Original Article

Maternal Serum Ferritin Levels and its effect on Cord Blood Hemoglobin in patients with Gestational Diabetes Mellitus

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Abstract

Introduction: Gestational diabetes mellitus (GDM) is a common medical complication of pregnancy that can have negative impacts on maternal and neonatal outcomes. Literature shows that elevated serum maternal ferritin levels may cause dysregulation in glucose metabolism in GDM. This study aims to determine the association between serum ferritin, iron and hemoglobin levels in GDM patients at the time of delivery as well as cord hemoglobin and iron levels in new-borns.

Materials and Methods: In this case-control study, a total of 100 patients were included i.e., 50 cases (GDM) and 50 controls (non-GDM) having aged-matched individuals of normal pregnancy. The hemoglobin, iron and serum ferritin, and hsCRP levels of the mother were determined using maternal blood. A cord blood sample was taken to determine neonatal iron and hemoglobin levels.

Results: The mean age of the study participants was 29.2 ± 5.6 years. The ferritin levels of GDM mothers (42.3 ± 6.7) were significantly higher than non-GDM patients (34.4 ± 3.8) with $p<0.001$. Similarly, Cord hemoglobin levels of newborns of GDM mothers were significantly lower than newborns of non-GDM patients ($p<0.01$). In GDM mothers, maternal ferritin levels were inversely correlated to cord hemoglobin levels ($r= - 0.29$, $p =0.004$). This means that increased serum ferritin levels means lower levels of cord hemoglobin levels.

Conclusion: Elevated maternal serum ferritin levels are linked to increased oxidative stress and effects fetal intrauterine and post-partum health. This oxidative stress might affect placental iron transfer and fetal hemoglobin synthesis.

Keywords: Gestational diabetes mellitus (GDM), neonatal iron and hemoglobin levels.

Introduction

Gestational diabetes mellitus (GDM) is a type of diabetes characterized by the development of intolerance to hyperglycemia with its first onset and recognition during pregnancy[1]. GDM is a commonly rising health problem with a prevalence estimated to be 1% to 15% worldwide[2]. GDM not only causes the development of various genetic and structural fetal abnormalities but also increases the risk of various maternal and fetal cardiovascular diseases[3]. Therefore, in time diagnosis of GDM is very important. There are multiple risk factors found to be associated with the development of GDM such as high body metabolic index, old age, ethnicity, family history of GDM or diabetes mellitus etcetera [4]. Recent studies have pointed out the idea that an acute-phase protein i.e., serum ferritin may have a causality associated with GDM[5].

Serum ferritin is a protein responsible for maintaining iron stores in correlation with bone marrow iron[6]. Iron is an extremely important micronutrient possessing strong oxidative properties[7]. Therefore, iron can cause beta-cell dysfunction of the pancreas resulting in the development of various metabolic abnormalities such as GDM[1]. A pregnant female requires approximately 1000 mg of iron per day to meet the demands of expanding blood volume and fetal red cell mass[8]. The body tries to address the increased body's iron demand by increasing iron absorption. However, more than 50% of pregnant females still suffer from gestational iron deficiency anemia[8]. Therefore, the World Health Organization (WHO) recommends the intake of 30-60mg of iron by pregnant females to prevent iron deficiency anemia and ensure adequate fetal iron stores [9]. Even so, fetal iron stores are affected by GDM due to its effect on iron transport and cord blood hemoglobin.

GDM causes fetal hyperglycemia, hyperinsulinemia, fetal metabolic derangements, and increased oxygen consumption[10]. This increased oxygen consumption results in a hypoxic intrauterine environment which stimulates erythropoiesis causing expansion of fetal red cell mass. Subsequently, this enhances the expression of transferrin receptors on the placental membrane and decreases the affinity of maternal transferrin to transferrin receptors limiting iron transport in cord blood[11]. Moreover, GDM causes placental vascular disease which further limits iron transport in cord blood hemoglobin despite increased fetal iron demand.

Moreover, cord blood hemoglobin of a GDM mother is glycated which reflects glycemic control of the mother and in turn, can be used to predict the risk of fetal genetic and structural abnormalities[10]. Previous studies have discussed separate effects of GDM on ferritin and cord blood hemoglobin. However, the causality between serum ferritin, cord blood hemoglobin, and GDM is still debated and underdefined in a developing country like ours. Moreover, some of the limitations in the relevant literature in complete control of confounding factors and a lack of subgroup analysis to assess the source of heterogeneity, and contradictory findings instigated us to do this study. Our study aims to find out the association between serum ferritin levels to cord blood hemoglobin in gestational diabetes mellitus.

