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Cord Serum Lipid Profile of Infants of Diabetic Mothers

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ABSTRACT

Background: Infants of diabetic mothers (IDM) is a critical issue in pediatrics, which is regarded as a major risk factor for birth trauma, respiratory distress syndrome (RDS), birth asphyxia, transient tachypnea of the newborn (TTN) and jaundice. IDM is also a risk factor for microvascular (e.g., ocular and renal complications) and macrovascular complications (e.g., cerebrovascular accident, atherosclerosis and cardiovascular complications). Lipids are a heterogeneous group of hydrophobic organic molecules which can be extracted from tissues using non-polar solvents. Lipids, due to their hydrophobic property, are mainly found in membranes enclosing various cell organelles. Diabetes mellitus management with insulin (nowadays also with oral hypoglycemic medications) has improved the outcomes of gestational diabetes mellitus (GDM) (most infants born to diabetic mother are large for gestational age). The neonatal mortality rate in IDM is over five times higher than that of infants of non-diabetic mothers. In this study, therefore, we aimed to assess the effect of maternal diabetes on cord serum lipid profile.

Methods: This prospective (case-control) study was carried out on 60 infants born in Al-Zahra teaching hospital during February 2014–October 2014. The study group consisted of 30 randomly chosen IDM, and the control group comprised 30 infants who were born to healthy mothers.

Results: The results of this study demonstrated that there are significant differences between IDM and infants of healthy mothers regarding lipid profile and birth weight.

Conclusion: This study confirms that cord serum lipid profile (serum cholesterol, serum triglycerides and low-density lipoprotein) is higher at birth in IDM. Moreover, this study shows a significant association between lipid profile and body weight.

Keywords: Diabetic mothers, Infant, Cord Serum Lipid

Introduction

The world health organization (WHO) has defined gestational diabetes mellitus (GDM) as carbohydrate intolerance resulting in hyperglycemia. GDM can have detrimental effects on fetal development and might lead to metabolic disorders in neonates. The most important effect of diabetes on the fetus is macrosomia. In this case, fetal insulin level elevates in response to maternal hyperglycemia which in turn, results in macrosomia (1). Alteration in the growth hormone/insulin-like growth factor-1 axis is a risk factor for cardiovascular diseases. Both hyper- and hyposecretion of growth hormone are believed to increase the risk for cardiovascular diseases as well (2). Abnormalities in lipoprotein composition and concentration are also associated with macrosomia at birth and elevated lipoprotein levels, which might persist after birth, playing a role in the development of atherosclerosis and diabetes in adulthood (3).

Clinical manifestation of atherosclerosis in adults is rooted in childhood (4). Tracy et al. (5) pointed to early atheromatous alterations in the aorta. With technological advancements, early vascular alterations related to atherosclerosis can be detected from peripheral vessels by sonography (6).

GDM is associated with adverse maternal or neonatal outcomes (5). These adverse outcomes include increased likelihood of birth defects, preterm births, cesarean deliveries, macrosomia, congenital abnormalities, preeclampsia and hypertension (6-8). In IDM, the rate of congenital anomalies is 6-10%. Alteration in lipid profile is also believed to occur in GDM (9). Women with GDM are at high risk for long-term morbidity and mortality due to cardiovascular diseases (10-13).

Lipid metabolism in macrosomia

Diabetes has been considered as an important factor altering maternal metabolism and complicating fetal development, regardless of diabetic type (14, 15). Changes in lipoprotein metabolism during normal pregnancies are

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reflected by elevated serum concentrations of non-esterified fatty acids (NEFAs; free fatty acids), triacylglycerols (TAGs; triglycerides), cholesterol, phospholipids and apolipoproteins (apos) (16).

Diabetes mellitus is also associated with alterations in lipid and serum lipoprotein levels (17). It may be hypothesized, therefore, that GDM may further alter lipoprotein metabolism by promoting serum TAG and apolipoprotein B (apoB) concentrations (4, 5).

Increase in glucose and placental transfer of NEFA in diabetic mothers could explain raised hepatic very low density lipoprotein (VLDL) secretion and hypertriglyceridaemia in macrosomic newborns, as glucose and NEFA are the major substrate determinants of hepatic secretion (18). Indeed, hyperinsulinaemia boosts lipid and protein synthesis (19). Furthermore, significant positive correlations between maternal glycosylated haemoglobin (HbA1c) and TAG levels in late gestation have been found. TAG levels and apoB 100 concentrations in macrosomic neonates support these findings (14).

