Association of Maternal Serum Ferritin Level in Gestational Diabetes Mellitus and its Effect on Cord Blood Hemoglobin

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ABSTRACT

Introduction: Gestational Diabetes Mellitus is the development of carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. Many studies had suggested that an elevated serum ferritin level in maternal blood in early as well as mid-pregnancy is an independent risk factor for development of GDM. In the present study we aim to find the association of serum ferritin levels with serum iron and Hb% in the GDM patients at the time of delivery and also correlate it with cord blood Hb% and iron levels of the new born.

Material and Methods: The study group was composed of 50 diagnosed cases of GDM and the control group comprised of age matched 50 cases of normal pregnancy. Maternal blood was used to measure mother's hemoglobin, iron levels, serum ferritin and hsCRP. Cord blood sample was used to estimate hemoglobin and iron levels of the newborns.

Results: Our study shows that in the GDM cases the level of serum ferritin was significantly higher ($p < 0.001$) than in the non GDM controls at the time of delivery. Cord blood hemoglobin is negatively correlated with maternal serum ferritin levels in GDM.

Conclusion: Elevated serum ferritin level in GDM is a marker of inflammation due to increased ROS production caused by iron overload. This oxidative stress might affect the placental iron transfer to the fetus and fetal Hb synthesis

Keywords: Gestational Diabetes Mellitus (GDM), Ferritin, Reactive Oxygen Species (ROS). Hemoglobin (Hb), Serum Iron (SI), Cord Blood Hemoglobin, Cord Blood Iron

INTRODUCTION

Gestational Diabetes Mellitus is the development of carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. Globally, the prevalence of GDM is estimated to be ~15%.[1] Indian women are known to have 11-fold higher risk of developing GDM compared to Caucasian women.[2] Diagnosis of GDM is essential for identifying the new born at risk of adverse outcome like macrosomia, hypocalcemia, hypoglycaemia, hyperbilirubinaemia, preterm delivery etc.[3]

There are multiple risk factors for development of GDM like increased BMI, increased maternal age, family history of diabetes mellitus etc. Recently many studies are suggesting that an elevated maternal serum ferritin level, in early as well as mid-pregnancy is an independent risk factor for development of GDM.[4-7]

Ferritin is an iron storage protein. Serum ferritin concentration provides an indirect estimate of body iron stores because it is highly correlated with bone marrow iron. It is also a positive acute phase protein and is so an equally accepted marker of inflammation.[8] Elevated levels of ferritin has been associated with many acute and chronic inflammatory diseases including diabetes and cardiovascular disease. Hence an elevated ferritin level may indicate iron overload or an inflammatory process.

Although the exact mechanism for its association with GDM is not very clear, it has been postulated that it is due to the effect of iron overload, which it reflects. In pregnancy, the placental environment is one of enhanced oxidative stress, producing huge amount of free radicals, but the body has mechanisms to counteract it in normal pregnancy. If this fine equilibrium is disturbed, it will lead to free radical injury.[9] Some studies have also raised concern about the association of excess iron in non-pregnant people, including hereditary hemochromatosis, as a risk factor for development of insulin resistance.[10]

Iron deficiency is very common among pregnant women and remains a global public health concern. The World Health Organization (WHO) recommends intake of 30–60 mg of elemental iron by all pregnant women to prevent maternal iron deficiency anemia and to ensure adequate fetal iron stores.[11]

But various studies have shown that although adequate maternal iron is necessary for normal fetal growth and development, iron overload has adverse effects as iron is a strong pro-oxidant. Adequate iron is required for β cell function and glucose homeostasis, but excess maternal iron leads to generation of increased amount of free radicals which is toxic to the pancreatic beta cells. This leads to and impairment in the glucose metabolism and insulin resistance. Thus iron might act as a double edged sword in pregnancy.[12-15]

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The effect of GDM on the distribution of iron and the hemoglobin level in the new born is still debated and very few studies have been done on the association of elevated ferritin levels on these parameters. In the present study we aim to find the association of serum ferritin levels with serum iron and Hb% in the GDM patients at the time of delivery and also correlate it with cord blood Hb% and iron levels of the new born.

