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Lipoprotein Heterogeneity at Birth and its relationship with Gestational Age, Gender and Birth Weight: A Cross-sectional Study from a Rural Teaching Hospital of Central India

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Abstract :
Introduction: Intra-uterine fetal metabolic aberrations produce several life-threatening ailments in adult life, including atherosclerotic disease. In that context, though lipid profile has been extensively studied in adults as an excellent marker of the cardiovascular status, similar studies involving pediatric population are largely lacking, especially on umbilical cord-blood.
Aims and Objectives: The aim of the present paper is to improve upon the existing knowledge about cord-blood lipid profile in newborns and its correlation with gestational age, gender and birth-weight in newborns.
Materials and Methods: This is a hospital-based cross-sectional study involving 105 neonates born at a rural tertiary-care teaching hospital of central India for the calendar year 2015. Umbilical cord-blood samples of all these newborns were biochemically assessed and statistically analyzed for various parameters of lipid profile, including apolipoproteins.
Results: Small-for-gestational-age neonates had markedly significant higher levels of all the lipid panel values. Amongst them, female neonates had slightly higher readings than their male counterparts, though the variations did not reach statistical significance. However, the difference of Atherogenic Index between small (4.24±16.67) and appropriate (1.59±1.39) for gestational age neonates was not statistically significant.
Discussion: Findings in our study were discussed in the light of the present-day literature to arrive at clinically valuable implications.
Conclusion: Cord-blood lipid screening provides an opportunity to identify and treat high risk neonates, like the small-for-gestational-age, for prevention of impending coronary artery disease in their adult lives.
Key Words: Lipoproteins, Neonates, Lipid profile, Gestational age, Low birth weight
Running Title: Lipoprotein Screening for Neonatal Atherosclerosis

Introduction

Today, cardiovascular disease (CVD) is considered a modern epidemic and the primary cause of adult mortality and morbidity in both, the developed and the developing countries. It is posing a major public health challenge by undermining the socio-economic development by rapidly escalating financial burden on health systems across the globe. As a result, the mortality rate (25-30%) for CVD is creeping up steadily over the last two decades, and, India is no exception.[1] Logically, it is not surprising that the World Health Organization (WHO) clearly

suggested a convincing possibility of CVD to be the leading cause of death and disability in India by the very year 2020.[2]

Primarily, the incidence of the CVD depends on the prevalence of the un-modifiable (age, gender, genetic, etc.) and modifiable (addiction, lifestyle, environmental, etc.) risk factors. And, obesity, metabolic syndrome, insulin resistance, diabetes mellitus and dyslipidemia are its well-known secondary risk factors.[3] However, the much discussed recent concept of Barker's fetal programming hypothesis has totally revived the understanding of triggering events of these diseases.[1,4] It suggests that the pathogenetic metabolic alterations in a dynamic intra-uterine milieu that are deemed responsible for inducting various ailments in the later life, especially the coronary artery atherosclerosis, tend to initiate during the fetal life itself.[4] In that context, derangements in major lipoproteins like very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL), have been extensively studied in adult population. Accordingly, elevated levels of LDL cholesterol, VLDL triglycerides, and low levels of HDL cholesterol predict the development of coronary artery disease (CAD).[5] Similarly, human umbilical cord-blood (UCB) has been studied for the heterogeneity of plasma lipoproteins at birth by employing density gradient ultracentrifugation gel electrophoresis.[6] However, these methodologies are tedious, labor-intensive, sparsely available and generally have sample sizes too small to make a clinical impact. Nonetheless, these innovations underscore the importance of identifying high-risk neonates and offer an opportunity to commence preventive interventions right at the beginning of life. In this paper, we analyze UCB lipoproteins and apolipoprotein levels collected from our hospital-born neonates and correlate them with birth weight, gender, and gestational age in an effort to draw clinically useful inferences.

Materials and Methods

This is a hospital-based cross-sectional study which was carried out at our tertiary level rural medical college over the calendar year 2015, with the aims to study UCB lipid profiles of small-for-gestational-age (SGA), appropriate-for-gestational-age (AGA) and large-for-gestational-age (LGA) neonates as well as to study the relationship of UCB lipid profile with other fetal factors, if any.

