

Cord Blood Serum Ferritin of Infants of Diabetic Mothers

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ABSTRACT

Introduction: Maternal diabetes mellitus is associated with depleted fetal iron stores and this is proportionate to the degree of maternal control, presence or absence of diabetes-related complications, and is not related to maternal iron status. In this study, we aim to assess the effect of maternal diabetes on cord blood serum ferritin.

Methods: The present prospective (case-control) study was carried out in AL-Zahraa Teaching Hospital (March 2012-October 2012). Umbilical cord blood samples were collected from 100 newborn infants who were delivered normally or by caesarean section. Fifty infants of diabetic mothers (IDMs) and 50 normal control neonates were randomly recruited. A serum sample was obtained to measure ferritin concentrations by mini VIDAS machine, which compares the results with the standards.

Statistical analysis was performed using SPSS (statistical package for social sciences) Version 17. Independent sample t-test was used for data measurement and chi-square test for analyzing the categorical data. Also, Pearson's correlation coefficient was used to compare two measurement variables. P -value <0.05 was considered statistically significant.

Results: There was no significant difference between IDMs and infants of healthy mothers, regarding the gestational age at the time of delivery ($P=0.31$). Also, there was no significant difference between the two groups, regarding their packed cell volume (PCV), mean corpuscular volume (MCV), and red cell distribution width (RDW) ($P>0.05$). Finally, there was a highly significant difference between the two groups, regarding cord blood serum ferritin ($P<0.05$).

Conclusion: This study shows that IDMs have lower tissue iron stores (S. ferritin) at birth. Also, according to the results, there is a significant association between S. ferritin, gestational age and birth weight in these neonates.

Key message: Maternal diabetes mellitus is associated with depleted fetal iron stores.

Introduction

Infants born to diabetic mothers have been at significantly higher risks for spontaneous abortion, stillbirth, congenital malformations, and perinatal morbidity and mortality. Fetal and neonatal mortality rates were as high as 65% before the development of specialized maternal and neonatal care (1).

The infant of a diabetic mother (IDM) is at increased risk for periconceptional, fetal, neonatal, and long-term morbidities (1, 2). The causes of fetal and neonatal sequelae of maternal diabetes are likely to be multifactorial; however, many of the adverse effects on the fetus can be prevented by appropriate periconceptional and prenatal care (2).

The effects of maternal diabetes on the developing fetus

Uncontrolled maternal diabetes can adversely affect fetal growth, glucose metabolism, oxygenation, iron metabolism, and cause cardiac abnormalities and congenital anomalies.

Fetal growth

Much of the consequent weight accretion occurs after 32 weeks' gestation, and hepatomegaly, splenomegaly, and cardiomegaly (caused by intra-ventricular septal hypertrophy) are particularly prominent; however, head circumferences do not typically increase (1). Also, macrosomia places the IDM at a higher risk for birth trauma due to cephalopelvic disproportion (3).

Glucose metabolism

Maternal diabetes mellitus causes the fetus to become hyperglycemic and stimulate islet cell proliferation and insulin production. As long as maternal glycemic status is controlled and transplacental glucose delivery remains steady, fetal glucose metabolism remains stable. Fetal glucose metabolism is most likely to be compromised by wide swings in maternal serum glucose concentrations caused by inconsistent maternal glycemic control (4).

Fetal oxygenation

Chronic fetal hyperglycemia and hyperinsulinemia affect the fetal basal metabolic rate, with secondary effects on fetal oxygenation and erythropoiesis (5-10).

Iron metabolism

As the fetal red cell mass expands by up to 30%, the need for fetal iron expands in parallel, since each gram of hemoglobin requires 3.46 mg of iron. The diabetic placenta responds to this increased iron need by expressing more transferrin receptor on its apical (maternal facing) surface (11). This compensation is incomplete, potentially because of the decreased transferrin binding affinity of the hyperglycosylated receptor (12). The result is only an 11% increase in potential iron transport (11). The fetus must draw on fetal iron stores primarily in the liver and prioritize available transplacental iron. The resultant redistribution supports the red cell mass, which becomes polycythemic, at the expense of other developing organs, including the heart and brain, which become iron deficient (13).

An autopsy study of newborn IDMs with severe islet cell hyperplasia demonstrated a 55% reduction in heart iron concentration and a 40% reduction in brain iron concentration (13). Low cord serum ferritin concentrations, which indicate reduced fetal hepatic iron stores, are found in 65% of live-born IDMs at birth (14). Maternal diabetes mellitus is associated with depleted fetal iron stores. This is proportionate to the degree of maternal diabetes control and presence or absence of diabetes-related complications and not the maternal iron status (14).