Materials and Methods

This case-control study was conducted at the Department of Gynecology and Obstetrics at Holy Family Hospital, Rawalpindi which is affiliated with Rawalpindi Medical University. The study was conducted from April 2019 to April 2020. The sample size of the study was calculated using the WHO sample size calculator and a total of 100 participants were recruited for the study. The patients were divided into two groups. Group A (cases) included 50 GDM patients aged between 20-35 years while group B (control group) comprised 50 females with normal pregnancies. Diagnosis of GDM was made at 24-28 weeks of gestation that was consistent with American Diabetic Association (ADA) guidelines[1]. Both cases and controls were age-matched. Patients who were known cases of diabetes mellitus, hypertension, seizure disorder, pre-eclampsia, eclampsia, thyroid disorders, and chronic liver disease were excluded from the study. Moreover, patients with an abnormal anomaly scan were also subjected to exclusion. This study was ethically approved by the research association forum of the Rawalpindi Medical University. Information including clinical characteristics, physical examination findings, and demographics was recorded. Thereafter, blood samples were drawn from maternal blood for complete blood count with hemoglobin percentage, serum ferritin, iron, and maternal C-reactive protein levels. Regarding the neonatal data, the weight of the newborn and placenta were recorded and cord blood samples were taken for estimation of fetal hemoglobin and iron levels.

All data were analyzed using Statistical Package of Social Sciences version 25. Categorical data were expressed in terms of frequency and percentages. Numeric data were expressed as means ± standard deviations. The normality of the data was assessed using the Shapiro Wilk test (which showed normally distributed data with a p-value>0.05). Independent samples t-test was used to compare the means of cases and controls. Pearson's correlation was used to determine the association between maternal serum ferritin levels with hemoglobin and iron levels of newborns among GDM patients. A p-value of <0.05 was considered statistically significant.

Results

The mean age of all the study participants was 29.2 ± 5.6 years. The mean age of the GDM patients (cases) was 28.9 ± 4.5 years and that of non-GDM patients was 29.4 ± 4.9 years. A total of 32 patients were primigravida while 68 patients were multigravida. Table 1 shows the baseline characteristics of the study participants.

Table 1: Baseline characteristics of the study participants

Parameters	*All Patients (n=100)*	*GDM patients (n=50)*	*Non-GDM (n=50)*
Mean Age (years)	29.2 ± 5.6	28.9 ± 4.5	29.4 ± 4.9
Primigravida	32 (32%)	14 (28%)	18 (36%)
Multigravida	68 (68%)	36 (72%)	32 (64%)
Mean BMI (kg/m^2)	24.1 ± 2.9	25.7 ± 3.1	22.4 ± 2.2

Regarding the maternal blood analysis, the serum ferritin levels of the GDM patients (cases) were significantly higher than non-GDM patients (controls) p<0.001. Further information regarding maternal blood analysis is shown in Table 2.

Table 2: A comparison of maternal blood in GDM vs non-GDM patients

Maternal parameters	*GDM patients (n=50)*	*Non-GDM (n=50)*	*P-value*
Ferritin Levels (µgm/L)	42.3 ± 6.7	34.4 ± 3.8	<0.001
Iron Levels (µgm/L)	106 ± 9.3	81 ± 8.9	<0.001
Hemoglobin levels (g/dl)	11.6 ± 2.4	10.9 ± 1.5	0.041
hsCRP levels	0.79 ± 0.21	0.74 ± 0.17	0.183

Regarding the neonatal outcomes, newborns of GDM mothers had significantly higher weight as compared to the new-born of non-GDM mothers (p = 0.021). This is shown in Table 3.

Table 3: An elucidation of the neonatal parameters among cases and controls

Neonatal parameters	*GDM patients (n=50)*	*Non-GDM (n=50)*	*P-value*
Cord Hemoglobin(g/dL)	13.2 ± 2.6	14.7 ± 3.1	0.01
Newborn weight (kgs)	3.5 ± 0.7	2.6 ± 0.4	0.003
Placental weight (gms)	593.7 ± 21.8	483 ± 19.5	0.001
Cord Iron Levels (µgm/L)	111 ± 8.1	91 ± 7.1	<0.001

While performing the analysis of GDM patients it was noted that maternal ferritin levels in GDM mothers were inversely correlated to cord hemoglobin levels (r=-0.29, p=0.004). The results of the Pearson's correlation are shown in Table 4.

