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Research Article

Studies of Lipid Profiles Among Infants with Respiratory Distress Syndrome

Nehad Refhat Mostafa Sallam, Shymaa El-Sayed Ali Mohamed, Lamyaa Hussain Abdulrahman Seliem, Hebatallah Shoukry Mohamed Soliman, Marwa Foad Abdelrahman Asker, Ibrahim Mohamed Eladel Ibrahim Abouelkhir

Pediatrics department, Shebin Elkom Teaching Hospital, Shebin Elkom, Menoufia, 6132415, Egypt.

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Abstract:

Background: Respiratory distress syndrome (RDS) is known as hyaline membrane disease (HMD). It is the major cause of neonatal respiratory distress, especially in preterm infants Infants with RDS present with tachapnea, cyanosis, grunting, subcostal and intercostal retractions and nasal flaring. Oliguria with mild generalized edema may be present. Oxygen requirement may increase rapidly and is typically higher than that seen in infant with transient tachapnea of the newborn (TTN).

Objective: to evaluate the relationship between the maternal and cord blood lipid profiles in preterm babies 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 2020 and October 2021.

Results: the mean of total cholesterol was significantly higher in infants whose mothers had received antenatal steroid for lung maturity than those whose mothers had not ($P<0.05$). But there was no significant difference in the mean of levels of TG, HDL-cholesterol, LDL-cholesterol and VLDL cholesterol between both groups. Also, There is a positive correlation between weight gain during pregnancy and neonatal cord blood levels of (Total cholesterol, TG, HDL-C, LDL-C and VLDL-C), There is a positive correlation between maternal blood levels of (total cholesterol, TG, LDL-C and VLDL-C) and their neonatal cord blood levels of (total cholesterol, TG, HDL-C, LDL-C and VLDL-C), There is a positive correlation between the maternal blood level of HDL-C and their neonatal cord blood levels of (total cholesterol and HDL-C).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% and86.7% and with specificity of 95%, 80% and 70% respectively.

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

Keywords: cord serum, hyaline membrane disease, respiratory distress syndrome, preterm infants.

Introduction

Respiratory distress syndrome (RDS) is also known as hyaline membrane disease (HMD). It is the major cause of neonatal respiratory distress, especially in preterm infants **(Kim, 2010).** Typically, RDS affects preterm infants below 35 weeks of gestational age, however, older infants with delayed lung maturation of different etiologies can also be affected (**Rodriguez, 2003).** The outcome of RDS has improved in recent years with the increased use of antenatal steroids to improve pulmonary maturity, early postnatal surfactant therapy to replace surfactant deficiency, and proper advanced techniques of ventilation to minimize damage to the immature lungs **(Mantan and Arulkumarans, 2006).** Infants with RDS present with tachapnea, cyanosis, grunting, subcostal and intercostal retractions and nasal flaring. Oliguria with mild generalized edema may be present. Oxygen requirement may increase rapidly and is typically higher than that seen in infant with transient tachapnea of the newborn (TTN) (**Keszler and Abubakar, 2012**).

The severity of respiratory distress is assessed by Silverman-Anderson Score and Downes' Score. While the Silverman Anderson Retraction Score is more suited for preterms with HMD, the Downes' Score is more comprehensive and can be applied to any gestational age and condition. Scoring should be done at half hourly intervals and a chart maintained to determine progress. A progressively increasing FiO_2 requirement to maintain a saturation of 90-92% in a preterm and 94- 96% in a term baby is also a sensitive indicator of the severity and progress of distress **(Mathai et al., 2007).**

Lipids are heterogeneous group of water insoluble (hydrophobic) organic molecules that can be extracted from tissues by non-polar solvent. Because of their property of insolubility in water they are mainly found in different compartments, mostly associated with membranes enclosing various cell organelles. In adiposites as droplets of triglycerides, when transported in cytosol, they are in the form of lipoprotein particles **(Pamela et al., 2008).** This study aims to evaluate the relationship between the maternal and cord

blood lipid profiles in preterm babies with respiratory distress syndrome.

Patients and Methods

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 2020 and October 2021.The newborns were divided into two groups: Group A: (STUDY GROUP) 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. The diagnosis of RDS was established by meeting all 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.

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.

1. **Serum total cholesterol:** The cholesterol present in the sample originates a colored complex, according to the following reaction:

$$\text{Cholesterol esters} + H_2O \xrightarrow{\text{CHE}} \text{Cholesterol} + \text{fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{\text{CHOD}} \text{4-cholestenona} + H_2O_2$$

$$2\ H_2O_2 + \text{Phenol} + \text{4-Aminophenazone} \xrightarrow{\text{POD}} \text{Quinonimine} + 4H_2O$$

The intensity of the color formed is proportional to the cholesterol concentration in the sample.