Macrosomic newborns also have high low-density lipoprotein (LDL) levels as a result of high concentrations of VLDL, as most LDL particles are derived from VLDL by the action of lipoprotein lipase (LPL) (4, 5). Chan et al. (50) have reported that VLDL and low-density lipoprotein cholesterol (LDL-C) concentrations are significantly elevated in IDM.

In the recent studies, increased LDL-C levels (20) in infants of GDM and type I diabetes mothers have been reported. High activities of LPL and hepatic TAG lipase (HTAGL) have also been found in IDM (21, 22). Macrosomic newborns present with high levels of high-density lipoprotein (HDL), which are accompanied by high HDL apoA-I and apoA-II concentrations, suggesting an increase in the number of HDL particles, probably as a result of their enhanced synthesis (5, 14).

Since HDL is primarily responsible for lipid transport during fetal life, elevated HDL level might reflect growing need of cholesterol and phospholipids for membrane, hormone and surfactant synthesis in macrosomic newborns. In these cases, lecithin cholesterol acyltransferase (LCAT) activity is not significantly different from that of cholesterol. The body uses cholesterol to help build cells and produce hormones. Too much cholesterol in the blood can build up inside arteries, forming what is known as plaque. Large amounts of plaque promote individuals' chances of myocardial infarction or cerebrovascular accident.

Method

The present hospital-based, prospective (case-control) study was carried out in AL-Zahra teaching hospital during February 2014-October 2014 in Najaf, Iraq. Umbilical blood samples were collected from 60 (30 IDM and 30 normal controlled) randomly chosen infants, who were delivered by normal vaginal delivery (NVD) or cesarean section (CS). Blood samples were taken after clamping or milking of the umbilical cord. The samples were put into serum tubes.

The inclusion criteria were as follows: full-term birth (completed 38 weeks), birth weight of 2.5-3.5 kg, no obvious congenital abnormalities, mothers aged between 25 and 37 years and not having other systemic illnesses for diabetic mothers.

Names of the used materials:
1) Cholesterol investigation material: Bio Labo (S.A.S) cholesterol choD-P Ap
2) Triglyceride investigation material: Bio Labo (S.A.S) Triglyceride–Gpo
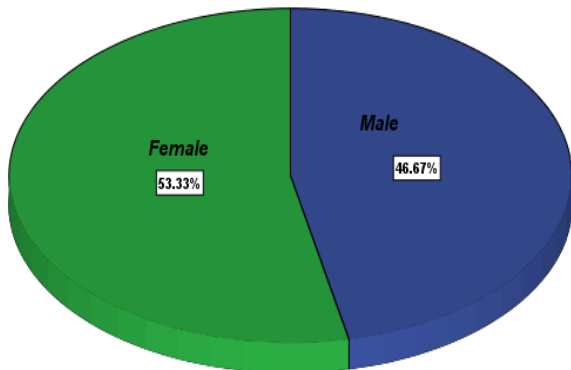3) HDL investigation material: Bio Labo S-A-HDL-cholesterol

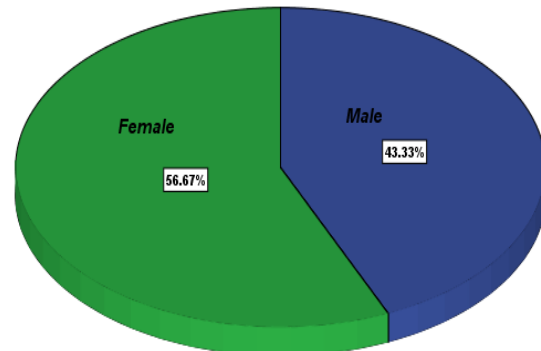**Figure 1.** Gender distribution of the infants of normal mothers

Figure 2. Gender distribution of the infants of diabetic mothers

Cholesterol measurement was performed using spectrophotometer (PD–303, Apel, Japan), which was set to wavelength of 500 nm. We standardized the readings by distilled water and then by blank material. We read the standard, and read the test thereafter. The following formula was applied to read the results: Factor=200/(the standard results). Eventually, the factor was multiplied by the test result to achieve the final result. For TG measurement, the same method as cholesterol measurement was applied using the TG material and its specific standard.

