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Research Article

Using Lipid Parameters in Predicting Preterm Infants with Respiratory Distress Syndrome

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Abstract:

Background: Respiratory distress syndrome is a clinical diagnosis which is warranted in a preterm newborn with respiratory difficulty, including tachypnea (>60 breaths/min), chest retractions, and cyanosis in room air that persist or progress over the first 48-96 hr of life, and a characteristic chest radiographic appearance.

Objective: to assess the cord blood lipid profile for predicting of preterm infants with respiratory distress syndrome.

Methods: This is a case control study which was conducted on 50 preterm neonates admitted to the neonatal intensive care unit of Shebin El-Kom teaching hospital between January 2011 and October 2011.

Results: the mean of weight gain during pregnancy in mothers of preterm with RDS was lower than the control group and the difference was statistically highly significant (P<0.01). Also, there was significant difference (P<0.05) regarding mode of delivery and antenatal steroid, however; no statistical significant difference was detected regarding maternal age, maternal weight, maternal BMI, pre-gravid height, the ruptured membrane > 24 hr and parity between both groups. the mean of total cholesterol, HDL-cholesterol and LDL-cholesterol in the cord blood was lower in group A than in group B and the difference was statistically highly significant (P <0.01), but there was no significant difference regarding the mean of both triglycerides and VLDL-cholesterol in both groups (P>0.05).the mean of total cholesterol, HDL-cholesterol and LDL-cholesterol was lower in mothers of preterm infants with RDS than in control group and the difference was statistically highly significant (P <0.01), but there was no significant difference was detected regarding the mean of levels triglycerides and VLDL-cholesterol in both groups (P >0.05).the cutoff values of cord blood (total Cholesterol, HDL-C, and LDL-C) below which RDS can be predicted are 80, 45.5 and 23.2 mg/dl respectively with a sensitivity of 83.3%, 86.7% and 86.7% and with specificity of 95%, 80% and 70% respectively.

Conclusion: We conclude that RDS is accompanied with lipid alteration in the infants and their mothers. The results of this study point to the importance of measuring of maternal serum and cord blood lipid profile as a predictor for the occurrence of RDS.

Keywords: cord serum, respiratory distress syndrome, preterm infants.

Introduction

Respiratory distress syndrome (RDS) can occur in preterm infants as a result of surfactant deficiency and underdeveloped lung anatomy (Hermansen and Lorah, 2007). It occurs in 60-80% of infants less than 28weeks of gestational age, in 15-30%of those between 32 and 36 weeks, in about 5% beyond 37 weeks and rarely at term **(Stoll and Kliegman, 2011).**

Respiratory distress syndrome is a clinical diagnosis which is warranted in a preterm newborn with respiratory difficulty, including tachypnea (>60 breaths/min), chest retractions, and cyanosis in room air that persist or progress over the first 48-96 hr of life, and a characteristic chest radiographic appearance (uniform reticulogranular pattern and peripheral air bronchograms) **(Tammela, 2009).**

World Health Organization defines prematurity as babies born before 37 weeks from the first day of the last menstrual period **(moser et al., 2007).** The major constituents of surfactant are dipalmitoyl phosphatidylcholine (lecithin), phosphatidylglycerol, apoproteins (surfactant proteins SP-A, -B, -C, -D), and cholesterol. With advancing gestational age, increasing amounts of phospholipids are synthesized and stored in type II alveolar cells. These surface-active agents are released into the alveoli, where they reduce surface tension and help maintain alveolar stability by preventing the collapse of small air spaces at end-expiration **(Stoll and Kliegman, 2011).**

Lipid metabolism has an important role in fetal development during the late stage of gestation, including growth and fat accretion in utero, transport of cholesterol to the fetal adrenal for hormone synthesis, increasing amniotic fluid lecithin levels with maturation of pulmonary function **(Lane et al., 2002).** Cholesterol is obtained endogenously by de novo synthesis and exogenously by transfer of maternal cholesterol to the fetus. Interestingly, maternal plasma triglyceride and cholesterol concentrations increase during pregnancy in humans, possibly an adaptation to maternal and fetal **needs (Burke et al., 2009).** The developing fetus is highly dependent on the availability of lipid substrates, such as fatty acids, that are utilized for the biosynthesis of phosphatidylcholine. Potential sources of fatty acids include de novo synthesis within the fetus or placenta, or transport of free fatty acids from the maternal circulation. However, the fetus cannot solely rely upon de novo fatty acid synthesis, as up to 50% of fatty acids are derived maternally.

