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Effect of Maternal Diabetes on Cord Blood Concentrations of Iron Status Parameters

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ABSTRACT

Background: iron is essential element involved in a broad range of biologically important reactions critical for cellular function and also plays a role in oxygen transferring and despite its low daily requirements iron deficiency is the most common nutritional disorder in the world. Increased serum concentration of TfR is a sensitive and quick response to the development of iron deficiency. Conversely, the serum TfR concentration decreases in response to treatment with iron before a change in hemoglobin occurs, so the response to iron can be monitored by changes in serum TfR. TfR-F index is proposed to be a more accurate reflection of tissue iron status than ferritin. Many factors can influence the iron status of the fetus at birth، Maternal diabetes mellitus was thought to be associated with depletion of fetal iron stores in proportion to the degree of maternal control and presence or absence of complications of diabetes, but not maternal iron status.

Aim of the work: in this study we aimed to assess the effect of maternal diabetes on neonatal cord blood iron stores. **Patient and Method:** this case-control study was conducted on 100 maternal/cord blood pairs who were randomly included in the study from Obstetrics and Gynecology Department at El- Nile Insurance Hospital, Shubra El Khema, during the period from November 2015 to July 2016.

Results: this study was done on the fetal iron status in the diabetic mothers and the control group using the transferrin receptos-ferritin index**(TfR-F index)** as a measure of cellular iron status and results showed that infants of the diabetic mothers**(IDM)** had significantly lower iron stores represented as lower s.ferritin (P=0.000) and significantly higher serum transferring receptors**(STfR)**levels than infants born to the control mothers **(P=0.038**) and also higher sTfR level in insulin dependent diabetes mellitus (IDDM) mothers ; this was suggesting a state of increased erythropoiesis.

Conclusion: this study confirmed that iron stores are lower at birth in infants of women with diabetes mellitus. This appeared to be due to the effects of increased erythropoiesis secondary to chronic intrauterine hypoxia. Fetal iron stores were affected by maternal glycemic control and not related to maternal iron supplement.

Keywords: maternal diabetes , TfR-F index , STfR, ferritin , neonatal cord blood, iron stores**.**

INTRODUCTION

Iron is essential to many cellular processes and transport across the cell membrane is facilitated by the transferring receptor (TfR) on the cell surface. The number of surface transferrin receptors is inversely proportional to intracellular iron. Cellular iron homeostasis is regulated through the action of iron regulatory proteins (IRPs). The IRPs bind to the mRNA of both ferritin and transferrin receptors and as intracellular iron concentration falls the IRPs upregulate the expression of transferrin receptors, while simultaneously reducing serum ferritin [(3)].

Ferritin concentration is an important indicator of total body stores and its concentration is taken to indicate deficient iron stores. However, the synthesis of ferritin is stimulated by infection, which may obscure an iron deficiency or indicate a larger iron store that truly exists [(11)].Increased serum concentration of TfR is a sensitive and quick response to the development of iron deficiency. Conversely, the serum TfR concentration decreases in response to treatment with iron before a change in hemoglobin occurs, so the response to iron can be monitored by changes in serum TfR**.** TfR-F index is proposed to be a more accurate reflection of tissue iron status than ferritin [(1)]. Maternal diabetes mellitus was thought to be associated with depletion of fetal iron stores in proportion to the degree of maternal control and presence or absence of complications of diabetes, but not maternal iron status. Infants of mothers with type 1 diabetes were found to have higher fetal iron demands at least partly explained by increased erythropoiesis secondary to intra-uterine hypoxia [(12)].

This study was performed to reveal the effect of maternal diabetes on fetal iron status parameters: STfR, ferritin levels and their ratio (TfR-F index), in cord blood samples of infants with and without maternal diabetes.

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PATIENTS AND METHODS

Subjects

Two groups of mothers were categorized into **group A**: mothers confirmed as the diabetic group before pregnancy (n=50). IDDM: n=10(20%) and NIDDM: n=40(8o%). **Group B**: non-diabetic control mothers, (n=50) who had normal glucose tolerance test on routine screening, no previous gestational diabetes or a first degree relative with diabetes mellitus. The ages of all mothers (n=100) ranged from 19- 43 years (Mean± SD = 28.42 ± 5.56), duration of maternal diabetes ranged from1 - 8 years (Mean ± SD =3.44 ± 1.63). They were pre-gestational diabetes 1 - 8 years in NIDDM

Exclusion criteria: maternal blood diseases, maternal infection, maternal hypertension, maternal smoking and extremely premature.

