Comparative study of cord blood lipid profile in relation to gestational age, birth weight, and sex

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ABSTRACT

Objectives: The objective of the study was to compare the cord blood lipid levels in healthy newborns according to gestational age (GA), weight, and sex. **Methods:** This study included 1000 healthy term and preterm neonates after obtaining parental consent at birth. The GA was confirmed using New Ballard Score. Fenton's growth charts were utilized to classify study subjects as appropriate for GA, small for GA, and large for GA at birth. Lipid profile was measured by enzymatic colorimetric method. Serum low-density lipoprotein-cholesterol (LDL-C) was calculated by Friedewald's formula. **Results:** Preterm neonates with GA of 28–36 weeks had higher mean total cholesterol, LDL, very LDL, and triglycerides levels than term neonates in contrast to their mean high-density lipoprotein (HDL) levels which was significantly lower as compared to that of term neonates. A statistically significant decline in all lipid fractions was observed with an increase in birth weight from <1.5 kg to ≥2.5 kg. Females had higher lipid fractions in comparison to male neonates; however, only the difference in HDL levels was statistically significant (p<0.001). **Conclusion:** Low birth weight neonates exhibit higher lipid levels at birth giving scope for future research and regular follow-up of these high-risk neonates.

Key words: *Gestation, Lipids, Neonates, Sex, Weight*

Cardiovascular disease is the primary cause of morbidity and mortality in developing countries. According to Fetal origin's Hypothesis proposed by David Barker "intrauterine growth retardation, low birth weight (LBW) and premature birth have a causal relationship to the origins of hypertension (HTN), coronary heart disease in middle age" [1]. Premature and growth-restricted neonates are unable to accumulate glycogen deposits in the later part of pregnancy leading to activation of lipid metabolism for promoting gluconeogenesis and generating energy. As a result, these neonates have abnormal lipid profile compared to appropriate for gestational age (AGA) babies, thus predisposing them to coronary heart disease, HTN, and Type 2 diabetes mellitus later in life [2]. Keeping in view the fact that nearly one-third neonates born in India are LBW, of which two-thirds are having intrauterine growth restriction (IUGR) [3] and also the malnutrition profile of pregnant women in India, this study was undertaken to document the variable neonatal lipid profile with respect to GA, birth weight, and sex.

METHODS

This hospital-based, prospective, and observational study was conducted in the department of paediatrics of a tertiary care teaching hospital from January 2017 to July 2018 involving in-house delivered 1000 neonates. As it was a time-bound study, a sample size of 1000 neonates was considered by convenient sampling method. The consent for participation in this study was obtained at birth from parents or attendants. The GA was determined based on last menstrual period (LMP) and confirmed using criteria described by New Ballard Score [4]. Fenton's growth charts were utilized to classify study subjects as AGA, small for GA (SGA), and large for GA (LGA) at birth.

All neonates born to mothers with definitely known LMP and Ballard score correlation <2 weeks and delivered between 28 and 42 weeks of gestation were included in the study. Neonates with congenital malformations, suspected sepsis, and Apgar score <7 at 5 min were excluded from the study. 2.5 ml of cord blood sample was collected from the placental end of the cord just after the delivery of the baby in a plane dry test tube, and lipid profile was assessed employing Humastar 200® Biochemical Analyzer based on the principle of enzymatic colorimetry. Serum low-density lipoprotein (LDL) was derived after estimating total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG) concentration, and deploying them in Friedewald's formula: LDL cholesterol (LDL-C) (mg/dl) = total cholesterol (mg/dl) – HDL cholesterol (mg/dl) – TG (mg/dl)∕5.

All relevant statistical analysis was performed using SPSS Version 21.0 statistical analysis software. This study was approved by the Institutional Ethics Committee.

RESULTS

Out of 1000 neonates enrolled in the study, 511 (51.1%) were males and 489 (48.9%) were females and male:female ratio was 1.04:1. The most common GA was 37–40 weeks (55.7%) followed by 28–36 weeks (35.4%) and 40–42 weeks (8.9%). The majority (64%) of the neonates enrolled in the study was AGA followed by 29.5% neonates who were SGA and 6.5% neonates who were LGA. The birth weight of majority (60.6%) of the neonates was >2.5 kg followed by neonates having weight 1.5–2.5 kg (38.4%) and <1.5 kg (1%). The mean total cholesterol, LDL, HDL, TG, and very LDL (VLDL) levels were found to be significantly higher in neonates with GA of 28–36 weeks in comparison to neonates with GA of 37–40 weeks (Tables 1 and 2).