Thus, a major pathway for free fatty acids to the fetus appears to be from maternal lipids carried within lipoproteins **(Ryan et al., 2002).** Inadequate total fatty acids supplied in utero could interfere with normal fetal growth and maturation, leading to development of neonatal RDS as one manifestation of risk for postnatal morbidity and mortality **(Lane et al., 2002).** This study aims to assess the cord blood lipid profile for predicting preterm infants with respiratory distress syndrome.

Patients and Methods

Study design and patients grouping

A case control study which was conducted on 50 preterm neonates admitted to the neonatal intensive care unit of Shebin El-Kom teaching hospital between January 2021 and October 20122.The newborns were divided into two groups: Group A: *(STUDY GROUP)* It included 30 preterm newborns that developed RDS and their mothers, Group B: *(CONTROL GROUP)* It included 20 preterm newborns that did not develop RDS and their mothers.

Patients' criteria

We included Preterm neonates ≤ 36 weeks gestational age, Mature neonates > 36 weeks gestational age, Small /large for gestational age, Neonatal asphyxia, Major congenital anomalies, Mothers whose pregnancies were complicated by hypertension and pre-eclampsia, or with history of endocrine disorders as diabetes, thyroid or adrenal problems, Infant whose mothers were taking drugs affecting lipid metabolites such as steroid (except for fetal lung maturation) and ritodrine.

All the included newborns were subjected to the following:

Maternal history: Maternal age, Menstrual history including the first day of last menstrual period, Maternal illness during pregnancy, Maternal medication during pregnancy, Obstetric history including gravity, parity, mode of delivery, premature rupture membrane.

Full physical examination of the neonates: Assessment of gestational age by using Ballard score, Assessment of Apgar score at1 and 5 minutes, Assessment of sex, birth weight, height, ponderal index (birth weight divided by height cubed), Assessment of respiratory distress signs (respiratory rate, chest wall retraction, grunting, and cyanosis on room air)

Clinical assessment of the mothers: Prepregnant weight and Weight gain during pregnancy, Maternal height, Prepregnant body mass index (weight in kilogram divided by height square in meter).

The diagnosis of RDS was established by meeting all of the following criteria: Physical examination notable for chest wall retractions and cyanosis on room air, Compatible X-ray demonstrating diffuse alveolar atelectasis, Arterial blood gas documentation of metabolic acidosis, hypoxemia and hypercapnia

Laboratory Investigations: Samples collection and storage, before withdrawing the samples consent was taken from the mother.

Maternal blood sample: Venous Blood sample (2 ml) was taken from peripheral vein of the mother after an overnight fast of at least 10 hr within 48 hr after the delivery for the measurement of lipid profile. It was obtained in a plain tube (Gunes et al., 2007).

Cord blood sample: Cord blood sample (2ml) was withdrawn from the umbilical vein immediately after delivery in a plain tube for the measurement of lipid profile. Maternal and cord blood samples were left to clot at room temperature for 20 minutes then centrifuged for 20 minutes at 2500 round per minute and samples stored at -20˚c until analysis within 15 days, for estimation of the following elements: Serum total cholesterol, serum HDL-cholesterol, serum LDL-cholesterol, serum VLDL- cholesterol and serum Triglyceride.

Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA). Qualitative data were described using numbers and percentages. Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. Student's t-test, Pearson correlation coefficient test, chi square test (X2-value), P value, probability of chance, indicates significance when P value ≤ 0.05, highly significant when P value ≤ 0.01 and P value >0.05 was considered not statistically significant.

Results

In the current study, the mean of gestational age, birth weight, length, Apgar scores at 1 & 5 min and podernal index were lower in group (A) than the group(B) and the difference was statistically significant (P <0.01, <0.01, <0.01, <0.05, <0.01 and <0.01 respectively). Also, RDS was significantly higher in males than females (P<0.05), **(Table 1).**

Table (1): Comparison between group A (RDS) and group B (control) preterm infants as regards clinical data.

		Group (A) Preterm with RDS		Group (B) Control preterm		t-test	p-value
		Mean	SD	Mean	SD		
GA		31	2	33	1	-4.727	<0.01**
Weight (kg)		1.4	.4	2.0	.3	-5.402	<0.01**
length (cm)		39	4	44	3	-3.923	<0.01**
Ponderal index		22.35	2.10	23.81	2.18	-2.258	<0.05*
Apgar 1		5	1	5.3	1	-3.539	<0.01**
Apgar 5		8	1	9	0	.001	0.943
		No.	%	No.	%	Chi-square	p-value
Sex	Male	22	66.7%	9	45.0%	4.089	<0.05*
	Female	8	33.3%	11	55.0%		

Also, the mean of weight gain during pregnancy in mothers of preterm with RDS was lower than the control group and the difference was statistically highly significant (P<0.01). Also, there was significant difference (P<0.05) regarding mode of delivery and antenatal steroid, however, no statistically

significant difference was detected regarding maternal age, maternal weight, maternal BMI, pre-gravid height, the ruptured membrane > 24 hr and parity between both groups. **(Table 2).**

Table (2): Comparison of some clinical data of mothers of preterm with RDS and control group.

