of iron supplementation in pregnancy in terms of development of GDM.

MATERIALS AND METHODS

A case control study was conducted in the Department of Obstetrics and Gynecology at a tertiary referral hospital in South India. The study was conducted after getting clearance from the research committee and ethical committee. The study period was one year. The study group included 85 cases and 85 controls.

Cases were women with GDM at 24 to 28 weeks gestation who attended the antenatal clinic during the study period. Controls were pregnant women at 24-28 weeks gestation who attended the antenatal clinic. GDM was diagnosed and excluded as per guidelines of National diabetes data group and American Diabetes Association.

CASES

Pregnant ladies of 24-28th week of gestation who satisfy the following criteria

Glucose challenge test > 200 mg% or

Glucose tolerance test: 2 or more values abnormal

CONTROLS

Glucose challenge test < 130 mg%

This is as per guidelines of National diabetes data group and American Diabetes Association.

The exclusion criteria included women with pre-existing diabetes, poly cystic ovarian disease, A/c or C/c liver disease and acute infections like UTI, Respiratory Infections etc.

Data for the study was collected using a preformed tested questionnaire. Study variables included age, BMI, parity and family history of type 2 diabetes mellitus. All subjects were provided with iron supplementation according to the national programme.

Ferritin estimation: 2ml of blood was obtained by venepuncture then and immediatly allowed to clot. The serum was separated by centrifugation and immediately stored in the deepfreezer. Estimation of serum ferritin was done by microplate immunoenzymometric assay (using accu bind elisa microwells)

STATISTICAL ANALYSIS

The data were entered into the personal computer using MS Excel. Suitable statistical analysis were performed using the statistical software SPSS15. Quantitative variables were expressed as mean+/- SD. Qualitative variables were expressed as proportion or %. Chi square test was applied to find an association between serum ferritin and GDM. A p value ≤ .05 was taken as statistically significant.

RESULTS

The study was conducted in 170 pregnant women (85 cases and 85 controls) between 24 to 28 weeks of gestation.

Tables 1shows the age and BMI distribution of the study group.

Table 1: age and BMI distribution of study group

parameter	mean	standard deviation	maximum value	minimum value
age in years	25.7	4.5	37	18
BMI kg/m2	30.15	4.2	40.5	18.3

Distribution of parity in study population

Among the study population 103 subjects were primi gravid (60%), 47(27.6%) were second gravid, 18(10.6%) were third gravid and 2 (1.2%) were fourth gravid

Distribution of family history of type 2 diabetes mellitus in the study population

Among the study population 80 subjects (47%) had a positive family history of type 2 diabetes mellitus and 90 subjects (53%) did not have a family history of diabetes mellitus.

Table 2. Distribution of serum ferritin (ng/ml) in cases and controls

Serum ferritin (ng/ml)			
Group	Mean	Std. Deviation	p-value
Case	55.1	28.9	<0.001
Control	31.3	18.7	<0.001

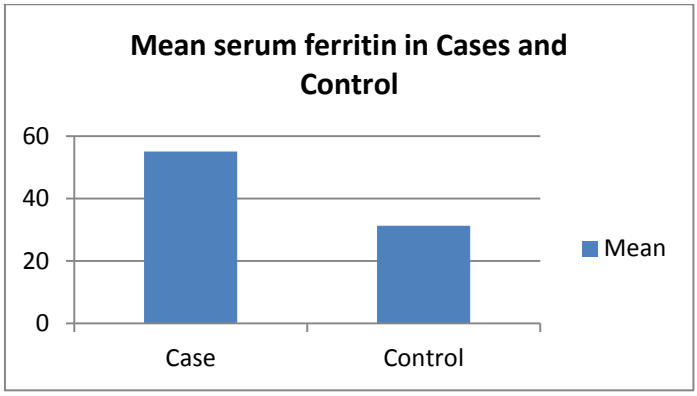

Fig. 1. Mean serum ferritin (ng/ml) in cases and controls.

Mean serum ferritin is higher in cases 55.06 ng/ml than in controls (31.26 ng/ml). This difference in serum ferritin in cases and controls was found to be statistically significant. (p value <0.001) by Chi-Square analysis.

Discussion

Serum Ferritin and Risk of GDM

In the present study elevated serum ferritin is associated with increased risk of developing GDM. Several epidemiological studies have reported a positive association between high body iron levels, as measured by circulating ferritin levels, and the risk of GDM[4,6]. In addition, increased dietary intake of iron, especially that of haeme iron, is associated with risk of Type 2 diabetes in apparently healthy population[3]. Frequent blood donations, leading to decreased iron stores, have been demonstrated to reduce post-prandial hyperinsulinemia in healthy volunteers, to improve insulin sensitivity and to constitute a protective factor for the development of Type 2 diabetes.

Serum ferritin is an index of body iron stores and it plays a key role in iron metabolism. Ferritin circulates in the plasma of healthy adults at a concentration in the range of 15 to 200 nanogram per ml.

Serum Ferritin Levels in Pregnancy

Serum ferritin concentration shows marked decrease after 12 weeks of gestation with relatively constant values after 32 weeks. This decline is more common in those who start pregnancy with inadequate stores and in those who have had 3 or more pregnancies.

Table 3. Mean ferritin in Pregnancy

	Nanogram per ml
First trimester (mean 12.60 weeks)	46.80 ± 2.50
Third trimester (32 weeks)	20.80 ± 1.30
Term (38 weeks)	21.70 ± 1.60

Serum ferritin value is stable, not affected by recent ingestion of iron and appears to reflect the iron stores accurately and quantitatively. Moreover, there is a lag period of several days between a stimulus to alter iron absorption and the actual change in absorption. This is because signals from the body to alter iron absorption have to be detected by nascent enterocytes in the crypts of the duodenum and the lag period was interpreted as the time required for the programmed crypt cells to mature and become absorptive enterocytes on the villus[4].