A total of 105 conveniently selected neonates delivered at our institute were included in this study. It was commenced after obtaining approval from the Institutional Ethical Committee. Before enrolling the subjects for the study, one-to-one discussion sessions regarding the nature, purpose and method of study followed by counseling about the required blood collections with the respective parents/guardians of each of the participating neonate were arranged before obtaining a written informed consent from them. The inclusion criteria consisted of gestational age >28 weeks, absence of any congenital anomalies, neonates with one minute APGAR score > 7 and willingness to give consent, as well. And, the exclusion criteria included neonates with congenital anomalies, maternal conditions like addictions, medical co-morbidities, obstetric or other diseases that are likely to alter lipid profile, births which have no maternal records, and, unwillingness to participate in the study.

After each delivery the neonates were examined in detail by our final-year pediatric resident to rule out any congenital anomalies as well as to record APGAR score, birth-weight and gestational age to segregate them into full-term (born between 37 and 40 completed weeks of gestation), pre-term (born before 37 completed weeks of gestation) and post-term (born after 40 completed weeks of gestation). Using intra-uterine growth charts, these newborns were also classified into AGA (birth-weight between the 10th and 90th percentiles for the respective age), SGA (birth-weight less than the 10th percentile for the respective age) and LGA (birth-weight more than 90th percentile for the respective age). Rest of the fetal as well as maternal data were meticulously

entered in respective case-sheets to complete the records. At this point, the UCB samples of participants were collected from the placental side of the umbilical cord immediately post delivery and sent for detailed biochemical analysis for lipid panel, apolipoprotein A-1 (Apo A-1), apolipoprotein B (Apo B). Following this, an Atherogenic Index defined as the ratio of Apo B to Apo A-1 was calculated and recorded for each neonate. The biochemical analysis was carried out using either ERBA XL300 or EM360 Random Access fully automated analyzer. The compatible reagent kits and protocols by ERBA Diagnostics Mannheim GmbH, Germany were used for all. Subsequently, the parents of neonates having deranged test results were counseled regarding the need for adopting prevention strategies for CVD.

The statistical analysis was performed by using descriptive and inferential statistics by employing z-test for calculating the statistical differences between the two means. The software used in the analysis was SPSS version 21.0 and EPI info version 7.50, and, $p<0.05$ was considered as the level of significance.

Results

Out of total 105 neonates included in our study, 51 (48.57%) were males and 54 (51.43%) were females. While 99 (94.29%) neonates were full-term and 6 (5.71%) were pre-term, 70 (66.67%) were AGA and 35 (33.33%) were SGA. Out of that, we had 68 (64.8%) full-term AGA, 31 (29.5%) full-term SGA, 2 (1.9%) pre-term AGA and 4 (3.8%) pre-term SGA neonates. Amongst them, 41 (58.57%) were male AGA and 29 (41.43%) were female AGA neonates. And, there were 10 (28.57%) male SGA neonates, 25 (71.43%) female SGA neonates in our study. It was also noticed that the mean birth-weight of the male neonates (2705.09 gm) was significantly higher than that of the female neonates (2470.44 gm). (Table 1, Graph 1) Further, the difference between the mean birth-weight of AGA neonate (2806.91 gm) and that of SGA neonates (2139.37 gm) was found to be statistically significant. (Table 2, Graph 2)

The detailed analysis of lipid panel showed that the SGA neonates had statistically significant higher levels of serum total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C) and very low density lipoprotein cholesterol (VLDL-C) (p values of 0.001, 0.0001, 0.0001 and 0.0001, respectively) and statistically significant lower levels of serum high density lipoprotein cholesterol (HDL-C) (p value of 0.0001) as compared to AGA neonates. (Table 3, Graph 3)

The difference between UCB lipid profile of male and female neonates was not statistically significant, except for LDL and HDL. The female neonates had slightly higher levels of serum TC, TG, LDL-C and VLDL-C (p values of 0.94, 0.84, 0.022 and 0.050, respectively) while slightly lower levels of serum HDL-C (p value of 0.016) compared to male neonates. (Table 4, Graph 4) Moreover, the pre-term neonates had statistically significant higher levels of LDL-C and VLDL-C and statistically insignificant higher levels of serum TC, TG (with p values of 0.001, 0.005, 0.13, 0.22 and 0.005, respectively) compared to full-term neonates. (Table 5, Graph 5)