The absolute mean levels of total cholesterol, LDL, and TG in neonates with GA of 28–36 weeks were found to be significantly higher than in neonates of 37–40 weeks GA in contrast to HDL levels which were significantly higher in 37–40 week neonates as compared to neonates in 28–36 weeks category. Total cholesterol and LDL levels were also found to be significantly higher in 40–42 weeks GA neonates in comparison to neonates with GA of 37–40 weeks. A statistically significant decline in all lipid fractions was observed with an increase in birth weight from <1.5 kg to ≥2.5 kg (Tables 3 and 4).

All lipid fractions were numerically elevated in SGA as compared to AGA neonates, but on the comparison, only levels of LDL and HDL were statistically significant. As compared to AGA, LGA neonates exhibited significantly elevated levels of total cholesterol, TG, and VLDL (Tables 5 and 6).

The absolute concentration of all components of the lipid profile was higher in females as compared to males (Fig. 1), but only the mean HDL level was found statistically significant (p<0.001).

DISCUSSION

Lipid levels are a recognized marker for cardiovascular risk as early identification of lipid dysfunction helps to avert the risk by appropriate interventions. The usefulness of lipid levels in assessment of cardiovascular risk among adults has motivated researchers to search whether they hold any relevance in childhood and for that matter to check whether, at birth, lipid levels hold any significance at all. This study was conducted to compare lipid levels in neonates to identify high-risk neonates susceptible to develop cardiovascular disease in adulthood.

The proportional distribution of neonates with different GAs at birth has shown a tremendous variability in different studies performed on lipid levels in the past. In the present study, both preterm and late-term (40–42 weeks) neonates were included. However, some workers had focused only on normal term newborns with GA at birth between 37 and 40 weeks [5,6]. Some studies that included both preterm and term neonates reported the proportion of term to be higher [7,8]. There are some studies that have been conducted using a purposive

Table 1: Comparison of the lipid profile of study subjects with respect to gestational age

Lipid profile	28–36 weeks (n=354)	37–40 weeks (n=557)	40–42 weeks (n=89)	p values
	Mean±SD (95% CI)			
Total cholesterol	79.01±13.82 (72.3–94.9)	62.87±15.03 (61.6–64.1)	70.83±20.54 (66.5–75.16)	<0.001
LDL	47.21±7.92 (43.3–52.5)	31.32±16.55 (29.9–32.6)	39.42±15.79 (36.1–42.7)	<0.001
HDL	23.49±8.75 (14.0–34.8)	24.34±8.54 (24.6–25.6)	23.49±9.53 (21.4–25.5)	<0.051
Triglyceride	43.37±15.4 (29.0–64.4)	36.87±13.32 (35.7–37.9)	39.56±13.94 (36.6–42.5)	0.003
VLDL	8.68±3.09 (5.96–12.9)	7.37±2.66 (7.15–7.60)	7.90±2.79 (7.33–8.50)	0.003

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, SD: Standard deviation, CI: Confidence interval

Table 2: Significance of differences between gestational ages – P values

Gestational age (in weeks)	Total cholesterol	LDL	HDL	Triglycerides	VLDL
28–36 versus 37–40	<0.001	<0.001	<0.001	0.010	0.010
28–36 versus 40–42	0.148	0.301	0.975	0.449	0.449
37–40 versus 40–42	<0.001	<0.001	0.451	0.270	0.270

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein

Table 3: Comparison of the lipid profile of study subjects with respect to birth weight

Lipid profile	<1.5 kg (n=10)	1.5–2.5 kg (n=384)	>2.5 kg (n=606)	p value
	Mean±SD (95% CI)			
Total cholesterol	94.88±3.26 (93.2–96.5)	75.52±17.87 (69.5–84.8)	63.54±15.42 (62.3–64.7)	<0.001
LDL	56.79±5.69 (53.8–59.7)	44.54±16.19 (40.1–51.7)	32.48±15.56 (31.2–33.7)	<0.001
HDL	29.53±5.28 (26.8–32.2)	23.03±8.16 (21.2–25.5)	24.34±8.74 (23.6–25.0)	0.001
Triglyceride	42.82±9.00 (38.2–47.4)	42.12±13.86 (37.6–48.7)	36.75±12.7 (35.7–37.7)	<0.001
VLDL	8.56±1.80 (7.6–9.4)	8.42±2.77 (7.5–9.7)	7.30±2.55 (7.1–7.5)	<0.001

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, SD: Standard deviation, CI: Confidence interval

Table 4: Significance of differences between birth weights – p values

Birth weight (in kg)	Total cholesterol	LDL	HDL	Triglycerides	VLDL
<1.5 versus 1.5–2.5	<0.001	0.001	0.005	0.647	0.647
<1.5 versus >2.5	<0.001	<0.001	0.054	0.224	0.224
1.5–2.5 versus >2.5	<0.001	<0.001	0.825	<0.001	<0.001

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein

Table 5: Comparison of the lipid profile of study subjects with respect to growth status at birth