Table 4: Pearson's correlation between serum ferritin levels and cord hemoglobin among GDM patients

Parameters	*Cord hemoglobin levels*	*Cord Iron Levels*
Serum Ferritin Levels	r= - 0.29, p = 0.004	r = -0.014, p = 0.142

Discussion

A rise in the incidence of gestational diabetes mellitus (GDM) has been noted in the last 20 years. Previous studies have elucidated several long-term and short-term risks to the mother and child. However, the most common risk of GDM is fetal macrosomia leading to shoulder dystocia, perineal tears, and increased cesarean sections thereby, complicating the delivery. It has also been proposed that GDM can cause various maternal and fetal metabolic and hematological disturbances such as glucose intolerance, and derangements in serum ferritin and hemoglobin levels. Primarily, the demographics of the pregnant female were recorded in a tabulated form. This showed that the mean age of all participants was 29.2 ± 5.6 with a greater percentage i.e., 72% of multigravida were

suffering from GDM. This finding is consistent with a study done at a university hospital in Saudi Arabia which also concluded that multigravida has a higher incidence of GDM[12]. Contrarily, another study done in the setup of a developing country showed that the number of parity or gravidity does not affect the incidence of GDM[13]. Moreover, it has also been observed that patients suffering from GDM had a high body mass index compared to those experiencing a normal pregnancy. This outcome is similar to risk factors of GDM evaluated by Shah A et. al. who ascertained that patients with high BMI are more likely to suffer from GDM attesting that BMI can be used as a screening tool for GDM[14].

Secondarily, maternal blood analysis was done to evaluate and compare iron, ferritin, hemoglobin, and hs-CRP levels among GDM and normoglycemic patients. Our study showed significantly high ferritin i.e., 42.3 ± 6.7 levels among GDM females as opposed to those with normal pregnancy who had a mean serum ferritin level of 34.4 ± 3.8. Similarly, a study conducted at a tertiary care hospital of a developing country reported comparable results with significantly elevated ferritin levels among GDM patients[1]. However, a study conducted by El-raggal NM et. al. shows contrasting results with non-significant difference between ferritin levels among GDM and non-GDM patients [6].

On evaluation of maternal iron levels among GDM and normoglycemic participants, a similar finding of significantly high irons i.e., 106 ± 9.3 levels in GDM patients were observed. This finding is parallel with the conclusion drawn in a study conducted by Guo W et. al who also observed a significantly high iron levels in patients suffering from GDM[15]. In contrast, a study conducted by Sakar MR showed significantly lower iron levels i.e., 6(2-19) among GDM patients as compared to non-GDM patients i.e., 12(2-36)[16]. Howbeit, Sarkar MR postulates that this low iron maybe due to chronic inflammatory state of diabetes rather than iron deficiency.

Besides, on further evaluation of maternal hemoglobin and hs-CRP levels, no significant difference was noted among GDM or non-GDM patients. Another study conducted at Iran showed no significant correlation between CRP of GDM or non-GDM patients[17]. This finding is incompatible with a systematic review conducted by Amirian A which proved a significant association between raised CRP levels with GDM patients[18].

On evaluation of neonatal parameters from cord blood, it was observed that cord hemoglobin was significantly lower among newborns of GDM patients than those of non-GDM patients. A comparable finding was observed in a study conducted at El-Nile Insurance Hospital, Shubra El Khema which also proved a significantly low hemoglobin in newborn of GDM patient[6]. Moreover, our study concluded that neonatal and placental weight (3.5 ± 0.7 and 593.7 ± 21.8) was significantly higher among newborns of GDM females. A study conducted by Chuhan et. al. also reported that weight of newborn and placenta was significantly higher in babies born to GDM mothers[1]. A contradictory finding was observed in a study that concluded no significant difference in placental or newborn's weight amid GDM and normoglycemic patients[19].

Ultimately, Pearson's correlation was applied to find out relationship between serum ferritin in GDM mothers to the cord hemoglobin levels. It was observed that serum ferritin levels were inversely correlated to cord hemoglobin and these results were statistically significant. Similar negative correlation between serum ferritin and cord hemoglobin was observed in another study with an r-value of -0.35[1].

Maternal hematological indices are imported in prediction and evaluation of intrauterine fetal health and post-partum maternal health. The above results of our study indicate the role of serum ferritin levels (a maternal hematological parameter) on cord hemoglobin. Therefore, further studies should be conducted that evaluate other hematological indices like mean corpuscular volume, and platelet count, etc. on fetal and maternal outcome.

Conclusion

Serum ferritin level is significantly increased in GDM, indicating its role in oxidative stress and a marker of inflammation in fetal intrauterine and post-partum health. The oxidations stress may affect the transport iron from placenta to fetus which leads to decreased cord hemoglobin levels in GDM patients.

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