Two groups of babies were defined

1- Infants of the diabetic mothers (IDM): it included 50 fullterm neonates. They were 22 males (44%) and 28 females (56%).Their gestational ages ranged between 37-40 wks with a mean 37.86 ± 0.69 wks and birth weight between 3-5 Kg with a mean 3.87 ± 0.41 kg.

2- Infants of non diabetic mothers (**Control group**): it included 50 fullterm neonates they were 18 males (36%) and 32 females (64%). Their gestational ages ranged between 38-41 wks with a mean 38.54 ± 0.91 wks and birth weight between 2.8-4 kg with a mean 3.34 ± 0.30kg.

Exclusion criteria: extremely premature, congenital anomalies or inborn error of metabolism.

METHODS

Thorough history taking with laying stress on:

Maternal: age, parity, exclusion of any chronic or blood diseases. Diabetes: onset, type, control, complications, iron supplementation during pregnancy, doses, duration.

Neonatal: mode of delivery, natal history, Apgar score, examination of gestational age, weight, length, head circumference, body mass index.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

RESULTS

Table 1: comparison between **IDMs** and the control group as regard clinical and demographic data

	IDM group no. =50	Control group no. =50	T	P-value
Gender				
Female	28 46.0%)	32 (54.55%)	1.909	0.167 **(NS)**
Male	22 (44.0%)	18 (36.45%)		
MOD				
C.S	37 (74%)	15 (30%)	19.391	0.001 (**HS**)
SVD	13 (26%)	35 (70%)		
APGAR score 1 min	6 (6 – 7) 5 – 8	6 (5 – 6) 3 – 7	2.409	**0.007(S)**
APGAR score 5 min	9 (8 – 9) 8-10	9 (8 – 9) 8-9	0.931	**0.325(NS)**
Gestational age	38.54±0.91	37.86±0.69	4.202	0.001
Birth Weight (kg)	3.87 ± 0.41	3.34 ± 0.30	**-7.267**	**0.001 (HS)**
Length (cm)	48.66 ± 1.42	47.76 ± 1.06	**-3.586**	**0.001 (S)**
HC (cm)	34.36 ± 0.96	34.34 ± 0.87	**-0.109**	**0.914 (NS)**
BMI	16.27 ± 1.43	14.56 ± 1.26	**-6.340**	**0.000 (HS)**

Table 2: comparison between the diabetic mothers and the control group mothers as regard clinical data

Variables		Diabetic mothers	Control group	T	P-value
Age		29.48 ± 5.04	28.42 ± 5.56	-0.999	0.320 **(NS)**
Iron dose		24.30 ± 6.13	24.84 ± 6.12	0.441	0.660 **(NS)**
Iron duration		3.46 ± 0.91	3.46 ± 1.30	0	1.000 **(NS)**
Parity	**PG**	4 (8%)	12 (24%)	6.872	0.032* **(S)**
	P1-P3	41 (82%)	37 (74%)	6.872	0.032* (**S**)
	P>3	5 (10%)	1 (2%)	6.872	0.032* (**S**)

Table 3: comparison between the diabetic mothers as regard IDM Vs NIDDM as regard clinical data