MATERIAL AND METHODS

This study was conducted in a 400 bedded, tertiary care, super specialty hospital in New Delhi. The study group was composed of 50 diagnosed cases of GDM in the age group of 20 to 35 years. The control group comprised of age matched 50 cases of normal pregnancy.

Diagnosis of GDM was made at 24-28 weeks of gestation according to ADA criteria.[16]

Patients with history of diabetes mellitus, hypertension, seizure disorder, malignancy, acute or chronic liver disease or history of drug abuse were excluded.

The study was approved by Institutional Review Board and Ethics Committee. Informed written consent was obtained from each participant before their inclusion in the study.

Clinical history, complete physical examination and routine blood tests were done in all the patients at the time of inclusion. At the time of delivery, blood samples were collected from the mother and cord blood was collected from the maternal end of umbilical cord to coincide precisely with the newborn's venous blood sample. Maternal blood was used to measure mother's Hb%, iron levels, serum ferritin and hsCRP. Cord blood sample was used to estimate Hb% and iron levels. The newborn birth weight and placenta weight were also recorded.

Hb% was measured on Sysmex auto-analyzer, model KT-21N. Serum Iron and hsCRP were estimated spectrophotometrically and serum Ferritin by Electro Chemiluminescence. All measurements were done on the same day.

STATISTICAL ANALYSIS

The data was analyzed using SPSS 21 software. Data was expressed as mean ±SD with mean differences and 95% confidence intervals. Student's t-test was applied to compare data of cases and controls. Welch correction was applied where the assumption of equal variances was violated and correlations were computed using Pearson correlation coefficient. Our data followed normality and it was determined using Shapiro Wilk Test.

RESULTS

The mean age of the GDM cases was 29.94± 3.1 and in the non GDM control group the mean age was 26.24 ± 2.4

Table 1 shows that both Hb% and serum iron are significantly (<0.05) raised in GDM cases compared to the non GDM controls. The mean ±SD of serum ferritin levels (38.1± 4.6 µgm/L) of the GDM cases was much more than that of the controls (33.5 ± 2.7 µgm/L){p < 0.001, highly significant}. The mean ±SD of hsCRP of cases too was raised but p value (>0.05) was not significant.

Parameter	GDM cases (n=50)	Non GDM controls (n=50)	p value
Hb in gm %	11.8± 0.85	11.3 ± 0.68	<0.05
Iron in µgm/dL	96 ± 8.9	73.7 ± 14.1	<0.05
Ferritin in µgm/L	38.1± 4.6	33.5 ± 2.7	<0.001
hsCRP	0.73±0.16	0.69±0.14	>0.05
* p< 0.001, 0.05 is statistically significant			

Table-1: Maternal blood analysis in GDM cases and non GDM pregnant controls in study group.

Parameter	Newborns of GDM cases (n=50)	Newborns of Non GDM controls(n=50)	p value
Birth weight in Kg	3.15± 0.32	2.4± 0.45	<0.001
Placental weight in gm	573± 18.3	454.2±17.1	<0.001
Cord blood Hb in gm%	14.4±0.76	13.4±0.63	<0.001
Cord blood iron µgm/dL	114±10.8	96.9±10.1	<0.001
* p< 0.001 is statistically significant			

Table-2: Birth weight, placental weight and cord blood Hb and iron in newborns of cases and controls.

	Cord blood Hb in Newborns	Cord Blood Iron in Newborn
Ferritin levels in maternal serum	p <0.001	p > .05
	r = - 0.35	r = + .23

Table-3: Table showing correlation between maternal serum Ferritin of GDM cases with Cord blood Hb% and Iron levels of newborns of GDM cases

Table 2 shows that mean ±SD of both the placental weight and birth weight of the newborns of cases was higher than that of the controls (p<0.001).