2. **Serum high density lipoprotein-cholesterol (HDL-C):** The chylomicrons, very low-density Lipoproteins (VLDL) and low-density lipoproteins (LDL) are precipitated by phosphotungstic acid and magnesium chloride. After centrifugation the clear supernatant containing high density lipoproteins (HDL) is used for the determination of HDL cholesterol.
3. **Estimation of low-density lipoprotein-cholesterol (LDL-C):** The LDL cholesterol concentration (LDL-C) is calculated from the total cholesterol concentration (TC), the HDL cholesterol concentration (HDL-C) and the triglycerides concentration (TG) according to Friedwald equation.

LDL-C = total cholesterol - HDL - triglyceride/5 [mg/dl]

This formula is not used for triglycerides levels above 400 mg/dl

4. **Estimation of Very low-density lipoprotein-cholesterol (VLDL-C)**

This will be calculated from the equation: VLDL = $\frac{TG}{5}$

5. **Estimation of serum triglycerides:** Sample of triglycerides incubated with lipoprotein lipase (LPL), liberate glycerol and free fatty acids. Glycerol is converted to glycerol-3-phosphate (G3P) and adenosine-5-diphosphate (ADP) by glycerol kinase and adenosine-triphosphate (ATP). G3P is then converted by glycerol phosphate dehydrogenase (GPO) to dihydroxyacetone phosphate (DAP) and hydrogen peroxide (H_2O_2). In the last reaction, hydrogen peroxide (H_2O_2) reacts with 4-aminophenazone (4-AP) and p-chlorophenol in presence of peroxidase (POD) to give a red colored dye: Triglycerides + H2O $\xrightarrow{\text{LPL}}$ Glycerol + free fatty acids

$$\text{Glycerol} + \text{ATP} \xrightarrow{\text{Glycerol kinase}} \text{G3P} + \text{ADP}$$

$$\text{G3P} + O_2 \xrightarrow{\text{GPO}} \text{DAP} + H_2O_2$$

$$H_2O_2 + \text{4-AP} + \text{p-cholorophenol} \xrightarrow{\text{POD}} \text{Quinone} + H_2O$$

The intensity of the color formed is proportional to the triglyceride's concentration in the sample.

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 studied mothers and their newborns includes 15 neonates whose gestational age from 34 to 36 weeks; they represent 13.3% of infants with RDS and 55.0%of infants without RDS, 22 neonates whose gestational age from 31 to 33 weeks; they represent 43.3% of infants with RDS and 45.0% of infants without RDS, 13 neonates whose gestational age from 28 to 30 weeks; they represent 43.3% of infants with RDS and 0% of infants without RDS. **(Table 1).**

Table (1): Gestational age among the studied groups.

	Gestational age in weeks	Group (A) Preterm with RDS		Group (B) Control preterm	
		No.	%	No.	%
GA groups	28 – 30	13	43.3%	0	.0%
	31 – 33	13	43.3%	9	45.0%
	34 -36	4	13.3%	11	55.0%

Also, significant difference was observed as regarding the mean of levels of cord blood lipid profile between male and female (P >0.05). **(Table 2)** Also, there was no significant difference in the mean of levels of cord blood lipid profile between infants born vaginally and those born by cesarean section (P >0.05). **(Table 3)**.

Table (2): Cord blood lipid profile as regard neonatal sex.

	Sex				*t-test*	*P-value*
	Male		Female			
	Mean	SD	Mean	SD		
Total cholesterol	77	13	79	13	-.515	>0.05
TG	59	14	63	11	-1.146	>0.05
HDL	42	10	43	10	-.143	>0.05
LDL	23.1	3.5	23.8	3.9	-.642	>0.05
VLDL	11.8	2.8	12.6	2.2	-1.130	>0.05

Table (3): The effect of mode of delivery on the cord blood lipid profile.

	Delivery				*t-test*	*p-value*
	VD		CS			
	Mean	SD	Mean	SD		
total cholesterol	75	15	81	10	-1.747	>0.05
TG	58	13	63	13	-1.259	>0.05
HDL	40	11	44	8	-1.319	>0.05
LDL	22.5	3.1	24.2	4.0	-1.689	>0.05
VLDL	11.7	2.6	12.6	2.6	-1.239	>0.05

Additionally, the mean of total cholesterol was significantly higher in infants whose mothers had received antenatal steroid for lung maturity than those whose mothers had not (P < 0.05). But there was no significant difference in the mean of levels of TG, HDL-cholesterol, LDL-cholesterol and VLDL cholesterol between both groups**. (Table 4)** Additionally, there is a positive correlation between gestational age, birth weight, length, Apgar score at 1 and 5 min and the cord blood levels of (total cholesterol, triglyceride, HDL-C, LDL-C and VLDL-C), There is a positive correlation between ponderal index and each of total cholesterol and LDL-C. **(Table 5).**

Table (4): The effect of antenatal steroid as a drug used for lung maturity on cord blood lipid profile.