Variables		IDDM	NIDDM	Independent r-t-test	
		No. = 10	No. = 40	t / X^2*	P-value
Age	Mean±SD	27.80 ± 6.27	29.90 ± 4.68	-1.183	0.242(**NS**)
	Range	20 – 38	22 – 41		
Parity	PG	2 (20.0%)	2 (5.0%)	2.470*	0.291 **(NS)**
	P1-P3	7 (70.0%)	34 (85.0%)		
	P>3	1 (10.0%)	4 (10.0%)		
Duration of diabetes	Mean±SD	3.51 ± 1.31	3.43 ± 1.71	0.146	0.884 **(NS)**
	Range	2 – 5.6	1 – 8		
HbA1c	Mean±SD	7.37 ± 0.50	7.42 ± 0.62	-0.237	0.813 **(NS)**
	Range	6.8 – 8	6.5 – 8.5		
S.Ferritin	Mean±SD	30.71 ± 7.28	26.72 ± 7.03	1.505	0.139 **(NS)**
	Range	22.8 – 48.5	15.6 – 46		
STfR	Mean±SD	313.84 ± 72.16	278.20 ± 45.99	1.942	0.058 **(S)**
	Range	230 – 410	201 – 473.8		
TfR-F index	Mean±SD	10.83 ± 3.46	11.14 ± 3.46	-0.250	0.804 **(NS)**
	Range	6 – 16.7	5.7 – 19.6		

Table 4: comparison between the diabetic mothers and the control group as regard blood indices

Parametars	Diabetic mothers group	Control group Mothers	Independent t-test	
	No.= 50	No.= 50	T	P-value
Hemoglobin (gm/dl) Mean ± SD	11.63 ± 1.04	11.78 ± 1.01	0.731	0.466**(NS)**
MCV Mean ± SD	95.90 ± 2.53	94.80 ± 3.63	-1.758	0.082 (**NS**)
MCH Mean ± SD	30.60 ± 0.80	30.79 ± 0.96	1.078	0.283(**NS**)
MCHC Mean ± SD	31.59 ± 0.69	31.75 ± 1.02	0.923	0.358(**NS**)
RDW Mean ± SD	14.31 ± 0.85	14.00 ± 0.73	-1.908	0.059(**NS**)
Hematocrite % Mean ± SD	35.86 ± 4.56	36.63 ± 2.79	1.019	0.311(**NS**)

Table 5: comparison between cord blood of IDMs and the control group as regard blood indices

Cord	IDMs group	Control group	Independent t-test	
	No.= 50	No.= 50	T	P-value
Hemoglobin (gm/dl) Mean ± SD	15.75 ± 1.54	14.17 ± 1.32	-5.522	0.001(**HS)**
MCV (Mean ± SD)	97.93 ± 1.56	94.30 ± 6.48	-3.849	0.001(**HS**)
MCH (Mean ± SD)	31.76 ± 0.91	31.21 ± 1.68	-2.045	0.044**(S)**
MCHC (Mean ± SD)	31.71 ± 0.71	32.12 ± 1.30	1.958	0.053**(NS**)
RDW (Mean ± SD)	14.15 ± 0.77	13.82 ± 0.77	-2.120	0.036(**S)**
Hematocrite (Mean ± SD)	47.80 ± 5.14	43.69 ± 3.60	-4.636	0.001**(HS)**

Table 6: comparison between IDMs and the control groups as regard iron profile

	IDMs group	Control group	Independent t-test	
	N = 50	N = 50	T	p-value
S.Ferritin	27.52 ± 7.60	91.87 ± 14.02	28.537	0.001 **(HS)**
STfR	285.33 ± 53.36	266.61 ± 33.33	2.104	0.038 **(S)**
TfR-F index	11.07 ± 3.42	2.99 ± 0.73	16.324	0.001 **(HS)**

Table 7: comparison between infants of the diabetic mothers IDM Vs NIDDM as regard iron profile

	IDDM	NIDDM	Independent t-test	
	N = 10	N = 40	T	p-value
S.Ferritin	30.71 ± 9.28	26.72 ± 7.03	1.505	0.139 **(NS)**
STfR	313.84 ± 72.16	278.20 ± 45.99	1.942	0.058 **(S)**
TfR-F index	10.83 ± 3.46	11.14 ± 3.46	-0.250	0.804 **(NS)**

DISCUSSION

Iron deficiency is the most common nutritional disorder worldwide. Iron deficiency during the fetal and neonatal (Perinatal) period can result in multiple system dysfunctions of multiple organs, some of which might not recover despite iron rehabilitation [(9)].