We also found that the SGA neonates had higher values of Apo A and Apo B compared to AGA

Table 1. Gender wise comparison of birth weight

Gender	N	Mean	Std. Deviation	Std. Error Mean	z-value	p-value
Male	51	2705.09	379.07	53.08	2.98	0.004, **S**
Female	54	2470.44	423.33	57.60		

Table 2. Comparison of weight in AGA and SGA

	N	Mean weight	Std. Deviation	Std. Error Mean	z-value	p-value
AGA	70	2806.91	271.40	32.43	11.77	0.0001, **S**
SGA	35	2139.37	278.98	47.15		

Table 3.Comparison of cord blood lipid profile of AGA and SGA neonates

	AGA	SGA	z-value	p-value
LDL	24.80±6.86	70.14±8.03	30.67	0.0001**, S**
VLDL	10.77±4.01	45.53±7.79	30.15	0.0001**, S**
TC	77.27±22.52	91.02±11.66	3.53	0.001**, S**
TG	57.80±26.91	84.71±6.18	6.13	0.0001**, S**
HDL	41.66±7.58	13.36±6.40	17.46	0.0001**, S**

Table 4. Comparison of cord blood lipid profile according to gender

	Male	Female	z-value	p-value
LDL	36.34±20.76	46.64±24.41	2.32	0.022, S
VLDL	20.19±16.81	26.98±18.24	1.98	0.050, NS
TC	82.23±20.57	82.51±20.19	0.07	0.94, NS
TG	67.31±26.91	68.25±23.81	0.19	0.84, NS
HDL	35.69±13.64	29.03±14.08	2.45	0.016, S

Table 5. Comparison of cord blood lipid profile between full-term and preterm neonates

	Full Term	Pre Term	z-value	p-value
LDL	40.10±22.98	67±3.28	2.85	0.001, S
VLDL	22.49±17.50	43.33±9.99	2.87	0.005, S
TC	81.65±20.59	94.33±8.04	1.49	0.13, NS
TG	67.06±25.76	80±7.89	1.22	0.22, NS
HDL	32.21±14.01	16.66±6.05	2.86	0.005, S

neonates with *p* values 0.001 and 0.44, respectively. The ratio of Apo-B and Apo-A was higher in case of SGA neonates with *p* value of 0.44. (Table 6, graph 6) And, levels of Apo A, Apo B and the ratio were higher in female neonates compared to male neonates with *p* values 0.95, 0.63 and 0.38, respectively. (Table 7, Graph 7) Besides this, the levels of Apo A, Apo B lipoproteins and Atherogenic Index were higher in pre-term neonates compared to term neonates with levels statistically significant in Apo A lipoprotein with a *p* value of 0.011 and *p* values in case of Apo B and Atherogenic Index were 0.44 and 0.25, respectively. (Table 8, Graph 8) Finally, all lipid panel values were on the higher side

Table 6. Comparison of apolipoproteins A and B of AGA and SGA neonates

	AGA	SGA	z-value	p-value
APO A	73.33±21.16	86.15±29.47	2.58	0.001,**S**
APO B	98.53±74.23	109.61±66.02	0.77	0.44,**NS**
Atherogenic index	1.59±1.39	3.76±14.85	1.18	0.44,N**S**

Table 7. Comparison of cord blood lipid profile according to gender

	Male	Female	z-value	p-value
APO A	77.96±32.11	78.22±16.59	0.05	0.95,NS
APO B	99.16±74.87	105.90±68.04	0.48	0.63,NS
Ratio	1.59±1.46	3.16±12.63	0.87	0.38,NS

Table 8. Comparison of cord blood lipid profile between full-term and preterm neonates

	Full Term	Pre Term	z-value	p-value
APO A	73.33±21.16	86.15±29.47	2.58	0.011, S
APO B	98.53±74.23	109.61±66.02	0.77	0.44, NS
Ratio	1.59±1.39	3.76±14.85	1.18	0.25, NS

Table 9. Comparison of lipid panel with full-term AGA and full-term SGA Z-test for difference between two means