To determine HDL, we put 50 µl of the HDL material in a test tube with 1/2 ml of the neonates' serum, and then waited for 10 minutes. Afterwards, the mixture was centrifuged for 10 minutes. Then, 10 µl of the centrifuged material was taken and 1ml of the cholesterol material was added to it. After 10 minutes it was read by the spectrophotometer at wavelength of 500 nm. The result was multiplied by the same factor of cholesterol after standardizing the apparatus by distilled water and blank with 1ml of the cholesterol material.

LDL and VLDL were measured using the following formulas: LDL=cholesterol result–(HDL+VLDL) and VLDL=(TG result)/5.

Results

The results showed that the mean age of the mothers was 30.8±4.2 years, ranging from 25 to 39 years. Gender distribution of the infants is shown in Figure 1.

Table 2 exhibits a significant difference in neonatal weight between the IDM and infants of

Healthy mothers, while there is no significant difference in the two groups regarding the mothers' age and gestational age.

Table 3 demonstrates a significant difference between the two groups in serum cholesterol, triglyceride and LDL levels, which are higher among the IDM. Moreover, no significant difference was found in the two groups regarding HDL.
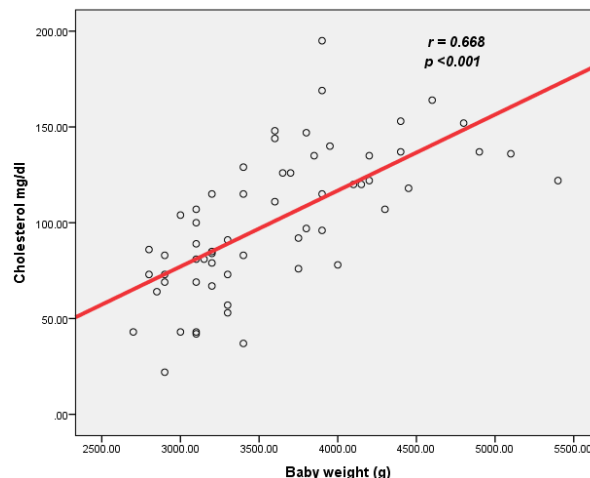
Figure 3. Correlation between serum cholesterol and neonatal weight in both groups (r=0.668, P<0.001)
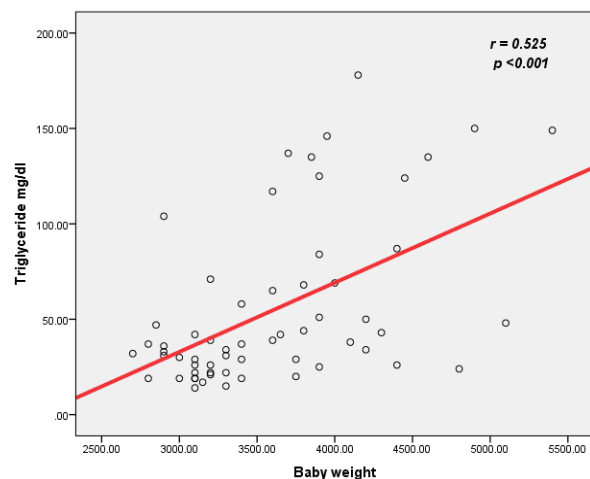
Figure 4. Correlation between triglyceride level and neonatal weight in both groups (r=0.525, P<0.001)

Table 1. Values considered normal at birth

	Males (mg/dl)	Females (mg/dl)
Total cholesterol	81.8±27.6	86.5±28.6
Triglycerides	63.4±44.5	66.5±42.4
High-density lipoprotein	31.8±15.5	33.4±14.5
Low-density lipoprotein	147.6±97.2	154.4±103.6

**Table 2.** Comparison between the infants of diabetic and normal mothers

| Variable	The infants of normal mothers	The infants of diabetic mothers	*P*-value
	Mean ±SD	Mean ±SD	
Mothers' age	29.86±4.03	31.86±4.24	0.068
Gestational age	37.93±0.827	37.96±1.017	0.894
Neonatal weight (g)	3100.0±191.63	4101.6±481.28	<0.001
Random blood sugar (RBS) of mother	102.66±15.21	196.23±22.31	<0.001
RBS of infant	78.50±14.81	37.23±8.05	<0.001