In this study we aimed to assess the effect of maternal diabetes on neonatal cord blood iron stores. This study was done on fetal iron status in the diabetic mothers and the control group using the transferrin receptos-ferritin index**(TfR-F index)** as a measure of cellular iron status and the results showed that infants of the diabetic mothers**(IDM)** had significantly lower iron stores represented as lower s.ferritin (P=0.000) and significantly higher serum transferring receptors**(STfR)** levels than infants born to the control mothers **(P=0.038**) and also higher sTfR level in insulin dependent diabetes mellitus (IDDM) mothers and this was suggesting a state of increased erythropoiesis. This result agrees with those of **Verner *et al.*** [(12)]. who stated that maternal diabetes caused depletion of fetal iron stores and it was associated with higher fetal iron demands as indicated by higher STfR (P <0.01) level and TfR-F index in cord blood (P <0.01) in cord blood of IDM compared to infants of non diabetic mothers. Also, **Hashim and Ameer** [(5)] documented that cord blood serum ferritin was lower in IDMs group compared to infants of non diabetic mothers (p <0.05). Serum TfR levels were increased during periods of increased erythropoiesis reflecting increases in red cell precursor production and expression of TfR. also, maternal diabetes mellitus decreases fetal hepatic iron stores as indexed by abnormally low serum ferritin concentrations [(10)]. In our study we found that there was a significant increase in STfR(P=o.o58) in infants of insulin dependent diabetic mothers **(IDDM)**compared to infants of non insulin dependent diabetic mothers **(NIDDM)**, while there was no significant statically difference in serum ferritin (P=0.139) and TfR-Findex between the two groups(P=0.804)**.** This may be due to limited number of IDDM diabetic mother in this case. AS with insulin dependent diabetes mellitus (IDDM) the transferrin binding capacity of the TfR in the placenta- of the diabetic mothers was reduced and the placental transfer capacity was decreased, there by reducing fetal iron stores and increase STfR expression due to increased erythropoiesis and increased fetal iron demand which may exceed placental iron transport capacity [(12)].

In our study, we found that IDMs were born earlier with cesarean section this is in agreement with the results of **Wagner *et al*** [(13)] who indicated that in IDMs preterm labor has a higher incidence. This is in contrast with the results of **Hashim and Ameer** [(5)]. who showed no significant difference between IDM and infants of non diabetic mothers groups regarding the gestational age at the time of delivery. In our study this was due to predominantly more elective sections being performed,

In our study we found that APGAR score at 1 minute in IDMS s (3-7) was significantly lower compared to the control group mostlyand this maybe

due to C-section, difficult birth and fluid in the baby's airway. Maternal diabetes is known to have many effects on the fetus and interaction of a number of hormones, such as insulin-like growth factor which may has significant influence. The insulin-like growth factor system is essential for growth and development [(7)]. The rates of macrosomia are 3.5–4.5 times greater among IDMs with pregestational diabetes than those found in infants born to non diabetic mothers [(8)].; the number of IDMs with macrosomia was declined from 60% to approximately to 20%-35%, probably secondary to aggressive diagnosis and the control of diabetes during pregnancy [(6)].

Our study showed a highly significant difference between IDMs and the control group regarding birth weight. The mean birth weight of IDMs was 3.87 ± 0.41gr, while that of the control was 3.34 ± 0.30gr (P≤0.001),. This agrees with the results of **Ceitin** [(2)]. Infant's birth weight (g) 3936 ± 681 (IDM)vs 3356 ± 174 infants of the healthy control group. This may be explained by the poor control of diabetes mellitus in our study due to hyperglycemia in the fetus results in stimulation of insulin, insulin like growth factors, growth hormone and other growth factors which, in turn, stimulate fetal growth and deposition of fat and glycogen. The positive correlation between levels of IGF-1and birth weight, cord hemoglobin and ferritin levels in healthy term infants was studied by **Kurtoğlu *et al.*** [(7)].

Adequate maternal transferrin saturation will impede absorption of supplemented iron from her gastrointestinal tract. Furthermore, placental iron transport may also be partially dependent on the degree of saturation of maternal transferrin. It is possible that iron supplementation after birth can rapidly replete the depleted iron stores in iron-deficient IDM. However, the efficacy of such therapy in normalizing the iron status and in correcting neurobehavioral impairments has not been studied [(9)].