Lipid profile	SGA (n=295)	AGA (n=640)	LGA (n=65)	p value
	Mean±SD (95% CI)			
Total cholesterol	69.69±20.5 (67.3–72.0)	66.50±14.74 (65.3–67.6)	68.9±15.02 (65.2–72.6)	0.020
LDL	37.95±18.1 (35.8–40.0)	35.84±15.72 (34.6–37.0)	41.4±11.63 (34.5–44.2)	0.012
HDL	24.30±8.50 (23.3–25.2)	23.99±8.39 (23.3–24.6)	20.1±6.42 (18.5–21.7)	0.001
Triglyceride	39.86±13.6 (38.2–41.4)	37.07±12.26 (36.1–38.0)	41.0±16.95 (36.8–45.2)	0.002
VLDL	7.97±2.73 (7.66–8.29)	7.41±2.45 (7.22–7.60)	8.20±3.39 (7.36–9.04	0.002

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, SD: Standard deviation, CI: Confidence interval, SGA: Small for gestational age, AGA: Appropriate for gestational age, LGA: Large for gestational age

Table 6: Significance of differences between growth status – p values

Growth status at birth	Total cholesterol	LDL	HDL	Triglycerides	VLDL
LGA versus AGA	0.018	0.154	0.850	0.007	0.007
LGA versus SGA	0.944	0.268	0.001	0.794	0.794
AGA versus SGA	0.495	0.023	0.001	0.052	0.052

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, SGA: Small for gestational age, AGA: Appropriate for gestational age, LGA: Large for gestational age
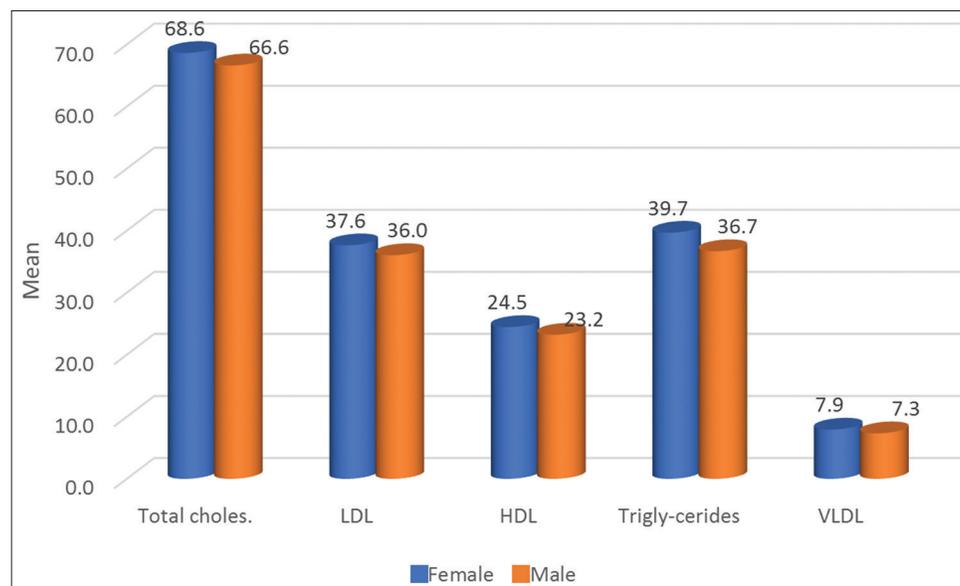
Figure 1: Comparison of the lipid profile of study subjects with respect to gender

sampling design that has included neonates with different GAs in an equal number [9,10].

The present study had a gender ratio of 1.04:1 indicating relatively higher male study subjects as compared to females. In different contemporary studies from India, the gender ratio shows a predominance of males over females. Sreekarthik *et al.* (1.5:1), Mishra *et al.* (1.17:1), and Murthy *et al.* (1.13:1) reported the male dominance [8,11,12]. However, a study by Kharb *et al.* exhibited equal participation of both sexes and other study by Kenchappa and Behera reported female predominance [13,14].

On overall evaluation, no significant gender differences were observed in total cholesterol, triglyceride, and VLDL levels; however, HDL levels were found to be significantly higher in females as compared to males, which is in consonance with other studies [11,13,15,16]. However, a few studies did not find any significant difference between the two genders [17-19]. As most of the previous studies have been carried out on a small sample size wherein gender differences could not have been substantiated statistically; nevertheless, this finding needs further corroboration on larger sample size.