	Full-term AGA (n=68)	Full-term SGA (n=31)	z-value	p-value
APO-A	73.86±21.12	88.22±32.28	2.63	0.010, S
APO-B	99.50±74.80	101.51±59.78	0.13	0.89, NS
AI	1.59±1.39	4.24±16.67	1.30	0.19, NS
LDL	25.62±8.79	71.87±5.95	26.58	0.0001, S
VLDL	11.69±6.73	46.19±7.40	22.91	0.0001, S
TC	77.67±22.34	90.38±12.47	2.95	0.004, S
TG	58.27±26.65	86.32±4.79	5.79	0.0001, S
HDL	40.83±8.97	16.49±6.44	13.57	0.0001, S

Table 10. Comparison of lipid profile of full term AGA neonate with different studies

Name of study	TC	HDL-C	LDL-C	VLDL-C	TG
Jategaonkar et al (Present study)	77.27±22.52	41.66±7.58	24.80±6.86	10.77±4.01	57.80±26.91
Molina et al[13]	64	24.9	28.3	-	37.5
Kalra et al[14]	76.6	22.5	-	-	20.7
Kumar et al[15]	85.83	-	-	-	35.27

in full-term SGA neonates except HDL in comparison with full-term AGA neonates, and, all these readings were statistically significant except APO B and Atherogenic Index. (Table 9)

Discussion

Today, considering the global distribution, India alone is burdened with approximately 25% of the deaths arising due to CVD, particularly atherosclerotic coronary artery disease, and would, in all probability, be the home to >50% of the patients with heart diseases in the years to come.[7] In that regard, the fetal programming hypothesis, the much discussed proposition of recent literature, suggests that certain critical metabolic changes occurring during fetal development are likely to be the basis of CVD in adult life.[8] Moreover, it is well-documented that low Apo A-1 and increased Apo B are associated with increased cardiovascular risk. Elevated LDL-C and Apo B levels in young adults are linked with cardiovascular disease in later life.[9] A link between low birth-weight and adult-onset atherosclerosis has been reported in literature, where elevated Apo B levels were observed in growth-retarded fetuses.[8] Levels of Apo A-1 and Apo B has been reported to be measured in fetuses with normal growth. These findings indicate that Apo B levels are elevated in growth-retarded fetuses and might be considered as confirmatory evidence on a link between low birth-weight and adult-onset atherosclerosis. Fetal growth retardation establishes a life-long irreversible atherogenic profile and those individuals with a history of low birth-weight are reported to have an atherogenic profile.[10] And, the results of comparison of UCB lipid profile in groups based on maturity as well as gestational age and birth-weight suggest that the combination of prematurity and low birth-weight have a more deleterious effect on UCB lipid profile. However, these findings need to be validated by further studies specifically planned to analyze the effect of prematurity and low birth-weight on UCB lipid profile.

Keeping all this in mind we carried out this study at our tertiary level rural hospital in order to establish correlation for UCB lipid profile and apolipoproteins of healthy, SGA, AGA neonates with other fetal factors. Out of 105 neonates selected in our study population, 99 were full-term and 6 were pre-term. Thus, the incidence of pre-term (5.71%) found in our study was less compared to the national incidence (21%). In the study by Hossain et al,[11] number of full-term SGA and AGA neonates remained 30 each which is less compared to our study (31 and 68, respectively). Similarly, in another study by Jones et al,[12] 38 SGA infants and 25 AGA infants were analyzed, which, again, is less as compared to the study presented. Also, the finding that the SGA neonates had significantly higher levels of TC, TG, LDL-C and VLDL-C, our results were comparable with that of the other authors in the recent literature. (Table 10)[13-15]

Yet, the underlying mechanism linking small for gestational age with adverse lipid levels is not well understood. The logic put behind it is the lack of glucose as fuel in these growth-restricted SGA neonates as a result of intra-uterine growth restriction

(IUGR),[16] in the process, compelling them to utilize substitute sources as a fuel (amino acid and lipids) to generate glucose through alternative metabolic pathways.[17] This results in increased hepatic generation of lipids (particularly VLDL-C and chylomicrons). Also, IUGR is also known to be associated with decreased lipoprotein lipase activity. Thus, eventually, the increased hepatic lipogenesis coupled with decreased peripheral utilization of lipids explains the plausible mechanism responsible for higher concentration of plasma lipids in SGA neonates.[17] Similarly, Low birth-weight infants, born with IUGR, have high levels of free fatty acids secondary to spontaneous lipolysis. And, the fatty acids that escape oxidation are then consumed for triglyceride synthesis in the liver. This phenomenon explains the mechanism of elevated levels of triglyceride in such newborns.