Among the estimations done in cord blood (Table 2), both Hb% and iron levels of the babies of the GDM mothers was very significantly (p< 0.001) higher compared to the babies of the non GDM mothers. However, 24% of newborn of GDM cases had Hb% less than 12 (p<0.001) and serum iron less than 90 µgm/dL (p<0.01).

Table3 shows that there was a moderately negative correlation {Pearson's coeff r = -0.35, p> 0.001} between the maternal serum Ferritin levels of GDM cases with Cord blood Hb% of the newborns of the GDM mothers. However, there was no significant correlation of the serum Ferritin levels of the GDM mothers with the Cord blood iron levels of their newborns.

DISCUSSION

Our study shows that in the GDM cases the level of serum ferritin was significantly higher (p <0.001) than in the non GDM controls at the time of delivery. Many previous studies have shown that patients with raised serum ferritin levels in the early and mid-pregnancy are at more risk of developing GDM. The levels of ferritin in both the cases (38.1± 4.6 µgm/L) and control (33.5 ± 2.7µgm/L) are

far less compared to the other studies[4-7], but still there is significant difference in the mean ferritin levels of both the groups. This comparatively low ferritin concentration is due to the fact that maximum amount of iron is transferred to the fetus after 30 weeks of gestation. The placenta regulates this process. This time also corresponds to the time when maximum maternal iron absorption takes place.[17] It is to support placental and fetal growth, sustain the expansion of erythrocyte mass and offset blood losses from delivery.[18-19] The Hb% and serum iron too are significantly ($p<.05$) higher in the cases compared to the controls (Table 1). This finding is in correlation with the meta-analysis done by Yachana K *et.al*.[20]

Ferritin, being an iron storage protein, may lead to insulin resistance via oxidative stress induced by excess iron. Iron being a transition metal, which fluctuates between Fe^{2+} and Fe^{3+}, hydroxyl radical is formed from oxygen by the Fenton Reaction, causing cell injury.[9] The excess iron which accumulate in the various tissues may cause impaired insulin signaling in the liver and also defective glucose uptake by the cells of muscle, adipocytes, liver etc.[21-23] So, if all the pregnant women are advised to take iron irrespective of their iron status, it might lead to iron overload and subsequent free radical generation which might lead to several complications including GDM.[24-26] However, Chan K *et.al*.in their study mentions that there is no association of iron supplement in pregnancy and development of GDM.[27]

In the newborns both birth weight and placental weight (Table2) were significantly ($p<0.001$) increased in the GDM cases. This is because, in diabetes, a higher amount of blood glucose passes through the placenta into the fetal circulation leading to increased birth weight in the baby.[28]

The serum iron and Hb% levels (Table2) too were increased significantly ($p <0.001$) in the newborns of cases compared to the controls. This could be due to the increased transfer of iron from the mother caused by elevated demands in the fetus of diabetic mothers. However, 24% of newborns of GDM cases had hemoglobin <12gm% ($p<0.001$) and iron level <90 µgm/dL ($p<0.01$). This suggests that iron transfer to the fetus did not occur at the rate at which was expected as per the increased iron levels in the GDM cases. It might be due to the ongoing inflammatory process leading to defective placental transfer. Moreover, although the mean of Hb% are more in the newborns of GDM, we have found that it has a negative correlation with ferritin levels of the mothers {Pearson's coeff $r = -0.35$, $p> 0.001$}. This was most probably due to the effect of the excess ROS, which was being produced in the GDM mothers, on the fetal Hb synthesis.[29-31] However, since the strength of the negative correlation was moderate, more studies with a larger number of cases need to be done to establish it.

We did not find any significant difference between hsCRP of cases and control (Table 1) in our study. Similar findings are also mentioned in the study done by Samreen S *et.al.* where they have stated that hsCRP is not a very sensitive marker of inflammation in GDM and that IL6 is a better marker in this condition.[32] But we have not estimated it in our study.

CONCLUSION

Elevated serum ferritin level in GDM is a marker of inflammation due to increased ROS production caused by iron overload. This oxidative stress might affect the placental iron transfer to the fetus and fetal Hb synthesis.

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