		Group (A) (RDS)		Group (B) (control)		t-test	p-value
		Mean	SD	Mean	SD		
Mother age (years)		26	5	28	5	-2.035	>0.05
Pre-pregnant (wt)		68	7	69	6	-.578	>0.05
Mother height		161	3	161	3	-.743	>0.05
Mother BMI		26.27	2.09	26.56	1.89	-.503	>0.05
Weight gain during pregnancy		8	1	9	1	3.639	<0.01**
		No.	%	No.	%	Chi-square	p-value
Delivery	VD	9	30.0%	12	60%	4.34	<0.05*
	CS	21	70.0%	8	40%		
PROM >24	Positive	16	53.3%	8	40.0%	0.855	>0.05
	Negative	14	46.7%	12	60.0%		
Antenatal steroid	Positive	11	36.7%	13	65.0%	3.855	<0.05
	Negative	19	63.3%	7	35.0%		
Parity	PG	11	36.7%	8	40.0%	6.215	>0.05
	P1	8	26.7%	2	10.0%		
	P2	8	26.7%	5	25.0%		
	P3	3	10.0%	2	10.0%		
	P4	0	0%	3	15.0%		

Additionally, the mean of total cholesterol, HDL-cholesterol and LDL-cholesterol in the cord blood was lower in group A than in group B and the difference was statistically highly significant (P <0.01), but there was no significant difference regarding the mean of both triglycerides and VLDL-cholesterol in both groups (P>0.05**), (Table 3).**

Table (3): Comparison between group (A) and group (B) regarding cord blood lipid profile (mg/dl).

	Group (A) (RDS)		Group (B) (Control)		t-test	p-value
	Mean	SD	Mean	SD		
Total cholesterol	70	10	90	6	-8.143	<0.01**
TG	65	10	71	10	-5.526	>0.05
HDL	37	8	50	7	-5.944	<0.01**
LDL	21.9	2.7	25.6	3.8	-4.043	<0.01**
VLDL	13.8	2.1	14.1	2.0	-5.607	>0.05

Additionally, the mean of total cholesterol, HDL-cholesterol and LDL-cholesterol was lower in mothers of preterm infants with RDS than in control group and the difference was statistically highly significant (P <0.01), but there was no significant difference was detected regarding the mean of levels triglycerides and VLDL-cholesterol in both groups (P >0.05**), (Table 4).**

Table (4): Comparison between mothers of preterm with RDS and control group regarding maternal lipid profile (mg/dl).

	Group (A)		Group (B)		*t-test*	*p-value*
	Mean	SD	Mean	SD		
Mother total cholesterol	172	22	207	19	-5.787	<0.01**
Mother TG	187	20	195	19	-1.359	>0.05
Mother HDL	36	2	45	4	-10.453	<0.01**
Mother LDL	95.5	19.7	123.5	18.7	-5.020	<0.01**
Mother VLDL	31.4	4.0	39.0	3.9	-1.350	>0.05

Also, the cutoff values of cord blood (total Cholesterol, HDL-C, and LDL-C) below which RDS can be predicted are 80, 45.5 and 23.2 mg/dl respectively with a sensitivity of 83.3%, 86.7% and 86.7% and 86.7% and with specificity of 95%, 80% and 70% respectively**. (Table 5, Figure 1).**

Table (5): Cord blood lipid profile in predicting RDS.

Test Result Variable(s)	Area Under the Curve (AUC)	RDS if Less Than or Equal To	Sensitivity	Specificity
Total cholesterol	.946	80.00	83.3%	95%
HDL-C	.888	45.50	86.7%	80%
LDL-C	.807	23.200	86.7%	70%