	Antenatal steroid				*t-test*	*p-value*
	Positive		Negative			
	Mean	SD	Mean	SD		
Total cholesterol	81	12	77	15	2.600	<0.05*
TG	63	13	59	13	1.132	>0.05
HDL	43	9	42	11	.250	>0.05
LDL	23.8	3.9	23.1	3.5	.663	>0.05
VLDL	12.6	2.5	11.7	2.7	1.158	>0.05

Table (5): Correlations between neonatal clinical characteristics and their cord blood lipid profile.

Correlations						
		Total cholesterol	TG	HDL	LDL	VLDL
GA	r	.727**	.500**	.693**	.353*	.503**
	P	<0.01**	<0.01**	<0.01**	<0.05*	<0.01**
wt (kg)	r	.790**	.555**	.748**	.388**	.557**
	P	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**
Length (cm)	r	.702**	.467**	.698**	.276	.468**
	P	<0.01**	<0.01**	<0.01**	<0.05*	<0.01**
ponderal index	r	.328	.231	.115	.339*	.234
	P	<0.05*	>0.05	>0.05	<0.05*	.101
Apgar1	r	.547**	.351*	.478**	.402**	.354*
	P	<0.01**	<0.05*	<0.01**	<0.01**	<0.05*
Apgar5	r	.598**	.418**	.530**	.396**	.422**
	P	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**

Also, there is a positive correlation between weight gain during pregnancy and neonatal cord blood levels of (Total cholesterol, TG, HDL-C, LDL-C and VLDL-C), There is a positive correlation between maternal blood levels of (total cholesterol, TG, LDL-C and VLDL-C) and their neonatal cord blood levels of (total cholesterol, TG, HDL-C, LDL-C and VLDL-C), There is a positive correlation between the maternal blood level of HDL-C and their neonatal cord blood levels of (total cholesterol and HDL-C). **(Table 6)**.

Table (6): Correlations between maternal (clinical and laboratory) data and their neonatal cord blood lipid profile.

Correlations						
		Total cholesterol	TG	HDL	LDL	VLDL
Mother age (years)	r	.134	.153	.105	.085	.151
	P	>0.05	>0.05	>0.05	>0.05	>0.05
Prepregnant (wt)	r	.107	.024	.142	-.021	.021
	P	>0.05	>0.05	>0.05	>0.05	>0.05
Mother height	r	.050	-.022	.058	.038	-.023
	P	>0.05	>0.05	>0.05	>0.05	>0.05
Mother BMI	r	.120	.040	.160	-.037	.037
	P	>0.05	>0.05	>0.05	>0.05	>0.05
Weight gain during pregnan	r	.468**	.380**	.418**	.361	.381**
	P	<0.01**	<0.01**	<0.01**	<0.05*	<0.01**
Mother total cholesterol	r	.896**	.679**	.840**	.430**	.679**
	P	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**
Mother TG	r	.821**	.707**	.750**	.388**	.710**
	P	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**
Mother HDL	r	-.334	-.177	-.336	-.069	-.163
	P	<0.05*	>0.05	<0.05*	>0.05	>0.05
Mother LDL	r	.865**	.636**	.817**	.412**	.634**
	P	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**
Mother VLDL	r	.821**	.707**	.750**	.388**	.710**
	P	<0.01**	<0.01**	<0.01**	<0.01**	<0.01**

Additionally, 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. **(Table 7, Figure 1).**

Table (7): cord blood lipid profile in predicting RDS

Test Result Variable(s)	Area Under the Curve (AUC)	RDS if =	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%

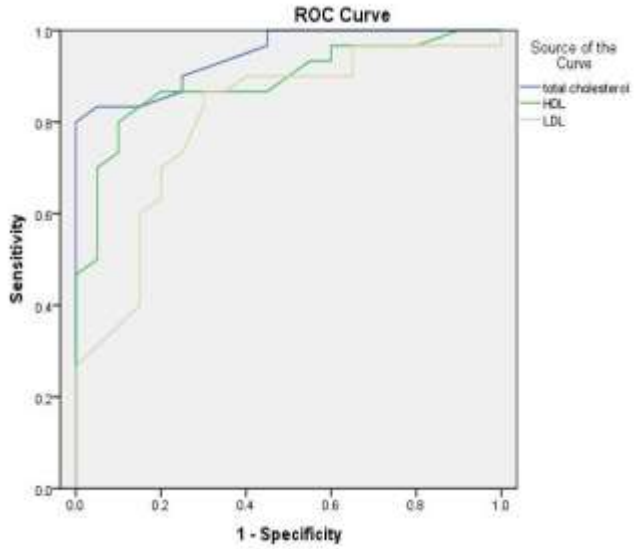

Figure (1): Receiver Operating Characteristic (ROC) curve.