Thus a fasting value is not required and recent iron intake will not alter serum ferritin.

GDM is pathophysiologically similar to Type 2 diabetes in that the abnormality is in islet cell function or at receptor level causing insulin resistance. Free radical mediated decrease in receptor number, post receptor defect in insulin action and alteration in glucose transport systems mediate the peripheral insulin resistance in GDM[5].

Iron is a strong pro-oxidant and high body iron levels are associated with increased oxidative stress that may elevate the risk of Type 2 diabetes and GDM[2].

Ferrous iron generates toxic hydroxyl radical (OH) in the presence of oxygen via Fenton's reaction[6].

$$Fe^{+2} + O2 \longrightarrow Fe^{+3} + O^{2-}$$
$$2O^{2-} + 2H^{+} \longrightarrow H_2O_2 + O_2$$
$$Fe^{+2} + H_2O \longrightarrow 2OH^{-} + Fe^{+3}$$

The hydroxyl radical is perhaps the most powerful oxidant in biological system. Under normal circumstances, the pool of intracellular NTBI is maintained at a lower level by rapid incorporation of iron into ferritin to reduce the risk of oxidative reactions. Further, the action of superoxide dismutase and catalase mediate effective disposal of free radicals formed in the body. A glutathione mediated mechanism also helps in this. Iron overload can promote the generation of free radicals and result in deleterious cellular damages. Free radical-mediated tissue damage is generally accepted as a major mechanism underlying the occurrence of GDM[7,8,9].

Pregnancy is a condition exhibiting increased susceptibility to oxidative stress. The placental environment is one of enhanced oxidative stress that induces protective mechanisms against free radicals as gestation progresses. Overall, the plasma free radical trapping and anti-oxidant potential are able to counteract oxidative stress in normal pregnancy. However, pregnancy is a state where this adaptation and equilibrium are easily disrupted as evidenced by the propensity towards the development of insulin resistance that in some cases can lead to GDM [10]. Free radical injury mediated by iron can worsen the situation.

In pregnancy iron absorption is not in proportion to body iron needs, that is if excess iron is presented to the GIT, excess will be absorbed[11]. This is due to body iron status independent factors like oestrogen involved in increasing the iron absorption[12]. Moreover, in pregnancy, transferrin that binds the iron leaving the mucosal cell and entering into circulation is overwhelmed by amounts of passively diffused iron (NTBI) when large iron bolus is presented to the intestine[11]. NTBI uptake by liver is independent of iron content of liver, is very rapid and more efficient than the liver uptake of transferrin-bound iron[13]. Thus, excessive iron supplementation in pregnancy can lead to iron overload. Hence,

routine iron supplementation to all pregnant women irrespective of their body iron stores may be more harmful than beneficial.

Insulin, an anabolic hormone, promotes uptake of free iron into cells and promotes ferritin synthesis[14,15]. The reduction of free iron leads to upregulation of transferrin receptors promoting enhanced iron absorption from GIT. Excess iron thus absorbed promotes insulin resistance and favours hyperinsulinism. Hyperinsulinism further increases iron absorption and a vicious cycle is generated[15].

Iron overload induces oxidative stress and oxidative stress induces insulin resistance[16]. The storage of iron is as Fe^{+3} in ferritin. When oxidative reactions are increased there is an increase in availability of free iron (Fe^{+2}) from ferritin molecules as well as from other molecules such as the haeme group. This in turn enhances and amplifies the process of generation of free radicals[2].

In the light of the above fact providing universal iron supplementation during pregnancy becomes controversial. Ferrous iron, the traditional form of iron supplementation is a potent pro-oxidant. Administration of iron causes local and systemic oxidative stress thus leading to oxidative stress induced insulin resistance. Thus prophylactic iron supplementation to pregnant mothers improve pregnancy outcome if mother is iron depleted but it may predispose to GDM and insulin resistance and GDM if mother is not.

Our study conducted in the department of obstetrics at a tertiary referral hospital in South India showed an association between serum ferritin levels and GDM. Mean serum ferritin was higher in cases 55.06 ng/ml than in controls (31.26 ng/ml). This difference in serum ferritin in cases and controls was found to be statistically significant. (p value <0.001) by Chi-Square analysis.

However, extensive studies in future are needed to determine whether antenatal iron supplementation exacerbates or is primarily responsible for inducing these syndromes in healthy non-anaemic woman or in woman recovering from iron deficiency being treated with excessive iron doses.

CONCLUSION

The present study found a statistically significant association between serum ferritin and development of GDM. In conclusion, iron is a pro-oxidant which can induce local and systemic oxidative stress thus leading onto oxidative stress induced insulin resistance. Prophylatic iron supplementation to pregnant mothers will improve pregnancy outcome if the mother is iron depleted but it may predispose to insulin resistance and GDM when the mother is not. Now there is increasing recognition that current international recommendations for iron supplementation in pregnancy may be higher than necessary. Anaemia and iron deficiency anaemia are not synonymous; hence it would be better to estimate serum ferritin in pregnant mothers to diagnose iron deficiency anaemia prior to starting iron therapy.

Although various mechanisms have been suggested to explain the association between serum ferritin and genesis of GDM, more studies at cellular and molecular levels are needed to further elucidate the mechanisms of this association.

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