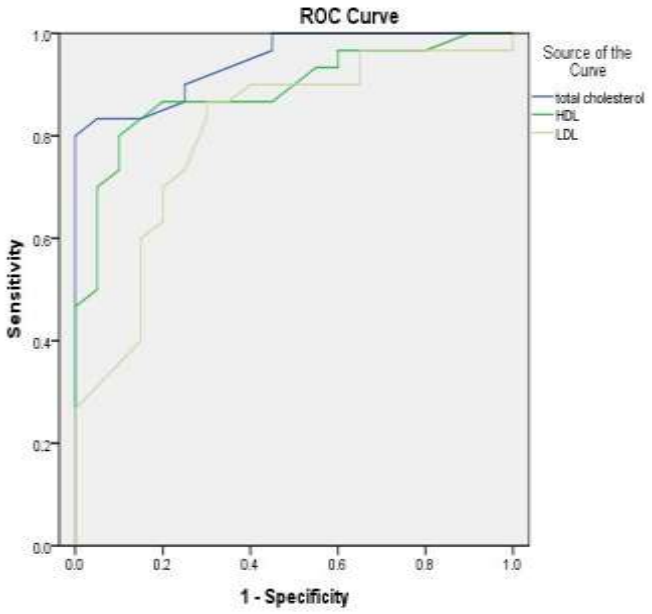

Figure 1. ROC curve for Cord blood lipid profile in predicting RDS.

Discussion

This study revealed that there was statistically significant difference between preterms who developed RDS and preterm who did not develop RDS as regard the gestational age, birth weight, length, Apgar scores at 1 and 5 min, podernal index and neonatal sex. This agrees **with Kumazawa et al. (2003)** who reported that there was significant difference between preterms

with and without RDS as regard gestational age and birth weight. Also, Lyra et al. (2011) reported that gestational age was the most important factor for the occurrence of RDS and the incidence of RDS increasses with decreasing gestational age. **Ersch et al. (2007)** found that respiratory distress syndrome (RDS) was significantly associated with male sex in the preterm neonates.

In the contrast, the studies of **Gunes et al. (2007) and Lane et al. (2002)** who did not find in their studies significant differences in neonatal characteristics as regards gestational age, birth weight, length, Apgar scores at 1 & 5 min, podernal index and neonatal sex between preterm infant with RDS and preterm infants without RDS. So, RDS may be a result of complex interactions between several environmental and genetic factors associated with prematurity, gender, race, and maternal diseases **(Haataja and Hallman, 2002).**

In the present study there was significant decrease in the mean of total cholesterol, HDL-C and LDL-C in preterm infant with RDS and their mothers compared to preterm infant without RDS and their mother. However, no significant deference was noticed regarding the mean of levels of triglyceride and VLDL-C among both groups. These results in agreement with **Gunes et al. (2007)** who found that mean total, HDL and LDL cholesterol levels were significantly lower in all gestational age groups of the infants with RDS and their mothers than the controls and no significant deference as regard triglyceride and VLDL levels among both groups. Lower levels of cholesterol and HDL-C, found in infants with RDS, indicated a limited ability to metabolize VLDL probably related to lipoprotein lipase impairment. Also, **Lane et al. (2002)** found that preterm infants developing RDS post-natally had significantly lower cord serum lipid levels than those of normal term infants or preterm infant not developing RDS. Significantly lower cord serum lipid levels are evidence of reduced essential fatty acids and long-chain polyunsaturated fatty acid supply, which could inhibit fetal growth in utero, delaying maturation of fetal lungs. **Moreover, Saleh et al. (2008)** documented that lipid levels in cord blood were markedly decreased in infants with RDS when compared to infants without RDS. **Gunes et al. (2007)** suggest that fetal metabolism and consequently fetal growth directly depends on the nutrients crossing the placenta, and therefore the mother adapts her metabolism to support this continuous draining of substrates. These results suggest that lower lipid parameters in RDS infants are evidences of reduced maternal supply, which could delay lung maturation. In the contrast, **Yonezawa et al. (2009)** suggested that neonates with RDS exhibited no difference in lipoprotein profiles when compared with gestational age-matched preterm neonates without RDS in gestational age groups from 28 to 34 weeks. Furthermore, **Karagiorga et al. (2006)** reported an increase of cholesterol in mothers of RDS infants over control. This discrepancy might be due to many genetic and environmental factors that can influence the concentration and composition of maternal and cord lipid profile **(Cohen, 2004).**

In this study, ROC analysis and area under the curve showed that cord blood total cholesterol of < 80 mg/dL, HDL-C of < 45.5 mg/dl and LDL-C of < 23.2 mg/dl were chosen as cutoff point below which RDS can be predicted in preterm infants, with the best sensitivity and specificity in predicting RDS. Our study has its limitation that the dietary intakes of the mothers during pregnancy were not evaluated. So that, more studies are needed to evaluate its reflection on serum lipid profile of mothers and their information.

Conclusion

In conclusion, RDS is accompanied by lipid alteration in the infants and their mothers. Cord blood total cholesterol of < 80 mg/dL, HDL-C of < 45.5 mg/dl and LDL-C of < 23.2 mg/dl were chosen as cutoff point below which RDS can be predicted in preterm infants, with the best sensitivity and specificity in predicting RDS.

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