Table 3. Lipid profile in the two groups

| Variable	The infants of normal mothers	The infants of diabetic mothers	P-value
	Mean±SD	Mean±SD	
Serum cholesterol (mg/dl)	73.70±23.56	128.23±26.15	<0.001
Serum triglyceride (mg/dl)	31.4±17.94	78.0±48.02	<0.001
High-density lipoprotein (mg/dl)	40.76±11.44	41.50±27.19	0.892
Low-density lipoprotein (mg/dl)	12.8±4.821	80.5±38.15	<0.001
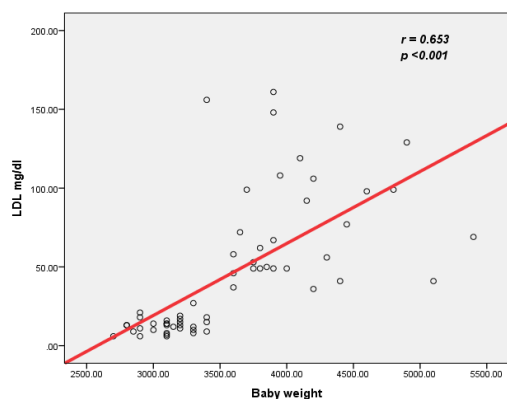
**Figure 5.** Correlation between low-density lipoprotein level and neonatal weight in both groups (r=0.653, P<0.001)
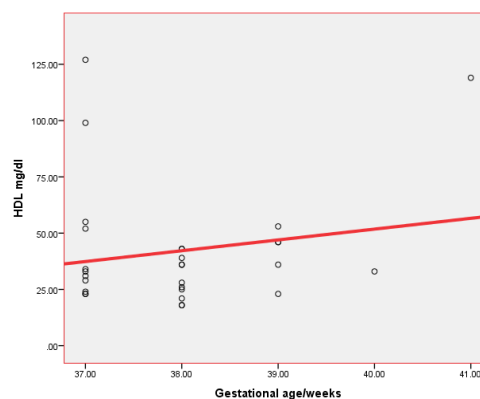
**Figure 8.** Correlation between gestational age and high-density lipoprotein in both groups (r=0.177, P=0.357)
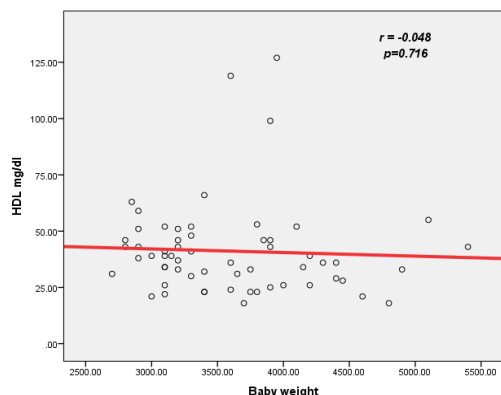
Figure 6. Correlation between high-density lipoprotein level and neonatal weight in both groups (r=-0.048, P=0.716)
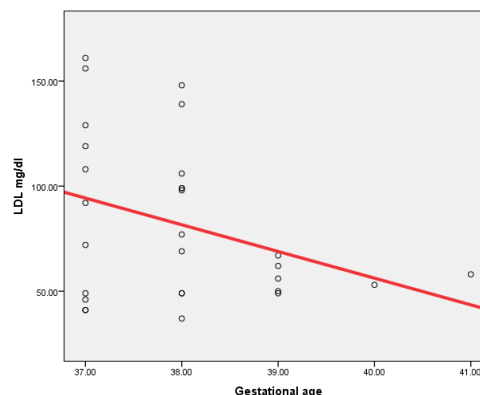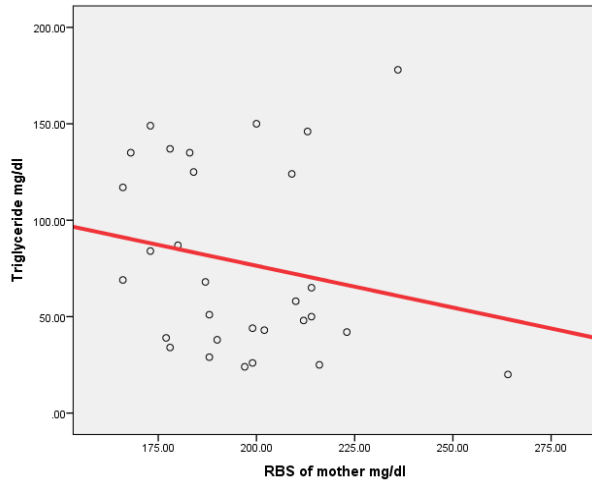