Discussion

Respiratory distress syndrome (RDS) in premature infants remains the major life-threatening neonatal disease affecting 1 to 2% of newborn infants despite antenatal steroid and surfactant treatments. RDS is principally associated with developmental deficiency in synthesis, intracellular processing, and secretion of pulmonary surfactant, required to reduce surface tension at the air–liquid interface of the distal conducting airways and alveoli **(Marttila et al., 2003).** It is most common in infants born at fewer than 28 weeks' gestation and affects one third of infants born at 28 to 34 weeks' gestation but occurs in less than 5 percent of those born after 34 weeks' gestation **(Hermansen and Lorah, 2007).** Lipids play a major role in fetal development. Changes in the availability of lipid components, like those produced by changes in dietary fatty acids, are known to have implications in fetal and postnatal development **(Herrera, 2002).** Cholesterol is the second most abundant lipid component of pulmonary surfactant, composing from 10 to 25% (by mole fraction) of total surfactant lipid. Cholesterol represents over 50% of the neutral lipid of both the surfactant and the lamellar body fractions. De novo synthesis of cholesterol accounts for only 1% of the surfactant cholesterol, the remainder is derived from lipoprotein **(Madsen et al., 2004).** Fetal metabolism and consequently fetal growth directly depend on the nutrients crossing the placenta, so lower maternal lipid profile could delay fetal lung maturation and increase the risk for RDS **(Chapman et al., 2000).**

The aim of this study was to compare the maternal and cord lipid profiles of preterm infants with respiratory distress syndrome and a control group without respiratory distress syndrome. The study groups consisted of 30 preterm neonates with RDS, their gestational ages ranging from 28 to 36 weeks, birth weights ranging from (850 to 2400 g) and their mothers; and 20 preterm neonates without RDS, their gestational ages ranging from 31 to 36 weeks, birth weights ranging from (1500 to 2400 g) and their mothers were enrolled in this study as a control group. The present study revealed that weight gain during pregnancy was significantly lower in mothers of preterm with RDS, and there was significant difference regarding mode of delivery and antenatal steroid, however; no statistically significant difference regarding maternal age, maternal weight, maternal BMI, pregravid height, the ruptured membrane > 24 hr. and parity between the mothers of RDS neonates and mothers of the control group.

In agreement with these results **Teslova et al. (2012)** who reported that inadequate maternal weight gain during pregnancy may play a significant role in immaturity of the pulmonary surfactant system and may thus offer a predictor of respiratory distress syndrome in premature babies. **Butte et al. (2003)** Suggested that appropriate, but not excessive, gestational weight gain is needed to optimize infant birth weight and minimize maternal postpartum fat retention. So, appropriate weight gain during pregnancy is related to the neonatal outcome. **Sollid et al. (2004)** observed that poor weight gain during pregnancy, associated with LBW, prematurity, and maternal delivery complications. On the other hand, **Gunes et al. (2007)** found no significant difference in weight gain of mothers of preterm infants with or without RDS.As regard mode of delivery, our findings agree with **Hansen et al. (2008)** and **Kolas et al. (2006)** who reported that newborn delivered by elective cesarean section around term have an increased risk of overall and serious respiratory morbidity than infant delivered vaginally. The relative risk increased with decreasing gestational age.

As regard the effect of sex of the newborn on the cord blood lipid profile, no significant difference was found between male and females in our study. This agrees with the studies done by **Descamps et al. (2004), Rodie et al. (2004)** and **Saleh et al. (2008**) that reported no significant differences in cord blood lipid levels were seen between male and female newborns. However, significant gender differences in cord lipids have been noted by **Kelishadi et al. (2007)** and **Kharb et al. (2010)** who found that Cord blood of female newborns had higher total cholesterol, HDL-C, LDL-C, Apo A as compared to male newborns. **Aasvee et al. (2004)** speculated that female fetuses need different hormonal stimulation, and a higher level of blood cholesterol, compared to males.