In this study, with increasing birth weight category, mean cord blood lipid levels (except HDL) showed a significant decline whereas mean HDL levels were found to be higher in birth weight category >2.5kg as compared to neonates with birth weight in the range of 1.5–2.5 kg. The relationship between birth weight and lipid levels has been found to be similar as observed for GA, i.e. with increasing birth weight; there is a significant decline in total cholesterol, LDL, TG, and VLDL levels except for HDL levels. However, contrary to the present study, Donegá *et al.* [17] and Esfarjani *et al.* [20] did not find a significant association between lipid levels and birth weight. Kelishadi *et al.* [15], on the other hand, found a correlation between birth weight and high cord triglyceride levels. Aletayeb *et al.* [18] found both LBW (<2.5 kg) and high birth weight (>4.0 kg) to be associated with significantly higher mean triglyceride, total cholesterol, LDL, and VLDL levels as compared to those in the normal birth weight category. Another study from India, having a high representation of neonates with birth weight >4 kg (32%) showed a positive correlation between birth weight and total cholesterol, Triglyceride, HDL, and VLDL levels but an inverse correlation between birth weight and LDL levels. Incidentally, in the present study, there was no category of >4 kg. In fact, we had only 3 (0.3%) neonates with birth weight >3.5 kg; hence, we are not in a position to comment over that. However, this relationship needs further exploration as it is reported only by a few studies and generally, there is an inverse trend between lipid levels (except HDL) and birth weight. A similar observation was also made for triglyceride levels by Ramy *et al.* [21]. A number of Indian studies have also supported the findings of the present study [14,22].

In this study, a binomial trend in lipid levels was observed. It was evident that lipid levels (total cholesterol, LDL, and HDL) of neonates with GA 37–40 weeks (term) were significantly lesser than those observed in both preterm and late-term (40–42 weeks). Pardo *et al.* [6] found lipid levels of near-term (34–36 weeks) newborns to be significantly higher as compared to term newborns, whereas, Ghaemi *et al.* [23], similar to the present study, found mean triglyceride, cholesterol, and LDL levels of preterm and near term newborns to be significantly higher as compared to term newborns. This finding is also in agreement with other studies [24]. This may be most likely due to its rapid uptake and metabolism of LDL by the fetal adrenal as precursor or substrate for steroid hormone synthesis with further progression in gestation as postulated by Parker *et al.* [25]. The mean HDL levels were significantly higher in full-term as compared to premature neonates. Spear *et al.* [26] demonstrated that the lecithin-cholesterol acyltransferase (LCAT) activity was lower in the near term than in term neonates. Hence, fall in HDL may be associated with an increase in the activity of LCAT activity during intrauterine life of the fetus.

In this study, on comparing the lipid levels among neonates with different growth status (SGA, AGA, and LGA), differences were seen for HDL levels which were significantly higher in SGA followed by AGA as compared to LGA neonates. Ramy *et al.* [24] and Lobo *et al.* [27] observed that mean levels of TG and LDL were significantly higher in the SGA compared with the AGA and significantly higher in the AGA compared with the LGA, respectively, which was in consonance with the present study. Katragadda *et al.* [7] found that the mean triglyceride and VLDL levels of preterm SGA babies were significantly higher as compared to AGA babies, which was again in consonance with this study. Contrasting results were seen by Jadhao *et al.* [19] who did not find any significant difference in lipid levels between SGA and AGA babies. Kelishadi *et al.* [15] found mean LDL-C and HDL-C of LGA were significantly lower compared with AGA and SGA neonates. A shortcoming of their study was that SGA comprised only 9.2% of their study population (n=35), and it would be inappropriate to generalize their trends, obtained on the basis of such a small sample size. As such most of the studies have compared the lipid levels between SGA and AGA babies only. Thus, the generalized trend indicates that SGA babies have a tendency to acquire higher lipid values as compared to AGA babies.

The strengths of this study were larger sample size as compared to other studies and reduced selection bias by enrolling consecutive newborns delivered in this hospital. This study had certain limitations. As it was a time-bound study; hence, a convenient sample size of 1000 neonates was considered as representative of a local rural population which may not render adequate power to this study. Further, antenatal maternal comorbidities (HTN, obesity, and diabetes) and lipid profile were not taken into consideration. Many mothers were not on regular antenatal monitoring, which impeded the accuracy of variables such as body mass index, maternal weight gain, hemoglobin levels, placental histopathology, fetal middle cerebral arterial Doppler assessment, and symmetric versus an asymmetric pattern of IUGR in SGA babies. Further, correlation with their lipid profile could not be performed owing to resource constraints. No, follow-up was performed to see the changes in lipid levels with age.

It may thus be hypothesized that SGA babies and premature babies due to higher lipid levels (except HDL) at birth are predisposed to develop atherosclerosis and coronary heart disease later in life, thus mandating regular monitoring of their lipid levels during childhood and adolescence.

CONCLUSION

As observed, all lipid fractions except HDL are higher in LBW babies as compared to term AGA babies, and the HDL fraction is relatively higher in the AGA than in the SGA. It is recommended that further prospective cohort studies need to be performed in LBW babies to monitor serum lipid levels and subsequent development of atherosclerotic lesions in adulthood.

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