Figure 9. Correlation between gestational age and low-density lipoprotein in both groups (r=-0.341, P=0.070)
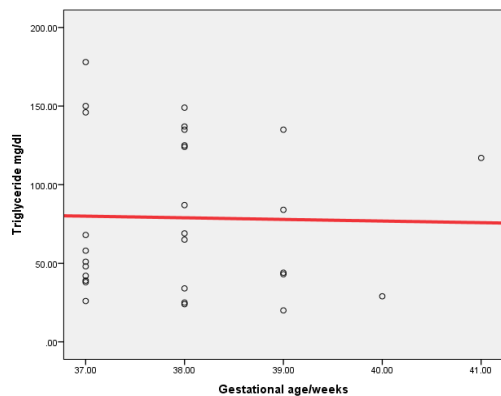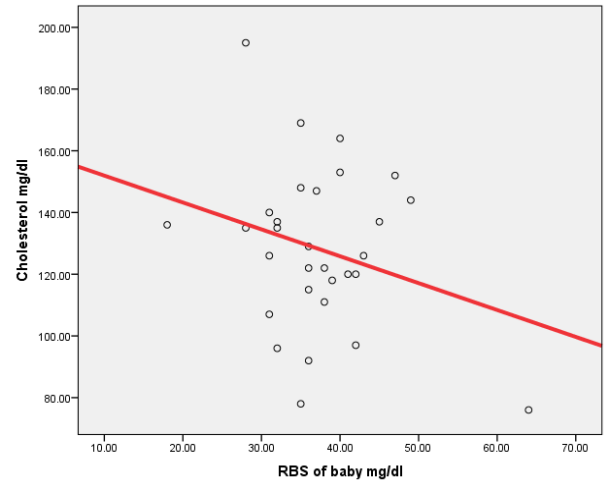

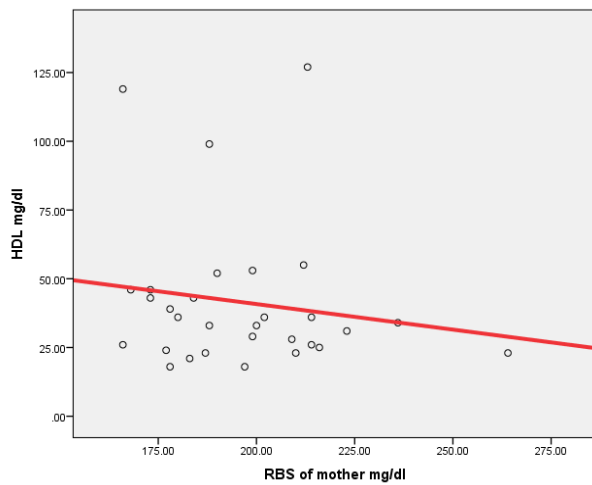**Figure 7.** Correlation between gestational age and triglyceride (r=-0.022, P=0.911)
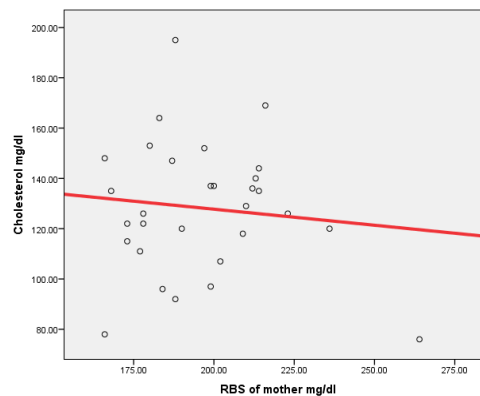
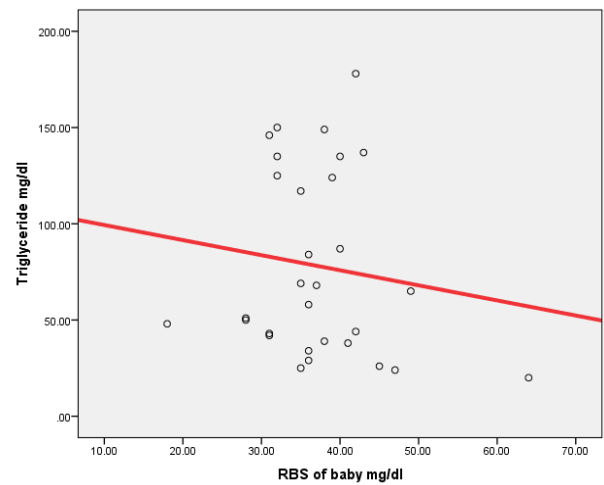**Figure 10.** Correlation between cholesterol level and random blood sugar of mothers in both groups (r=-0.109, P=0.567)