Many factors can influence the iron status of the fetus at birth. Iron stores are mainly deposited during the third trimester of pregnancy and are therefore reduced in preterm infants (15). Maternal diabetes increases fetal iron demand for augmented erythropoiesis, due to fetal hypoxia and rapid expansion of the fetal blood mass

associated with rapid somatic growth (16). Maternal diabetes mellitus decreases hepatic iron stores as indexed by abnormally low serum ferritin concentrations (14).

Cardiac abnormalities

Chronic fetal hyperglycemia and hyperinsulinemia can result in glycogen loading of the intra-ventricular septum. Although usually diagnosed in the neonatal IDM, a fetal cardiomyopathy can be visualized on prenatal ultrasound and can be slowly reversed with normalization of maternal glycemic control (17).

Congenital Anomalies

The pathogenesis of the increase in congenital anomalies among IDMs has remained obscure, although several causes have been proposed, including hyperglycemia (either pre- or post-conceptual), hypoglycemia, fetal hyperinsulinemia, uteroplacental vascular disease, and genetic predisposition (18).

Materials and methods

This prospective (case-control) cross-sectional study was carried out in AL-Zahraa Teaching Hospital from March to October 2012. Fifty IDMs and 50 control infants who were born in AL-Zahraa Teaching Hospital were randomly included in the study. It should be noted that mothers of both groups were non-anemic.

The patients who met the following criteria were included in the control group: full term infants (age ≥ 38 weeks), weight of 2.5-3.5 Kg, no obvious congenital abnormalities or sepsis, non-diabetic mothers, and absence of other systemic illnesses.

After clamping the umbilical cord, the blood sample was taken by milking the cord, and the collected blood was put into 2 tubes: EDTA (ethylenediaminetetraacetic acid) tube for complete blood count (CBP) [packed cell volume (PCV), mean corpuscular volume (MCV), and red cell distribution width (RDW)], and serum tube for S. ferritin where the blood was centrifuged at mean of 3000 cycle/min. The resultant serum (100 Mml) was put in mini-VIDAS machine which compared the results with the standards. The normal values were specified as follows: S. ferritin: 25-200 ng/ml, PCV: 48-69%, MCV: 95-121 fl, and RDW: 10-16%.

Statistical analysis was performed using SPSS (statistical package for social sciences) Version 17. Independent sample t-test was used for data measurement and chi-square test for analyzing

the categorical data. Also, Pearson's correlation coefficient was used to compare two measurement variables. P -value <0.05 was considered statistically significant.

Results

As it is demonstrated in Table (1), there was no significant difference between the two groups of infants regarding the gestational age at the time of delivery ($P=0.31$). In addition, there was no significant difference between IDMs and the controls, regarding PCV, MCV, and RDW ($P>0.05$).

There was a highly significant difference between infants of diabetic and healthy mothers, regarding serum ferritin level and birth weight; the mean serum ferritin was 53.393 ng/ml and 105.522 ng/ml in the IDM and control groups, respectively. The birth weight of IDMs was 3,841 gr, while the mean birth weight of the controls was 3,225 gr.

Table 1. Comparison between infant of diabetic mother and infant of healthy mother in different variables

Variable	Infant of diabetic mother(N=50) (mean±SD)	Infant of healthy mother(N=50) (mean±SD)	P-value
Gestational age	37.7±1.3132	37.94±1.0184	0.31
PCV	42.114±8.78812	40.772±8.76615	0.446
MCV	99.8±11.52237	103.058±8.1308	0.106
RDW	17.196±3.24961	17.568±12.34156	0.837
Serum ferritin	53.393±76.63413	105.522±65.27741	<0.001
Birth weight	3841±914.38	3225±410.232	<0.001

In the group of IDM the correlation between different variables (gestational age, PCV, MCV, RDW and birth weight and cord blood S.Ferritin shown in the Figures(1-5)

Discussion

This study shows no significant difference between IDM and control groups regarding the gestational age at the time of delivery ($P=0.31$) (Table 1). This is in contrast with the results of other studies which indicate that in IDMs, preterm labour (low gestational age) has a higher incidence (3); this inconsistency may be due to the limited number of cases in the present study.

There is no significant difference between IDMs and the controls regarding PCV, MCV, and RDW ($P>0.05$) (Table 1). However, according to previous studies, central hemoglobin concentrations >20 g/dL and hematocrit levels $>65\%$ are observed in 20%-30% of IDMs at birth (19); this may be due to the fact that the neonates were in early stages of iron deficiency in the present study, therefore, these biomarkers were not significantly affected.