Then, in this study, the difference between UCB lipid profile of male and female neonates was not statistically significant for VLDL, TC, and TG, but, it was significant for LDL and HDL. However, with the exception of the paper by Kharb et al,[18] other researchers differed in their observations.[19,20] This could logically be attributed to the lower mean weight of female neonate compared that of the males in our study.

In the present study, the pre-term neonates had higher levels of serum TC, TG, LDL-C and VLDL-C compared to full-term neonates. This is because the pre-term neonates remain deprived of the opportunity of energy storage in late gestation; thus, lack both, hepatic carbohydrate (glycogen) and subcutaneous adipose tissue (triacylglycerol).[16,17] The rise in UCB cholesterol levels may reflect the metabolic adaptation to provide adequate energy, especially to the "essential" organs like brain ("fetal brain sparing" phenomenon).[4,16,17,21] Though some authors corroborated with our findings,[22-24] others conflicted the findings.[19] Here, it could be argued that, as pre-term birth, being an abnormal physiological phenomenon itself, imposes a great amount of stress on the newly born baby. This, in turn, translates into escalating levels of triglycerides, which could vary in every study, subject to differing levels of stress inflicted upon the premature newborns. However, these ambiguous results merit further research at a high volume center.

Regarding apolipoproteins, Radunovic et al reported significant differences in Apo B level and its ratio to Apo A-1 (Atherogenic Index) in growth-retarded fetuses as compared to a normal fetus. They also reported that fetal Apo A-I and Apo B levels do not correlate with the respective gestational ages. However, in the present study, Apo A-1 and Apo B levels had a non-significant inverse association with the gestational age, whereas TG had a significant negative correlation with the gestational age. In a way, fetal growth retardation establishes a life-long irreversible atherogenic profile and those individuals with a history of low birth-weight are reported to have an atherogenic profile.[10] In the present study, Atherogenic Index showed a positive correlation with birth weight.

In addition, Barker et al. have reported an inverse correlation of birth-weight and neonatal abdominal circumference with adult serum cholesterol, LDL-C and Apo B levels, suggesting that the association between aberrant lipoprotein metabolism and low birth-weight is present by the time IUGR gets clinically evident.[8] Others have demonstrated that abnormal lipoprotein profiles in childhood persist well into adult lives.[25,26] Furthermore, the prevalence and severity of carotid artery atherosclerosis in later life are linked to lower birth weights.[27] A Swedish cohort study also found a strong relationship between impaired fetal growth and subsequent cardiovascular mortality.[28] These findings distinctly indicate that fetal growth restriction is associated with a chronic pattern of atherogenic lipoprotein metabolism.

Thus, based on the results of our study we propose that fetal programming (as a result of poor quality of maternal nutrition in rural areas, like ours) could be a major determinant for adulthood

predisposition to CVD. Moreover, UCB lipid panel analysis is a non-invasive and low-cost method to diagnose neonatal dyslipidemia, a major risk factor for CVD. However further studies comparing UCB lipid profiles of rural vis-à-vis urban neonates are required to validate our results.

However, this study has certain limitations. First, a long term longitudinal follow up with bigger sample size is required to further substantiate the findings. Second, maternal diseases that affect lipid profile were ruled out only on the basis of history; this could, though subtly, could adversely affect the objectivity of the study. Third, usage of convenient sampling method may predispose to selection bias. Lastly, incidence of any of diseases referred could not be quantified in this study.

Conclusion

UCB lipid screening helps in identifying high-risk SGA neonates and provides a vital opportunity for ameliorating the related risk factors, thus, preventing life-threatening cardiovascular disease, especially the coronary artery disease, in adult life. However further high volume studies with long-term follows up are required to validate this assumption.

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