As regards the effect of mode of delivery on the cord blood lipid profile, no significant difference was found in the present study. This agrees with **Gunes et al. (2007)** who demonstrated that the neonatal lipid profiles are not related to the mode of delivery.

However, **Bansal et al. (2005)** observed that methods of delivery that associated with higher fetal distress, such as vaginal delivery, appear to be associated with higher cord lipids compared with elective caesarean section. Also, **Rodie et al. (2004)** reported that emergency caesareans increase fetal stress and lipids more than that of elective section.

As regard the effect of antenatal steroid on the cord blood lipid profile, this study revealed that there was significant difference in total cholesterol, but no significant difference in TG, HDL-cholesterol, LDL-cholesterol and VLDL- cholesterol between both groups. **Parker et al. (2006)** reported that antenatal steroids stimulate hepatic production and secretion of lipids and certain lipoproteins in the fetus.

In the present study there was a positive correlation between gestational age, birth weight, length, Apgar score at 1 & 5 min and each of total cholesterol, triglyceride, HDL- cholesterol, VLDL- cholesterol and LDL- cholesterol levels. Also, significant positive correlations were found between ponderal index, and each of total cholesterol and LDL- cholesterol levels. In agreement with these results **Lane et al. (2002)** who reported that cord blood lipid profile in infants with RDS depends on their birth weight. They found that cord serum lipid and apolipoprotein levels were significantly elevated in large (2,000-2,499 g) RDS infants, but lower levels were found in smaller (1,000-1,999 g) RDS infants. Also, **Kelishadi et al. (2007)** found a significant correlation between birth weight and cord serum lipid. Moreover, **Huxley et al. (2004)** documented a retrospective association between birth weight and lipid levels and suggested that birth weight and body size have a great effect on blood cholesterol levels. But **Jain et al. (2011)** demonstrate that birth weight was inversely correlated with TC, LDL-C, VLDL-C, TG, Apo B. Moreover, **Badiee and Kelishadi R (2008)** found that There were no significant correlations between infant's ponderal index, birth weight, length, and TC, LDL-C, HDL-C, apolipoprotein A, apolipoprotein B. This difference between the results of these studies may be explained by the difference in the mean of gestational ages of the newborns selected in these studies; some may have included very near-term or very preterm newborns.

In the present study a positive correlation was detected between maternal weight gain during pregnancy and neonatal cord blood Total cholesterol, TG, HDL-C, LDL-C and VLDL-C. In agreement with our findings, **Gunes et al. (2007)** documented that weight gain during pregnancy was related to both maternal and infants' lipid profile and added the necessity of adequate gestational weight gain for optimal pregnancy outcome is recognized; however, the specific components of gestational weight gain that are critical for fetal growth and development are not delineated clearly. **Kaser et al. (2001)** suggested that both increased and decreased nourishment in utero affect the neonatal lipoprotein profile. However, **Kelishadi et al. (2007)** observed that maternal weight can affect fetal growth and maturation, but their impact on cord lipid profile remains controversial. Normal fetal growth is a result of complex interactions among the three components of the maternal–placental–fetal unit. Nutritional status of the mother is the most important maternal factor leading to intrauterine growth retardation **(Kelishadi et al., 2007**).

In this study a positive correlation was found between all maternal serum (total cholesterol, TG, LDL-C and VLDL-C) and each of cord blood (total cholesterol, TG, HDL-C, LDL-C, and VLDL-C). Also, a positive correlation between maternal HDL-C and neonatal cord blood (total cholesterol and HDL-C) was detected. In agreement with the present study **Bansal et al. (2005)** and **Gunes et al. (2007)** found that there was significant positive correlation between maternal and cord lipid profile of preterm infants that could be explained by the fact that maternal cholesterol can cross the placenta, and cholesterol concentrations in maternal serum affect concentrations in neonates. **Rodie et al. (2004)** found a strong correlation between maternal total cholesterol, HDL cholesterol and newborn HDL cholesterol. This could be explained by Studies done by **Burke et al. (2009)** and **Yoshida and Wada (2005)** who demonstrated the ability of maternal cholesterol to be transported to the fetus even if fetuses can synthesize cholesterol de novo. The fetus is dependent for its growth and development on the nutrients provided by the mother. The number of substrates reaching the placenta strictly depends on maternal diet and metabolism **(cetin et al., 2009).** Although lipids cross the placental barrier with difficulty, changes in lipid metabolism taking place on the maternal side could also contribute to the fetal development **(Herrera and Ortega-Senovilla, 2010)** Dietary deviations in maternal fatty acids intake throughout pregnancy may affect the nature of fatty acids crossing the placenta, having consequences to post-natal development.

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 infants.

Conclusion

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

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