There was a highly significant difference between IDMs and the control group regarding

serum ferritin. The mean serum ferritin of IDMs and control group was 53.393 ng/ml and 105.522 ng/ml, respectively ($P\leq0.001$) (Table 1). This is consistent with the results of previous studies, which showed that IDMs have abnormal (low) iron distributions, identified by measuring ferritin (10, 13, 20-22). This can be explained since chronic fetal hyperinsulinemia and hyperglycemia independently increase cellular oxygen consumption, causing significant fetal hypoxemia, which in turn stimulates erythropoietin secretion and thus increases erythropoiesis (10, 19, 22).

This study showed a highly significant difference between IDMs and the controls regarding birth weight. The mean birth weight of IDMs was 3,841 gr, while that of the controls was 3,225 gr ($P\leq0.001$) (Table 1). According to previous studies, number of IDMs with macrosomia is declining, from 60% to approximately 20%-35%, probably secondary to aggressive diagnosis and treatment of diabetes during pregnancy (1). On the other hand, a small subgroup of fetuses ($<5\%$) of mothers with advanced diabetic vascular disease, are at risk of fetal growth deceleration, defined as birth weight less than the fifth percentile for gestational age (3, 23); this may be explained by the poor control of diabetes mellitus in the current study (24). Also, in another study in Japan, it was revealed that the incidence of preterm labor and low birth weight is more prevalent in diabetic pregnancies (25, 26).

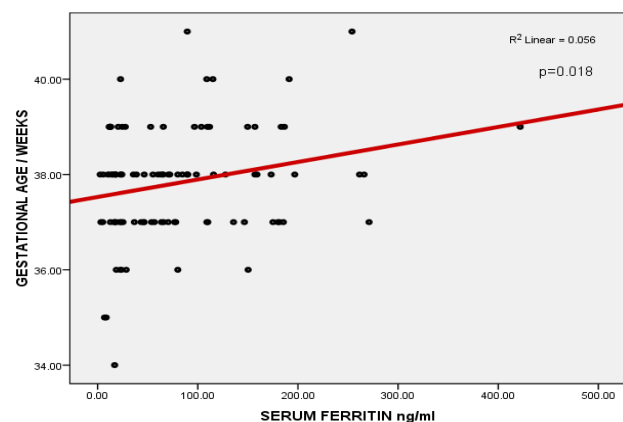


Figure 1. Correlation between gestational age and serum Ferritin in IDM

As it is indicated in Figure (1), there is a positive correlation between serum ferritin and gestational age; therefore, as the gestational age increases, serum ferritin levels elevate in parallel (P -value=0.018). These results are similar to another study which showed that in preterm