Figure 11. Correlation between triglyceride and random blood sugar of mothers in both groups (r=-0.201, P=0.286)

Figure 14. Correlation between cholesterol and random blood sugar of neonates in both groups (r=-0.268, P=0.152)

Figure 12. Correlation between high-density lipoprotein and random blood sugar of mothers in both groups (r=-0.152, P=0.060)
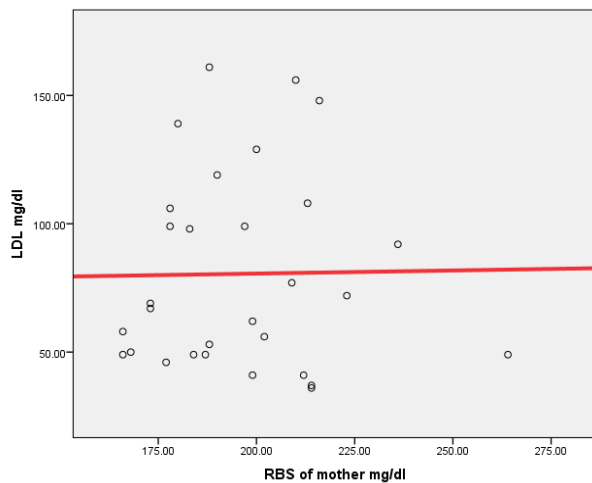

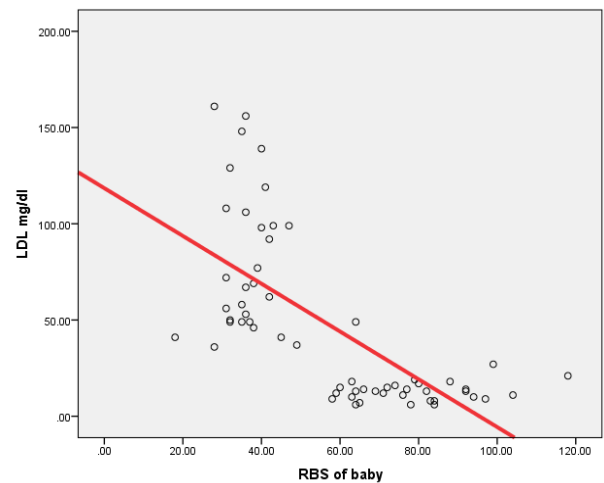**Figure 15.** Correlation between triglyceride and random blood sugar of neonates in both groups (r=-0.132, P=0.488)

Figure 13. Correlation between low-density lipoprotein and random blood sugar of mothers in both groups (r=0.014, P=0.941)

Figure 16. Correlation between low-density lipoprotein and random blood sugar of neonates in both groups (r=-0.074, P=0.698)

In Figure 3, a significant strong positive correlation can be observed between serum cholesterol level and neonatal weight.

In Figure 4, a significant moderate positive correlation between serum triglyceride level and neonatal weight is demonstrated.

Figure 5 depicts a significant strong positive correlation between LDL level and neonatal weight.

Figure 6 shows that correlation between HDL level and neonatal weight is not significant

Discussion

Serum lipid profile in childhood is considered as a predictive factor for serum lipid level later in life. This means that not only diet but also other risk factors affect serum lipid level from birth (22).

This study showed no significant differences between the two groups of infants regarding gestational age (P=0.894) (Table 2). However, as reported by other studies, IDM are at a higher of preterm birth (low gestational age) (3). The limited number of cases in our study may be the underlying cause of this discrepancy. Moreover, Table 2 demonstrated no significant differences between the two groups regarding mothers' age (P=0.068).

The results of this study reflect a significant difference between the IDM and infants of healthy mothers regarding birth weight (P<0001) (the mean birth weight of the IDM was 4101.6 g, while the mean birth weight of the infants of healthy mothers was 3100.0 g) (Table 2).