In our study, we found that there was no statistical difference between the diabetic mothers as regard age, parity, duration of diabetes and HbA1c; this inconsistency may be due to the limited number of cases in the present study.

In our study, there was no statistical difference between mothers of the diabetic and control group as regard hemoglobin and blood indices.

Our study showed a significant increase in hemoglobin (p=0.000) level, hematocrit, RDW (P=0.036) and MCV(0.000) in IDMs as compared to the control group, this may be explained by diabetes mellitus during gestation is associated with maternal and fetal hyperglycemia, fetal hyperinsulinemia, increased fetal metabolic rate and oxygen consumption, The increased fetal oxygen consumption in a relatively hypoxic intrauterine environment stimulates erythropoiesis and expands the fetal RBC mass**. Ceitin** [(2)] stated that infants of the diabetic women were often polycythemia at birth and this may be a reflection of fetal response to chronic intrauterine hypoxia which led to increased erythropoiesis. On the other hand **Hashim and Ameer**[(5)]. Stated that there was no significant difference between IDMs and the controls regarding PCV, MCV, and RDW (P>0.05) in their study.

There was a significant decrease in MCV in the control mothers compared to diabetic mothers group, while no significant statistically difference was detected between the two groups as regard hemoglobin and blood indices MCH, MCHC and RDW. This may be due to increased maternal age or nutritional status as the mothers were not divided into groups according to their ages to determine effects of age on the red cell indices in this study. In this study there was a positive correlation between maternal HbA1c and neonatal MCH, sTfR and TfR-F index, while there was a negative correlation between maternal HbA1c and neonatal S.ferritin and. Also, there was negative correlation between maternal age and neonatal MCH and MCHC

This disagrees with the results of **Danish *et al.*** [(4)]. who stated that maternal age has no influence on complete blood count parameters of newborns between two groups of mothers categorized according to their age. Correlation between HbA1C and other parameters was explained with the effect on intrauterine fetal hypoxia with fetal hyperglycemia, increased erythropoiesis and depleted fetal iron stores which were expressed with increased StfR, decreased s.ferritin and increased erythrpoiesis associated with maternal diabetes mellitus which was proportionate to the degree of maternal diabetes control and presence or absence of diabetes-related complications and not the maternal iron status [(10)].

Fetal iron stores are directly related to gestational age where earlier gestation is associated with lower iron stores showed positive correlation between s.ferritin and gestational age. The lowest stores were found in extremely preterm infants[(10)]. this is may be due to the late passage of iron through the placenta during the third trimester of pregnancy These results are similar to another study which showed that there was a significant association between S. ferritin, gestational age [(5)].

There was a statistically significant positive correlation between neonatal sTfR and maternal HbA1c (P=0.000), while there was a negative correlation between neonatal sTfR and APGAR score 1 min (P=0.017) and 5min(P=0.003) among the IDMs. This agrees with results of **Sweet *et al*[10]** who reported that depleted fetal iron stores were associated with maternal diabetes mellitus and it was is proportional to the degree of maternal diabetes control and presence or absence of diabetes-related complications and not the maternal iron status.

HbA1C as an indicator of maternal diabetes control during pregnancy was divided as

Excellent 4-6% =24% (n=12)

Good 7-8% = 60% (n=30)

Poor >8% = 16% (n=8)

This was explained by uncontrolled diabetes mellitus during gestation, associated with maternal and fetal hyperglycemia, fetal hyperinsulinemia, increased oxygen consumption in a relatively hypoxic intrauterine environment, stimulates erythropoiesis and expands the fetal RBC mass, thus reducing fetal iron stores and increasing sTfR expression also, sTfR was associated with lower APGAR score at 1and 5 minutes due to more cesarean sections associated with uncontrolled maternal diabetes mellitus.

CONCLUSION

This study showed that maternal diabetes affects fetal tissue iron stores at birth. S. ferritin was lower and sTfR was higher; this may be due to increased erythropoiesis, secondary to fetal hypoxia. Most IDMs were macrosomic and were born earlier with cesarean section. There was a significant association between S. ferritin, gestational age and birth weight.

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