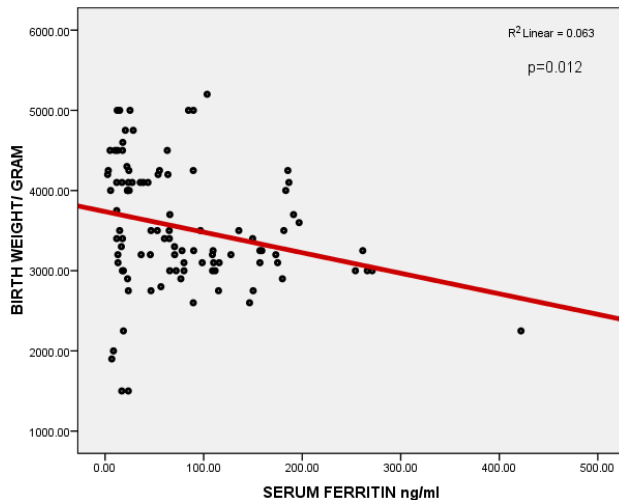


Figure 2. Correlation between serum Ferritin and birth weight in IDM

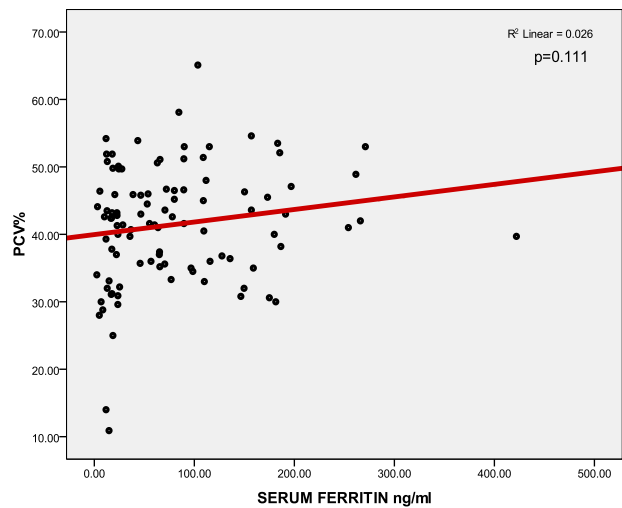


Figure 3. Correlation between serum Ferritin and PCV in IDM

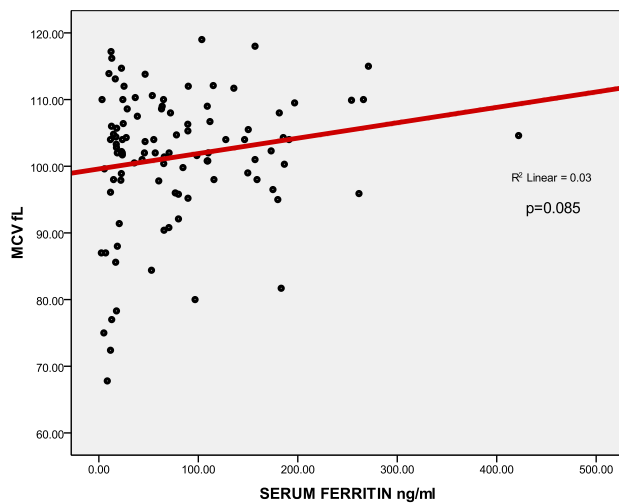


Figure 4. Correlation between serum Ferritin and MCV in IDM

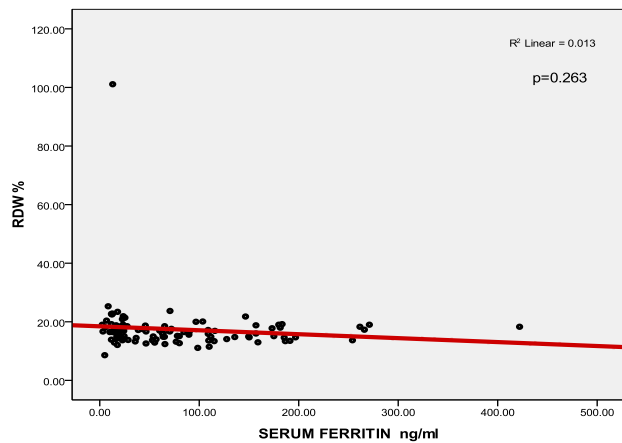


Figure 5. Correlation between serum Ferritin and RDW in IDM

infants <1,700 gr, a serum ferritin concentration <50 $\mu\text{g/l}$ at 2 months portends the risk of subsequent early-onset iron deficiency (27). Moreover, Jansson *et al* showed that serum ferritin concentration measured in preterm infants at 24–48 hrs of age was significantly lower in infants <34 weeks' gestation (range: 26–270 $\mu\text{g/l}$), compared with infants >34 weeks' gestation (range: 20–600 $\mu\text{g/l}$) (28); this is due to the late passage of iron through the placenta during the third trimester of pregnancy.

This study showed that there is a significant negative correlation between serum ferritin and birth weight (Figure 2) ($P=0.012$). Macrosomia at birth is considered an excellent marker for detecting IDMs at risk of subsequent neonatal morbidity, including hypoglycemia and iron abnormalities (9). In this study, there was no significant relationship between serum ferritin

and PCV, MCV, and RDW, as is indicated in Figures 3-5 ($P=0.111$, 0.085, and 0.263, respectively). This may be due to the fact these biomarkers are late markers of iron deficiency and may not reflect tissue iron status in newborn infants (27).

Conclusion

This study showed that tissue iron stores (S. ferritin) are lower at birth in IDMs, and this appears to be due to the effects of increased erythropoiesis, secondary to fetal hypoxia; also, according to the results, most IDMs are macrosomic. As it was shown, there was no significant relationship between IDM and other biomarkers including PCV, MCV, and RDW. There was a significant association between S. ferritin, gestational age, and birth weight; meanwhile there was no significant association between the infants of both groups, with regard to the mode of delivery.

Recommendations

Measurement of S. ferritin in IDMs at the time of delivery is required to demonstrate any depletion in iron stores. In addition, Infants with low serum ferritin can benefit from close monitoring of their iron status.

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