Other studies have reported a decline in the incidence of macrosomia in IDM from 60% to about 20%-35%, which might be secondary to aggressive diagnosis and treatment of GDM (1). In addition, a study carried out in Japan showed that the incidence of preterm labour and low-birth-weight are associated with GDM (23, 24). Whereas, several studies demonstrate that a small (<5%) number of fetuses, usually carried by mothers with advanced diabetic vascular disease, are at risk for fetal growth restriction (birth weight of less than fifth percentile for gestational age) (15, 16), this inconsistency might be explained by different ways of diabetes management in many studies.

This study also reflected a significant difference between diabetic and healthy mothers regarding mean random blood sugar (RBS). The mean RBS of the diabetic mothers was 196.2 mg/dl, while the mean RBS of the healthy mothers was 102.6 mg/dl (P<0.001) (Table 2). Table 2 depicts a significant difference between the IDM and infants of healthy mothers regarding RBS. This result highlights the importance of HbA1c blood test for diabetes. The mean RBS of the IDM was 37.2 mg/dl, while the mean RBS of the infants of healthy mothers was 78.5 mg/dl (P<0.001). These results are not in agreement with the obtained results of the studies conducted by Rollins et al. and Rooney (25, 26).

Table 3 presents a significant difference between IDM and infants of healthy mothers regarding serum cholesterol. The mean serum cholesterol was about 128.2 mg/dl in the diabetic mothers, while it was about 73.7 mg/dl in the healthy mothers (P<0.001). The same table demonstrates that TG and LDL levels were significantly higher in the diabetic mothers with mean of 78.0 mg/dl and 80.5 mg/dl, while the respective values in healthy mothers were 31.4 mg/dl and 12.8 mg/dl (P<0.001). These results might be due to decreased activity of LPL in adipose and liver (27).

HDL level was not significantly different in the two groups (P=0.890). These findings are partially consistent with the previous studies showing lowered levels of total serum cholesterol, TG, LDL and HDL.

Table 4 shows that 83.3% and 60% of deliveries were through caesarean section in the diabetic and healthy mothers, respectively (P=0.045). This difference might be due to macrosomia (1).

The obtained results reflect a significant strong positive correlation between serum cholesterol level and neonatal weight (Figure 3) (P<0.001, r=0.668), while Figure 4 shows a significant moderate positive correlation between serum TG level and neonatal weight (P> 0.001, r =0.525).

Table 4. Mode of delivery and gender distribution among the studied groups

Variable		The infants of normal Mothers n (%)	The infants of diabetic mothers n (%)	*P*-value
Mode	Cesarean section	18 (60%)	25 (83.3%)	0.045
	Normal vaginal delivery	12 (40%)	5 (16.7%)	
Gender	Male	14 (46.7%)	13 (43.3%)	0.795
	Female	16 (53.3%)	17 (56.7%)	

In Figure 5, a significant strong positive correlation between LDL level and neonatal weight is noted ($P < 0.001$, $r = 0.653$). These results are consistent with results of the studies conducted by Kalra and Mathur, in which these associations are explained through systemic placental nutrient transport and stressful conditions.

In this study, a non-significant weak negative correlation was observed between HDL level and neonatal weight (Figure 6). Lipid parameter also did not show a significant correlation between GA, TG, HGL and LDL ($P < 0.911$, $= 0.357$ and $= 0.07$, respectively). These results are shown in Figures 7-9 for both groups.

Regarding RBS of mothers, no significant correlation was found with serum cholesterol, TG, HDL and LDL ($P = 0.567$, 0.286, 0.060 and 0.941, respectively), which can be noted in Figures 10-13, respectively.

In addition, no significant correlation was observed between lipid parameters (serum cholesterol, TG and LDL) and RBS of newborns in both groups ($P = 0.152$, 0.488 and 0.698, respectively). These findings are presented in Figures 14-16, respectively. These results might be due to the small sample size.

Conclusion

This study did not show any significant differences between the two groups of infants regarding gestational age. However, a significant difference in serum cholesterol, TG and LDL levels was found in the two groups (which were higher in the IDM). Moreover, no significant difference was observed between the two groups regarding HDL level. A significant association between lipid profile and body weight was also found. This study shows that serum cholesterol and LDL levels have a significant strong positive correlation with neonatal weight. In addition, a significant moderate positive correlation between serum TG level and neonatal weight was found.

Recommendations

For further studies, measuring serum lipid profile of the newly delivered infants to diabetic mothers is recommended to demonstrate any increase in serum lipid profile. Additionally, infants with high serum lipid level may benefit from diet modification and close monitoring of their serum lipid status.

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